NOVARTIS

Patient Safety & Pharmacovigilance

Deferasirox

ICL670

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Deferasirox
Product concerned (brand name):	Exjade®
Document status:	Final
Version number:	22.0
Data-lock point for this RMP	Study CICL670A2429 DLP: 02-Sep-2024
Date of final sign off	17-Jan-2025

Rationale for submitting an updated RMP:

This RMP (v 22.0) is updated to reflect the completion of Study CICL670A2429 (Procedure No. EMEA/H/C/000670/II/0090).

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v 21.2
Part I	No updates.
Part II Module SI	No updates.
Part II Module SII	No updates.
Part II Module SIII	No updates.
Part II Module SIV	No updates.
Part II Module SV	No updates.
Part II Module SVI	No updates.
Part II Module SVII	Updated Table 8-11 to include the physician's survey results.
Part II Module SVIII	No updates.
Part III	Updated to remove the details of the Study CICL670A2429 from the list of additional PV studies.
Part IV	No updates.
Part V	Updated to remove the details of the Study CICL670A2429 under the additional PV activities for the risk 'Compliance with posology and biological monitoring'.
Part VI	Updated to remove additional PV activities.
Part VII Annexes	
Annex number	**Description of changes**
Annex 4	No updates.
Annex 6	No updates.

Other RMP versions under evaluation

No RMP versions are currently under evaluation.

Details of the currently approved RMP:

Version number: 21.2

Approved with procedure: EMEA/H/C/000670/II/0085

Date of approval (Positive opinion): 28-Sep-2023

QPPV name:

Dr Justin Daniels, PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ARF	Acute renal failure
AST	Aspartate aminotransferase
CI	Confidence interval
CHMP	Committee for Medicinal Products for Human Use
CrCl	Creatinine clearance
CSR	Clinical Study Report
CYP	Cytochrome P450
DBA	Diamond-Blackfan Anemia
DDD	Defined daily dose
DDI	Drug-drug interaction
DFO	Deferoxamine
DT	Dispersible tablet
dw	Dry weight
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FCT	Film-coated tablet
FDA	Food and Drug Administration
GI	Gastrointestinal
GVP	Good Pharmacovigilance Practices
Hb	Hemoglobin
HSCT	Hematopoietic Stem Cell Transplantation
LIC	Liver iron concentration
LLN	Lower limit of normal
MAH	Marketing Authorization Holder
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
NSAIDs	Non-steroidal anti-inflammatory drugs
NTDT	Non-Transfusion-Dependent Thalassemia
PASS	Post-Authorization Safety Study
PhV	Pharmacovigilance
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PTY	Patient treatment years
RBC	Red blood cell
RMP	Risk Management Plan
SCAR	Severe cutaneous adverse reaction
SCD	Sickle cell disease
SCT	Stem cell transplantation
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
TEN	Toxic epidermal necrolysis

UK	United Kingdom
ULN	Upper limit of normal
WHO	World Health Organization

1 Part I: Product Overview

Table 1-1 Part I.1 – Product Overview

Active substance(s) (INN or common name)	Deferasirox
Pharmacotherapeutic group (ATC Code)	Iron chelating agent (V03AC03)
Marketing Authorization (MAH)	Novartis Europharm Limited
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	Exjade
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class:** N-substituted bis-hydroxyphenyl-triazole
	Summary of mode of action: Tridentate ligand binds ferric iron with high affinity in a 2:1 ratio and promotes excretion of iron, primarily in the feces
	Important information about its composition: Not applicable
Hyperlink to the Product Information	[Current approved SmPC] [Proposed SmPC]
Indications in the EEA	**Current:** Deferasirox is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥ 7 ml/kg/month of packed red blood cells [RBC]) in patients with beta-thalassemia major aged 6 years and older. Deferasirox is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine (DFO) therapy is contraindicated or inadequate in the following patient groups: ● in pediatric patients with beta-thalassemia major with iron overload due to frequent blood transfusions (≥ 7 ml/kg/month of packed RBC) aged 2 to 5 years ● in adult and pediatric patients with beta-thalassemia major with iron overload due to infrequent blood transfusions (< 7 ml/kg/month of packed RBC) aged 2 years and older ● in adult and pediatric patients with other anemias aged 2 years and older Deferasirox is also indicated for the treatment of chronic iron overload requiring chelation therapy when DFO therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassemia (NTDT) syndromes aged 10 years and older.
	Proposed: None
Dosage in the EEA	**Current:** Film-coated tablets (FCT) and Granules Route of administration: per oral (po) Posology - Transfusional iron overload: Recommended initial daily dose: 14 mg/kg body weight (initial doses of 7 mg/kg or 21 mg/kg may be considered depending on transfusion intensity and treatment goal). Dose adjustments in steps of 3.5-7 mg/kg/day may be considered every 3-6 months. Doses above 28 mg/kg are not recommended because there is only limited experience with doses above this level. Posology - NTDT syndromes:

<table>
<tr><td></td><td>Recommended initial daily dose: 7 mg/kg body weight. Dose adjustments in steps of 3.5 - 7 mg/kg/day may be considered every 3 - 6 months. Doses above 14 mg/kg are not recommended because there is no experience with doses above this level in patients with NTDT syndromes. In patients in whom LIC was not assessed and serum ferritin is ≤ 2000 µg/L, as well as in pediatric patients, 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 ≤ 2000 µg/L.
Exjade Dispersible Tablet (DT) has been discontinued in the EU markets and is therefore no longer available for patients. However, generic versions of deferasirox DT may be available.
In case of switching patients between Exjade FCT/granules and generic versions of deferasirox DT, the dose of the Exjade FCT/granules should be adjusted.
As a reference, the corresponding doses for Exjade FCT/granules and Exjade DT are shown in the tables below.
Transfusional iron overload:
<table>
<tr><th></th><th>Exjade film-coated tablets/granules</th><th>Exjade Dispersible tablets</th></tr>
<tr><td>Starting dose</td><td>14 mg/kg/day</td><td>20 mg/kg/day</td></tr>
<tr><td>Alternative starting doses</td><td>7 mg/kg/day
21 mg/kg/day</td><td>10 mg/kg/day
30 mg/kg/day</td></tr>
<tr><td>Adjustment steps</td><td>3.5 - 7 mg/kg/day</td><td>5 - 10 mg/kg/day</td></tr>
<tr><td>Maximum dose</td><td>28 mg/kg/day</td><td>40 mg/kg/day</td></tr>
</table>
NTDT syndromes:
<table>
<tr><th></th><th>Exjade film-coated tablets/granules</th><th>Exjade Dispersible tablets</th></tr>
<tr><td>Starting dose</td><td>7 mg/kg/day</td><td>10 mg/kg/day</td></tr>
<tr><td>Adjustment steps</td><td>3.5 - 7 mg/kg/day</td><td>5 - 10 mg/kg/day</td></tr>
<tr><td>Maximum dose</td><td>14 mg/kg/day</td><td>20 mg/kg/day</td></tr>
</table>
</td></tr>
<tr><td></td><td>Proposed: None</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>Current: Film-coated tablets: Each FCT contains deferasirox 90 mg, 180 mg, or 360 mg as an active substance.
Granules: Each sachet of granules contains deferasirox 90 mg/180 mg/360 mg as an active substance.</td></tr>
<tr><td></td><td>Proposed: None</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>Yes</td></tr>
</table>

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

2.1 Indication

Deferasirox is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients with thalassemia, sickle cell disease (SCD), myelodysplastic syndromes (MDS) or other rare anemias, and for the treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes.

Incidence and prevalence:

Transfusional iron overload: Patients with conditions leading to chronic anemia develop transfusional iron overload as a consequence of multiple blood transfusions. The underlying conditions include beta-thalassemia, SCD, MDS, Diamond Blackfan anemia (DBA) and other anemias.

Beta-thalassemia

Beta-thalassemia is prevalent in the Mediterranean countries, the Middle East, Central Asia, India, Southern China, and the Far East as well as countries along the north coast of Africa and South America. The highest carrier frequency is reported in Cyprus (14%), Sardinia (10.3%) and Southeast Asia (Flint et al 1998). The total annual incidence of symptomatic individuals is estimated at 1 in 100000 throughout the world and 1 in 10000 people in the EU (Galanello and Origa 2010). In the United Kingdom (UK) there are approximately 800 transfusion dependent patients with homozygote beta-thalassemia and it is estimated that there are 30000 to 60000 births per year worldwide with the condition (Walker 2002). A neonatal screening program in Oman utilizing cord blood samples was conducted to evaluate the incidence of hemoglobinopathies. A total of 7837 neonates were studied. The one year estimated incidence of beta-thalassemia trait was 26 per 1000 neonates (Alkindi et al 2010). Population migration and intermarriage between different ethnic groups has introduced thalassemia in almost every country of the world, including Northern Europe where thalassemia was previously absent (Galanello and Origa 2010). A report from the World Health Organization (WHO) on the epidemiology of hemoglobin (Hb) disorders showed the following estimations (Table 2-1, Modell and Darlison 2008).

Table 2-1 Estimated prevalence of carriers of hemoglobin gene variants and affected conceptions

WHO Region	Affected conceptions per 1000	
	Sickle cell disorders[a]	Thalassemias[b]
African	10.68	0.07
American	0.49	0.06
Eastern Mediterranean	0.84	0.70
Europe	0.07	0.13
South-east Asian	0.68	0.66
Western Pacific	0	0.76
World	2.28	0.46

[a] Include SS, SC, S/ beta-thalassemia
[b] Include homozygous beta-thalassemia, HbE/ beta-thalassemia, homozygous α^0 thalassemia, α^0/α^+thalassemia

Source: Modell and Darlison 2008

Table 2-2 Estimated prevalence of conceptions (per 1000) with combinations of significant hemoglobin gene variants in Europe

Region	Country	Sickle cell disease	Beta-thalassemia
Northern Europe	Denmark	0.07	0.04
	Norway	0.10	0.04
	Sweden	0.10	0.06
	Finland	0.03	0.01
	England&Wales	0.63	0.10
	Scotland	0.04	0.03
	Ireland	0.17	0.01
Western Europe	Netherlands	0.32	0.05
	Belgium	0.22	0.02
	Luxembourg	0.07	0.02
	France	0.30	0.04
	Germany	0.08	0.03
	Austria	0.09	0.01
	Switzerland	0.16	0.05
Southern Europe	Italy	0.13	0.36
	Spain	0.11	0.01
	Portugal	0.31	0.01
	Greece	0.23	0.96
	Albania	0.99	0.65
	F.Yugoslavia	0	0.03
	Malta	0	0.24
	Cyprus	0.78	5.63
Eastern Europe	Bulgaria	0	0.25
	Romania	0	0.03
Turkey	Turkey	0.17	0.24

Source: Modell et al 2007

In Europe, the prevalence of affected conceptions for beta-thalassemia varies between regions with a higher prevalence in some Southern countries (Cyprus 5.63 per 1000 conceptions, Greece 0.96, Albania 0.65) and lower prevalence observed in Northern and Western countries (Austria, Finland and Ireland 0.01 per 1000 conceptions, (Table 2-2, Modell et al 2007). The National Registry for Haemoglobinopathies in Greece recorded 2485 patients with thalassemia major and of this, 88 births with hemoglobinopathy during the period 2000-2010 (Voskaridou et al 2012).

Sickle cell disease

There are approximately four million people with SCD worldwide (Locke 2009). Each year in Africa, about 300000 infants are born with major Hb disorders, including more than 200000 infants with SCD. In some areas of sub-Saharan Africa, up to 2% of all children are born with the condition (Creary et al 2007). In the UK, there are 12000-15000 affected individuals with SCD (UK Obstetric Surveillance System 2010). According to the centers for disease control and prevention (CDC 2012), SCD affects an estimated 90000 to 100000 Americans. The disease occurs in about 1 out of every 500 African Americans births and in about 1 out of every 36000 Hispanic Americans births. Sickle cell trait occurs in about 1 in 12 African Americans.

Sickle cell disease is prevalent in peoples whose ancestors came from sub-Saharan Africa, India, Saudi Arabia and Mediterranean countries. The estimated prevalence of conceptions with significant Hb gene variants for SCD in Europe is widely variable (0.03 per 1000 in Finland to 0.99 in Albania) (Table 2-2, Modell et al 2007). In Greece, the number of patients with SCD recorded until 2010 by the National Registry for Haemoglobinopathies is 1080 and the number of affected births for the period 2000-2010 was 43 (Voskaridou et al 2012).

Myelodysplastic syndrome

Based on 1806 cases from 26 counties in the UK, an incidence of 3.6 per 100000 was estimated among those less than 80 years old. Men had higher incidence rates than women (4.69 and 2.51, respectively), with the highest rates found in the 75- to 79-year age group (18.22) (Strom et al 2008).

Based on the Dusseldorf MDS registry, researchers in 2004 reported a crude incidence of 4.9 per 100000 (5.5 in men and 4.36 in women) for 1991 to 2001. In the United States of America (USA), the crude incidence rate for MDS, excluding chronic myelomonocytic leukemia (CMML), for the 3-year period was 3.4 per 100000 (4.5 in men and 2.7 in women) (Strom et al 2008).

Another study in the US showed that from 2003 to 2007 there were approximately 59722 cases of MDS throughout the US, averaging an estimated 11945 cases per year. For 2003 to 2007, the incidence of MDS (per 100000) was reported as follows (males versus [vs] females in parentheses): all races, 4.3 (5.8 vs. 3.3); blacks, 3.7 (4.6 vs. 3.3); whites, 4.3 (6.0 vs. 3.3). The overall incidence rate for MDS is 4.3 cases per 100000 population. For the five-year period from 2003 to 2007 there were a total of approximately 33108 cases in males (averaging 6622 per year) and a total of 26664 cases in females (averaging 5333 per year). This results in an incidence rate of 5.8 per 100000 population for males and a much lower 3.3 per 100000 population in females (Leukemia & Lymphoma Society 2011).

A study in Sweden investigated the incidence of MDS between 1970 and 1992. The overall incidence in this period was 3.6 per 100000 person years. The incidence in people aged 70 and more was 15.0 in 100000 person-years, being the average age of 74.1 for males and 78.2 for females (Radlund et al 1995).

The 1995-2002 MDS incidence rates per 100000 inhabitant-years adjusted to the European population and its corresponding 95% confidence interval in the EU and according to European region were (RARECARE project Executive Agency for Health and Consumers [EAHC] of the European Commission):

- EU (crude rate): 1.50, 1.47-1.53
- Northern Europe (Iceland, Norway, Sweden): 0.75, 0.71-0.80
- Central Europe (Belgium, Austria, France, Germany, The Netherlands, Switzerland): 0.26, 0.24-0.28
- Eastern Europe (Poland, Slovakia): 0.10, 0.08-0.12
- Southern Europe (Italy, Malta, Portugal, Slovenia, Spain): 0.38, 0.36-0.41
- UK (England, Scotland, Wales, and Northern Ireland) and Ireland (Republic of Ireland): 2.15, 2.11-2.20

About 80 to 85% of patients will receive blood transfusions at some point, often in the order of 2 units every 2 to 6 weeks (Malcovati 2007).

Diamond-Blackfan anemia

Diamond-Blackfan anemia is a very rare condition with approximately 350 known cases in the US and Canada. It can be assumed that all patients are at risk of iron overload from blood transfusions.

Retrospective studies in the UK and the Netherlands are consistent with an incidence of 4 to 5 per million live births with evidence of inheritance (dominant and recessive) in perhaps 12% to 25% of cases. The true incidence is difficult to ascertain, because of the protean clinical manifestations and the wide age range at presentation. Patients are increasingly diagnosed in early infancy, either with characteristic physical findings or on the basis of a positive family history. A proportion of infants may also present with hematological abnormalities during the first year of life. The majority of patients, however, are diagnosed between age 4 and 14 years, and 10% at over 16 years (Sieff et al 2000).

The estimated incidence of DBA in France is 7.3 cases per million live births over the 13-year study period (Willig et al 1999).

Diamond-Blackfan anemia is a rare condition, with no focal point for the collection of case prevalence data worldwide.

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

A study in 924 Thalassemia major patients in Italy found that the mean age of patients at the time of the study was 30.1 (9.1 years) -99.3% were aged 18 and older- with an approximately equal male and female distribution 48.8% and 51.2%, respectively (Piga et al 2013).

In California (US), based on data from the Registry and Surveillance System for Hemoglobinopathies (RuSH), the median age, sex and race distributions were (Paulukonis et al 2014):

- Confirmed SCD patients (n=1975): 7.65 years, 50% males, and 87% black, 5% white, 1% Asian, and 7% others;
- Probable SCD patients (n=3159): 32.3 years, 43% males, 83% black, 8% white, 5% Asian, and 8% others.

In 2008, the WHO published a report summarizing estimations of the global epidemiology of hemoglobin disorders in different regions of the World, using different data sources (Table 2-3, Modell and Darlison 2008).

Table 2-3 Estimated prevalence of carriers of hemoglobin gene variants and affected conceptions in 2003.

WHO region		% of the population carrying			Affected conceptions (per 1000)		
	Population (millions)	Significant variant	α+Thalassemia	Any variant	Sickle cell disorders	Thalassemias	Total
African	586	18.2	41.2	44.4	10.68	0.07	10.74
American	853	3.0	4.8	7.5	0.49	0.06	0.54
East Mediterranean	573	4.4	19.0	21.7	0.84	0.70	1.54
European	879	1.1	2.3	3.3	0.07	0.13	0.20
South-east Asian	1564	6.6	44.6	45.5	0.68	0.66	1.34
Western Pacific	1761	3.2	10.3	13.2	0	0.76	0.76
World	6217	5.2	20.7	24.0	2.28	0.46	2.73

Source: Modell and Darlison 2008

Risk factors for the disease

Thalassemia is an inherited disease in a Mendelian-recessive manner such that asymptomatic heterozygous parents, or carriers, both pass on one copy of a gene for a Hb variant to their children (Weatherall 2012).

The main existing treatment options:

In beta-thalassemia, transfusions have the goal of correction of anemia, suppression of erythropoiesis and inhibition of gastrointestinal iron absorption, which occurs in non-transfused patients as a consequence of increased, although ineffective erythropoiesis. Several transfusion regimens have been proposed. The most widely accepted aims at pre-transfusional Hb level of 9 to 10 g/dL and post-transfusion level of 13 to 14 g/dL. The frequency of transfusion is every two to four weeks. The amount of blood to be transfused depends on several factors including weight of the patient, target increase in Hb level and hematocrit of blood unit. In general the amount of transfused RBC should not exceed 15 to 20 ml/kg/day, infused at a maximum rate of 5 ml/kg/hour, to avoid fast increase in blood volume (Galanello and Origa 2010).

Despite therapeutic progress, Stem Cell Transplantation (SCT) remains the only curative treatment available today. Although more than 90% of patients who receive a transplant from a human leukocyte antigen (HLA)-identical related donor are surviving and 80-90% of them become disease-free, there are still some uncertainties how the curative, but potentially lethal SCT, can be applied for adults and patients with advanced disease or those having a matched unrelated donor (Aydinok 2012).

Sickle cell disease

The mainstay of therapy for pain episodes is supportive: hydration, anti-inflammatory agents and pain medication (e.g. non-steroidal anti-inflammatory drugs [NSAIDs] and narcotic analgesia). Early prevention of pulmonary infections and prompt evaluation and treatment of underlying infections are essential. Life-threatening or severe complications are often treated with transfusions to reduce the percentage of Hb S while increasing oxygen carrying capacity of the blood (Bender and Hobbs 2013).

Chronic RBC transfusion therapy is used to maintain the percentage of Hb S below 30% and suppress reticulocytosis. Hydroxyurea (HU) is the most frequently prescribed therapy for SCD to induce synthesis of Hb F, to decrease sickling, improve red-cell survival, lowering the white blood cell count and platelet count, and reducing vascular inflammation. Stem cell transplantation from a normal donor or one with sickle cell trait can be curative in individuals with SCD (Bender and Hobbs 2013).

Myelodysplastic syndrome

Until recently, there were no approved drugs for the treatment of MDS. Supportive care measures (e.g. transfusion of blood products, hematopoietic growth factors and antimicrobials) remained the mainstay of therapy. Within the last 6 years, two agents have been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of MDS: the immunomodulating agent, lenalidomide and the hypomethylating agent, azacitidine and the FDA also approved decitabine, which is also a hypomethylating agent. These agents have dramatically changed both the course of treatment for MDS and patient outcomes. (NCCN 2015, Malcovati et al 2013, Bryan et al 2010).

Treatment of lower-risk MDS include:

- Supportive Care: RBC transfusions and iron chelation therapy, erythropoiesis-stimulating agents, such as recombinant human erythropoietin or darbepoetin alfa, granulocyte colony-stimulating factors
- Immunosuppressive therapy
- Lenalidomide, thalidomide, anti-thymocyte globulin, cyclosporine A
- Hypomethylating agents (azacitidine, decitabine)

Treatment of higher-risk MDS include:

- Hypomethylating agents (azacitidine, decitabine)

Diamond-Blackfan anemia

Current treatments are red cell transfusions, corticosteroid therapy and hematopoietic SCT (HSCT). Approximately 80% of patients will initially respond to corticosteroid therapy, whereas 20% do not respond and require blood cell transfusion therapy.

At presentation the majority of patients require stabilization with red cell transfusion. Steroids have been found to affect linear growth and physical and neurocognitive development in infants. Thus to delay the start of corticosteroids and transfusions is the treatment of preference. Transfusions are indicated at Hb levels of 8 g/dL with 10 to 15 mL/kg of leukocyte-depleted, packed RBC (Vlachos and Muir 2010). Patients receiving chronic red cell transfusion therapy generally require transfusion of 10 to 15 mL/kg every 3 to 5 weeks to maintain Hb levels above 8 g/dL.

Stem cell transplantation is the only definitive treatment for the hematologic manifestations of DBA. Allogeneic matched sibling HSCT has been very successful. Data from the DBA registry study revealed an overall survival of 77.3% ± 8.3% for sibling HSCT and 31.5% ± 12.7% for alternative donor HSCT (Vlachos and Muir 2010). Other therapies with androgens, high dose corticosteroids, erythropoietin, Interleukin-3, cyclosporine ± prednisone, metoclopromide, valproic acid, and leucine have been used over the last 30 years, but most of them have been ineffective (Vlachos et al 2008).

Table 2-7 provides the concomitant medications in the target population.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Beta-thalassemia

There has been a steady improvement in survival following the introduction of effective chelation therapy with DFO during the 1980's. Table 2-4 shows the principal causes of death in 50 patients from a cohort of 720 patients with beta-thalassemia born after 1970 (Borgna-Pignatti et al 2004):

Table 2-4 Causes of death in patients with beta-thalassemia

Cause	Number of patients	Age at death (years)
Heart failure	31	51
Infection	9	15
Arrhythmia	4	7
Thrombosis	2	3
Malignancy	2	3
Diabetes	2	3
Unknown	5	8
Other	6	10
Source: Borgna-Pignatti et al 2004		

Thus, the majority of deaths are due to cardiac events. In this cohort 70% of patients were still alive at 35 years of age (Borgna-Pignatti et al 2004).

A Greek study reported the mortality ratios of transfusion-dependent beta-thalassemia patients compared with the general population. The standardized mortality ratio improved significantly from 28.9 in 1990-1999 to 13.5 in 2000-2010. While the cardiac mortality standardized ratio decreased from 322.9 to 106.6 in the same periods. At the age of 50 years, the overall survival was 65% (Ladis et al 2011). A later analysis of these Greek data reported the causes of death from Thalassemia in patients between the years 2000 and 2010.

The main causes of death were (Voskaridou et al 2012):

- Heart disease (52.3%)
- Liver carcinoma (13.8%)
- Microbial infections (8.0%)
- Malignancy (6.3%)
- Stroke (5.2%)
- Other causes (4.0%)
- Unknown causes (3.4%)
- Pulmonary disease (1.2%)
- Renal failure (1.2%)

The analysis of 447 transfusion-dependent beta-thalassemia patients in Egypt during 10 years of follow-up showed that the most common morbidities were endocrine (44.7%) followed by cardiovascular (41.3%) and renal (4%). The overall mortality rate was 1.5% in the observation period 2000-2010. The 5, 10 and 20 years survival proportions were 80%, 50% and 20% respectively (Mokhtar et al 2013).

Sickle cell disease

In a cohort of 3764 patients, there were 209 deaths. Median age at death was 42 years in males and 48 years in females with homozygous SCD but was 60 and 68 years, respectively, in patients with sickle cell-hemoglobin C disease. Eighteen percent of deaths occurred in chronically ill patients with clinical organ failure, predominantly renal, cardiac failure or chronic debilitating cerebrovascular accident. Thirty-three percent of patients died during sickle crises, mainly acute chest syndrome and stroke. The major cause of death in SCD <20 years of age is pneumococcal sepsis, possibly as a result of splenic atrophy (Platt et al 1994). The analysis of the mortality and causes of death in SCD patients in the Netherlands before the introduction of neonatal screening provided the following results (Table 2-5, Van der Plas et al 2011):

Table 2-5 Causes of death in SCD patients in Netherlands before introduction of neonatal screening

Cause of Death	N	Age (years)
Hemophilus meningitis	2	0.9, 2.3
Pneumococcal meningitis	1	1.8
Pneumococcal sepsis	1	7.1
Stroke	3	11.3, 20.5, 27.9
Sickle cell crisis NOS	3	2.9, 11.3, 27.4
Postoperative shock NOS	1	27.2
Pulmonary hypertension	1	27.3
Total	**12**	
Source: Van der Plas et al 2011		

In SCD patients the main causes of death reported by Voskaridou et al 2012 were:

- Liver failure-cirrhosis (18.8%)

- Pulmonary disease (18.8%)
- Stroke (17.2%)
- Microbial infection - septicaemia (7.8%)
- Heart disease (5.8%)
- Sickle cell crisis (5.7%)
- Multiorgan failure (4.1%)
- Malignancy (3.1%)
- Renal failure (3.1%)
- Human immunodeficiency virus (HIV)+ (1.5%)
- Other causes (7.8%)
- Unknown (4.7%)

An analysis of chart reviews on 104 consecutive adult sickle cell patients treated in Amsterdam from July 2005 to December 2006 reported the following results with respect to comorbidities (Van Beers et al 2008).

Myelodysplastic syndrome

The disease usually progresses to acute myeloid leukemia which is often treatment-refractory and therefore rapidly fatal. The main non-leukemic causes of death in 467 patients with MDS were as follows: cardiac failure (51%), infections (31%), hemorrhage (8%), and cirrhosis (8%) (Malcovati et al 2005). The association between iron overload and mortality has been suggested in multiple publications (Malcovati et al 2005; Sanz et al 2008). An analysis of 1708 MDS patients aged 65 and older showed that comorbidities significantly increased the risk of death. The Hazard Ratios were 1.19 (95% confidence interval [CI] 1.05-1.36) and 1.77 (95% CI 1.50-2.08) for those with Charlson index of 1-2 and ≥ 3, respectively (Wang et al 2009).

Diamond-Blackfan anemia

The exact mortality rate in this population is unknown. Some patients recover spontaneously. Fatal events are usually a result of tissue and organ damage due to iron overload, but patients are also susceptible to overwhelming infections.

Important co-morbidities:

Important co-morbidities in patients with chronic iron overload have been presented in Table 2-6.

Table 2-6 Patient's comorbidities

Organ damage (%)	HbSS (n=59)/ Sb0 -thal (n=5)	HbSC (n=29) /Sb+ -thal (n=11)
Microalbuminuria	34	5
Renal Failure	8	3
Pulmonary Hypertension	32	12
Retinopathy	24	61
Perceptive hearing loss	14	14

Organ damage (%)	HbSS (n=59)/ Sb0 -thal (n=5)	HbSC (n=29) /Sb+ -thal (n=11)
Iron Overload	17	0
Cholelithiasis	66	23
Clinical complications		
Avascular osteonecrosis	16	8
Leg ulcers	14	0
Acute chest syndrome	32	18
Number of crises/year		
None	27	38
Less than one	47	43
One or more	27	20
Stroke	11	0
Priapism (%males)	21	6
Source: RMP version 20.1-Table 2-6		

2.2 Indication: Treatment of chronic iron overload in Non-transfusion-dependent thalassemia syndromes

Incidence and prevalence

Incidence

Recent estimates suggest that approximately 68000 children are born worldwide each year with various forms of thalassemia. Approximately 19000 have inherited HbE beta-thalassemia, and about 50% of them will exhibit a less severe clinical course that would fall into the category of NTDT (Weatherall 2012). A smaller ill-defined numbers are born with the other NTDT form beta-thalassemia intermedia.

The annual number of births for the NTDT form of α-thalassemia, α-thalassemia intermedia or Hb H disease, is approximately 10000 (Vichinsky 2010). Voskaridou et al (2012), based on data from the Greek National Registry for Haemoglobinopathies, reported 22 births affected by thalassemia intermedia for the period from 2000 to 2010.

Prevalence

Premawardhena et al (2005) classified 109 patients with HbE/ beta-thalassemia aged 1 to 51 years into very mild to very severe groups. About one-quarter of patients were transfusion independent, whereas the remainder had been maintained on regular or intermittent (on demand) transfusion. The Greek National Registry for Haemoglobinopathies recorded information on 756 patients with thalassemia intermedia until 2010 (Voskaridou et al 2012).

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Five different forms of NTDT presented differently across countries or regions (Weatherall 2012):

- β-Thalassemia Intermedia: This form occurs at a low and varying frequency in every population with a high frequency of β-thalassemia and is particularly common in parts of Africa where mild β-thalassemia alleles predominate.
- Hemoglobin E β-Thalassemia: This condition is by far the most common form of severe thalassemia in the populations of East India, Bangladesh and Southeast Asia.
- Hemoglobin H Disease: This disorder, caused by the inactivation of 3 α-globin genes, is most common in Southeast Asia and it occurs sporadically in most other tropical regions.
- Hemoglobin S β-Thalassemia: The co-inheritance of the sickle cell gene with a β-thalassemia allele is most prevalent in parts of sub-Saharan Africa, though it may also occur in the Mediterranean region, Middle East, and parts of India where the sickle cell gene is common. Because the majority of β-thalassemia alleles in Africa are mild, this condition tends to be extremely mild in African populations.
- Hemoglobin C Thalassemia: This disorder is restricted to localized regions of sub-Saharan and North Africa and it is characterized by a mild form of NTDT.

Risk factors for the disease

Thalassemia is an inherited disease in a Mendelian-recessive manner such that asymptomatic heterozygous parents, or carriers, both pass on one copy of a gene for an Hb variant to their children. Several genetic and environmental modifiers have been identified which can explain transfusion independence in NTDT compared to other regularly transfuse forms (Weatherall 2012).

The main existing treatment options:

Treatment of patients with NTDT relies primarily on expert opinion and data from observational studies, with only few randomized clinical trials conducted to date (Musallam et al 2013). Aside from management of specific complications, the following general approaches are used:

- Splenectomy: can increase total Hb level by 1-2 g/dL and avoid blood transfusion therapy, however, can put the patient to a high risk of morbidity and mortality due to infection and multiplicity of adverse events (AEs).
- Transfusion therapy: NTDT patients may still require occasional blood transfusions during infection, pregnancy, surgery or any setting with anticipated blood loss.
- Iron chelation therapy: it is indicated in NTDT patients aged 10 years or above (or 15 years and over in deletional hemoglobin H disease) and having liver iron concentration levels 5 mg Fe/g dw (or serum ferritin level $\geq$ 800 ng/mL when liver iron concentration measurement is unavailable) as these thresholds indicate increased iron related morbidity risk.
- Fetal Hb induction: several fetal Hb inducers (e.g. HU) have been shown to increase total Hb level in small trials including NTDT populations; however, such treatment options remain investigational.

Table 2-7 Concomitant medications to treat disease-related complications in the target population

Underlying diseases and co-morbidities	Main co-prescribed medications
Beta-thalassemia and NTDT	
• Anemia	• Transfusions
• Heart disease	• Antiarrhythmics, diuretics, ACE inhibitors, calcium antagonists, beta-blockers
• Hypothyroidism	• Thyroxine
• Hypoparathyroidism	• Vitamin D2, calcitriol, calcium
• Diabetes mellitus	• Insulin
• Hypogonadism	• Testosterone, human chorionic gonadotropin, gonadotropin, gonadotropin-releasing hormone
• Infections	• Antibiotics
Sickle cell disease	
• Sickle cell crisis	• Blood transfusions, morphine, Nonsteroidal anti-inflammatory drugs (NSAIDs)
• Stroke	• Anticoagulants
• Seizures	• Antiepileptics
• Renal impairment	• Diuretics
• Infections	• Antibiotics
• Anemia	• Hydroxyurea, folate, transfusions
Myelodysplastic syndrome	
• Infection	• Antibiotics
• Cardiovascular disease	• Diuretics, ACE inhibitors, calcium antagonists, beta-blockers
• Chronic pulmonary disorders	• Bronchodilators, corticosteroids
• Diabetes	• Oral antidiabetics, insulin
• Osteoporosis	• Bisphosphonates
• Renal impairment	• Diuretics
Diamond-Blackfan anemia	
• Anemia	• Blood transfusions, corticosteroids
• Cardiac disease	• Diuretics
• Infections	• Antibiotics
• Leukemia	• Chemotherapy

Source: RMP version 20.1-Table 2-7

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

During a 10 year observation period at a Thalassemia Center in Lebanon, 18 out of 127 beta-thalassemia intermedia patients died, giving a cumulative 10 year mortality incidence of 14% (Matta et al 2014). In 584 patients with beta-thalassemia intermedia recruited at 6 comprehensive care centers in the Middle East and Italy, the frequency of disease-related complications was as follows (Taher et al 2010):

- Osteoporosis 22.9%
- Extramedullary hematopoiesis 21.2%
- Hypogonadism 17.3%
- Cholelithiasis 17.1%
- Thrombosis 14.0%
- Pulmonary hypertension 11.0%
- Abnormal liver function 9.8%

- Leg ulcer 7.9%
- Hypothyroidism 5.7%
- Heart Failure 4.3%
- Diabetes mellitus 5.7%

Important co-morbidities:

Across all target populations, patients who require regular blood transfusions will inevitably accumulate excess iron in the form of hemosiderin at toxic and ultimately lethal quantities in the heart, liver and endocrine organs. Target populations include thalassemia, SCD, MDS and DBA. Without chelation therapy to remove excess iron, regularly transfused patients acquire toxic accumulations of iron within 3 to 10 years (Gabutti and Piga 1996) resulting in iron induced tissue damage and organ failure. The majority of transfused beta-thalassemia patients receive chelation therapy. However, the rate of chelation therapy in other diseases that require regular transfusions is currently much lower. Despite their transfusion independence, patients with NTDT can still accumulate iron due to increased intestinal iron absorption. Cumulative iron overload may reach clinically significant levels and has been associated with hepatic, vascular, endocrine, and bone disease. Such iron-overload related morbidities start appearing beyond 10 years of age (Musallam et al 2013).

Co-morbidities in beta-thalassemia

Table 2-8 provides the incidence of co-morbidities by age in a cohort of 342 patients with β-thalassemia in North America.

Table 2-8 Co-morbidities in beta-thalassemia

Co-morbidity	0-15 years, %	16-24 years, %	>25 years, %
Heart disease requiring medication	0	5	23
Cirrhosis by biopsy	4	10	15
Liver failure/cirrhosis by clinical findings	0	5	6
Thyroid disease	0	8	17
Hypoparathyroidism	0	1	9
Diabetes mellitus	0	9	21
Hypogonadism requiring medication	0	41	62

Source: Cunningham et al 2004

Osteoporosis occurs in up to 50% of patients with beta-thalassemia (Schrier and Angelucci 2005). The causes are multi-factorial and include endocrinopathies and bone thinning due to bone marrow expansion which occurs in an effort to produce enough red cells. Chronic hemolysis can cause splenomegaly and hypersplenism, with the development of increasing leukopenia and thrombocytopenia. Splenectomy may be indicated which is associated with a markedly increased risk of overwhelming infections, especially septicemia, despite the use of immunization strategies and prophylactic antibiotics. Thalassemia patients also have an increased risk of thrombosis which may be aggravated by post-splenectomy thrombocytosis.

Regarding kidney stones, a retrospective cohort study in 166 participants with transfusion dependent thalassemia who had undergone dual-energy Xray absorptiometry between 2009 and 2011 in Australia, found a high prevalence of kidney stones (18.1%) which was greater in males compared to females (28.7 vs 9.7% respectively, Wong et al 2013).

Co-morbidity in sickle cell disease

Gallstone formation has been reported in 35% to 50% of children with SCD (Edwards 2002).

The sickled red cells can aggregate into large masses which obstruct blood vessels and result in pain and damage to tissues and organs. These so-called 'sickle cell crises' can affect a variety of organs including acute splenic or hepatic sequestration (where there is massive enlargement of the respective organ due to the accumulation of sickled red cells), acute chest syndrome (with dyspnea and pleuritic pain), cerebrovascular injury including stroke and seizures, priapism, avascular necrosis of bone, and sickle cell retinopathy. These episodes can be rapidly fatal or lead to death due to progressive organ failure when repeated episodes occur during the patient's lifetime (Platt et al 1994). In one study, 61% of transfused SCD patients reported a history of stroke (Fung et al 2007). Repeated splenic infarcts can result in splenic atrophy and such patients are at high risk of overwhelming infection.

Furthermore, SCD patients are particularly at risk of progressive renal dysfunction termed sickle cell nephropathy which affects 5% to 18% of the population (Scheinman 2003). In a prospective study of 964 adults with SCD, overall mortality was 18% and includes renal failure in 40% of patients at the time of death (or 7.6% of the total) (Platt et al 1994).

Co-morbidity in myelodysplastic syndrome

Myelodysplastic syndrome is associated with bone marrow insufficiency leading to peripheral blood cytopenias which can affect one or more cell lines. Patients are generally anemic (hence the need for regular blood transfusions); leucopenia and thrombocytopenia expose patients to the risks of severe infections and bleeding. Myelodysplastic syndrome affects predominantly elderly patients who are at risk for co-morbidities that occur with aging, including cardiovascular diseases, chronic pulmonary disorders, diabetes, osteoporosis and renal impairment. Patients with MDS will generally develop acute myeloid leukemia if death does not occur earlier due to a concomitant illness. A study in the US Surveillance, Epidemiology, and End Results (SEER)-Medicare database found that MDS patients with comorbid conditions had significantly greater risk of death than those without comorbidities. Among 1708 MDS patients diagnosed between 2001 and 2002 the major comorbidities found were diabetes, congestive heart failure, chronic obstructive pulmonary disease, cardiovascular disease and peripheral vascular disease (Wang et al 2009).

Co-morbidity in Diamond-Blackfan anemia

Patients with DBA frequently have congenital malformations, including craniofacial malformations, urogenital malformations and cardiac defects. The condition is often associated with growth retardation and symptoms secondary to anemia in children. Patients with DBA are also at higher risk of developing leukemia and other malignancies (Vlachos et al 2008).

Co-morbidity in NTDT

In 584 patients with beta-thalassemia intermedia recruited at six comprehensive care centers in the Middle East and Italy, the frequency of morbidity was as follows (Taher et al 2010):

- Osteoporosis 22.9%
- Extramedullary hematopoiesis 21.2%
- Hypogonadism 17.3%
- Cholelithiases 17.1%
- Thrombosis 14.0%
- Pulmonary hypertension 11.0%
- Abnormal liver function 9.8%
- Leg ulcer 7.9%
- Hypothyroidism 5.7%
- Heart Failure 4.3%
- Diabetes Mellitus 5.7%

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

The kidney, eye (lens), and hepatobiliary tract were identified as the major targets of deferasirox in animals. Other effects observed in animals were generally associated with the pharmacological effect of an iron chelator in animals with normal tissue iron status (e.g. changes in hematological parameters consisting mainly of anemia, with alteration of red cell morphology in some cases).

Table 3-1 Key Safety findings from non-clinical studies and relevance to human usage:

Key Safety findings (from non-clinical studies)	Relevance to human usage
Renal findings: Renal tubular degeneration, cytoplasmic vacuolization of cortical tubular epithelial cells, and tubular necrosis (Studies 0170121, 0270117, 974080, 987037, 982027, and 971974).	Increased serum creatinine, acute renal failure (ARF) and renal tubular disorders including Fanconi's syndrome and renal tubular necrosis have been observed in humans.
Lenticular changes: Rodents: varied in morphology from early cortical striations or vacuoles to mature cataracts, and demonstrated a dose relationship in severity (Studies 987037, 0270117 and 0370030). Primates: no changes observed (Studies 982027, 971053 and 974194).	Lens opacities have been observed in humans.
Hepatobiliary findings: Inflammatory and degenerative changes in the gallbladder and/or bile ducts (Studies 0170121 and 0270117)	Cholelithiasis, raised transaminases, hepatitis and hepatic failure have been observed in humans.
Gastrointestinal (GI) hemorrhage and ulcers: Erosions, ulcerations, hemorrhage and/or inflammation in the mucosa of the stomach and/or intestines were observed (Studies 0170121, 0270117, 974080, 987066 and 987037)	GI hemorrhage and ulcers (including GI perforation) and esophagitis have been observed in humans.
Fertility and Early Embryonic Development Study: There were no effects on mating, fertility or reproductive parameters in the Fertility and Early Embryonic Development Study in rats (Study 987102) at doses up to 75 mg/kg which induced toxicity. Secretion into maternal milk in animals (Report R00-0015).	It is not known if deferasirox is secreted into human maternal milk.
Embryo-fetal toxicity: No indication of teratogenicity in rats (Study 987055) or rabbits (Study 987056). In rats, at the dose of 100 mg/kg which induced maternal mortality and toxicity, there was an increase in common fetal skeletal variations. Developmental toxicity:	No dedicated clinical trial data on exposed pregnancies were achieved for deferasirox. The potential risk for humans is unknown. As a precaution, it is recommended that deferasirox not be used during pregnancy unless clearly necessary (Summary of Product Characteristics [SmPC]).

Key Safety findings (from non-clinical studies)	Relevance to human usage
An increase in stillborn pups and decreased pup weights were observed at a dose that induced maternal toxicity and mortality (90 mg/kg/day) (Study 997055).	
Juvenile toxicity: In the juvenile rat (Study 0370030) and mouse studies (Study 0480148), target organs identified were consistent with those observed in adults. The maximum tolerated dose in juvenile animals was lower than that in adult animals, due to higher exposure to deferasirox rather than increased sensitivity of tissues in juvenile animals.	These data support the use of deferasirox in children aged 2 years old and above.
Drug-drug interactions: In vitro studies suggested that the potential of deferasirox does not appear to be an inhibitor, or inducer of cytochrome P450 (CYP) isoenzymes as well as hepatic anion transporters (MRP2, MXR) in clinical settings, i.e., patients receiving multiple daily oral dosing of 20-40 mg/kg deferasirox. An interaction between deferasirox and HU in sickle cell anemia patients is unlikely.	These data were not confirmed with drug-drug interaction (DDI) study results in healthy subjects. Deferasirox affects various CYP isoenzymes in clinical settings.
Source: Study 0480148, Study 982027, Study 971974, Study 987037, Study 0270117, Study 974194, Study 971053, Study 0170121, Report R00-0015, Study 987102, Study 987055, Study 997055, Study 0370030, Study 987056, Study 974080, Study 987066, SmPC.	

At this stage, there is no need for additional non-clinical data if the product is to be used in special populations.

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

Approximately 8063 patients received deferasirox, comparator or placebo treatment in MAH sponsored global and local interventional clinical trials as well as compassionate use programs cumulatively since the Development International Birth Date until the PSUR datalock point, 31-Oct-2019.

Estimates of the cumulative patient exposure, based upon actual exposure data from completed clinical trials and the enrollment/randomization schemes for ongoing trials is provided in Table 4-1.

Table 4-1 Estimated cumulative subject exposure from investigational CTs

Treatment	Completed Studies**	Ongoing Studies***	Total
	Subjects	Subjects	Subjects
Deferasirox	7203	276	7479
Active Comparator	604	0	604
Placebo	218	0	218
Total	**7492***	**276***	**8063*,^**

Source: PSUR reporting period 01-Nov-2018 to 31-Oct-2019 - Clinical database, completed clinical trials with final data available in the Company biostatistics analysis system, ongoing clinical trials with interim analyses data available in the Company biostatistics analysis system and compassionate use programs as of 31-Oct-2019. Inclusive of global studies.

* Subjects randomized to comparator and placebo treatment schemes may have been treated with deferasirox as well. This means the total numbers displayed in each column is not the sum of the treatments.

** The subject exposure from the ongoing clinical trials with interim analysis is included in the completed studies.

*** Does not include exposure from ongoing randomized, double-blinded studies.

^ This includes the exposure numbers (295) from compassionate use programs CICL670A0117, CICL670ABE01, CICL670E2001I and CICL670AIT02. The number of patients exposed to deferasirox in completed Novartis-sponsored trials was erroneously reported to be 7967 in PSUR (reporting period: 01-Nov-2017 to 31-Oct-2018) (instead of 7052). The number 7967 erroneously included 798 subjects exposed to deferasirox in completed local Phase IV studies (non-interventional) and 117 patients from the global non-interventional CICL670A2301 trial.

PSUR: Periodic Safety Update Report.

Table 4-2 to Table 4-5 provide the patient-years of exposure to deferasirox by disease population and by demographic features (age, gender and race) as of the cut-off dates used for the analyses.

- All trials excluded breast feeding and pregnant women
- All trials are open-label except one ongoing MDS study

- Renal impairment is excluded from our studies and hepatic impairment was studied in Study CICL670A2125.

For non-transfusion dependent thalassemia, exposure data included the pivotal study for the NTDT indication, Study CICL670A2209 (THALASSA). The data cut-off date for database lock was 27-Jul-2011.

For transfusional iron overload, exposure data included the pooled data from the five studies used for the registration of deferasirox, namely, Study CICL670A0105, Study CICL670A0106, Study CICL670A0107, Study CICL670A0108, Study CICL670A0109 (core and extension) as well as the Study CICL670A2402 core study data. Cut-off date applied to the data for this analysis was 28-Sep-2007 for the extension studies, whereas all available data at time of core database lock were used for data from Study CICL670A2402.

Table 4-2 Clinical trial exposure to deferasirox (by disease)

Disease populations	Drug and dose	Number of subjects	Patient-years
Non-transfusion-dependent thalassemia	Deferasirox 5 mg/kg (DT)	55	52.2
	Deferasirox 10 mg/kg (DT)	55	53.6
	Placebo	56	54.5
Beta-thalassemia	Deferasirox	1002	2635.1
Sickle cell disease		185	406.1
Myelodysplastic syndrome		47	93.3
Diamond-Blackfan anemia		30	95.8
Other anemia		22	53.4

Source: RMP version 4 Annex 7-PT-Table 1.1a; RMP version 7 Annex 7-Table 1.2-1.1

Table 4-3 Clinical trial exposure by disease population and age

Disease population	Drug and dose	Age group	Number of patients	Patient-years
Non-transfusion-dependent thalassemia	Deferasirox 5mg/kg (DT)	< 18 years	6	6.0
		≥ 18 years	49	46.2
	Deferasirox 10mg/kg (DT)	< 18 years	7	7.2
		≥ 18 years	48	46.4
	Placebo	< 18 years	8	8.1
		≥ 18 years	48	46.3
Beta-thalassemia (n=1002)	Deferasirox	2 - < 6 years	83	203.3
		6 - < 12 years	221	551.5
		12 - < 16 years	187	478.6
		16 - < 65 years	511	1401.7
		≥ 65 years	0	-
Sickle cell disease (n=185)	Deferasirox	2 - < 6 years	5	12.7
		6 - < 12 years	43	104.4
		12 - < 16 years	42	101.6
		16 - < 65 years	95	187.4
		≥ 65 years	0	-
Myelodysplastic	Deferasirox	16 - < 65 years	19	45.4

Disease population	Drug and dose	Age group	Number of patients	Patient-years
syndrome (n=47)		≥ 65 years	28	48.0
Diamond-Blackfan anemia (n=30)	Deferasirox	2 - < 6 years	7	25.7
		6 - < 12 years	5	20.6
		12 - < 16 years	3	9.4
		16 - < 65 years	15	40.2
		≥ 65 years	0	-
Other anemia (n=22)	Deferasirox	2 - < 6 years	2	8.3
		6 - < 12 years	1	0.5
		12 - < 16 years	2	5.6
		16 - < 65 years	14	36.7
		≥ 65 years	3	2.3

For the NTDT disease population there were 21 (12.7%) patients <18 years of age, only 4 patients were below 12 years (aged 10 and 11 years) and only one patient was above 65 years of age PD
Source: RMP version 4 Annex 7-PT-Table 1.1 b; RMP version 7. Annex 7-Table 1.2-1.2, RMP version 7 Annex 7-Listing 1.2-1.

Table 4-4 Clinical trial exposure by disease population and gender

Disease population	Drug and dose	Gender	Number of patients	Patient-years
Non-transfusion-dependent thalassemia	Deferasirox 5 mg/kg (DT)	Male	29	27.6
		Female	26	24.5
	Deferasirox 10 mg/kg (DT)	Male	29	27.8
		Female	26	25.7
	Placebo	Male	31	30.3
		Female	25	24.1
Beta-thalassemia (n=1002)	Deferasirox	Male	486	1237.5
		Female	516	1397.6
Sickle cell disease (n=185)	Deferasirox	Male	74	176.5
		Female	111	229.7
Myelodysplastic syndrome (n=47)	Deferasirox	Male	26	44.7
		Female	21	48.7
Diamond-Blackfan anemia (n=30)	Deferasirox	Male	16	56.6
		Female	14	39.2
Other anemia (n=22)	Deferasirox	Male	9	27.7
		Female	13	25.8

Source: RMP version 4 Annex 7-PT-Table 1.1c; RMP version 7 Annex 7- Table 1.2-1.3.

Table 4-5 Clinical trial exposure by disease populations and race

Disease population	Drug and dose	Race	Number of patients	Patient-years
Non-transfusion-dependent thalassemia	Deferasirox 5 mg/kg (DT)	Caucasian	31	27.9
		Asian	23	23.2
		Black	1	1.0
	Deferasirox 10 mg/kg (DT)	Caucasian	30	29.7
		Asian	24	22.8

Disease population	Drug and dose	Race	Number of patients	Patient-years
		Black	1	1.0
		Caucasian	33	32.2
	Placebo	Asian	22	21.2
		Other	1	1.1
		Caucasian	724	2152.2
Beta-thalassemia (n=1002)	Deferasirox	Black	3	8.1
		Oriental	167	227.9
		Other	108	246.8
		Caucasian	11	23.2
Sickle cell disease (n=185)	Deferasirox	Black	167	371.3
		Other	7	11.6
		Caucasian	44	85.8
Myelodysplastic syndrome (n=47)	Deferasirox	Oriental	1	3.1
		Other	2	4.4
Diamond-Blackfan anemia (n=30)	Deferasirox	Caucasian	26	82.2
		Other	4	13.6
Other anemia (n=22)	Deferasirox	Caucasian	19	43.0
		Oriental	3	10.4

Source: RMP version 4 Annex 7-PT-Table 1.1d; RMP version 7 Annex 7- Table 1.2-1.4.

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Patients with abnormal renal function	Deferasirox is associated with renal disorders. Protocols and labels mandate renal function monitoring. Treatment with deferasirox may further worsen renal insufficiency.	No	Deferasirox is contraindicated in patients with estimated creatinine clearance (CrCl) < 60 mL/min, as per the EU SmPC. SmPC Section 4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients	Treatment with deferasirox cannot be administered in case of known hypersensitivity reactions.	No	Deferasirox is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients. SmPC Section 4.3 Contraindications
Combination with other iron chelator therapies	As per the EU SmPC, deferasirox should not be combined with other iron chelator therapies.	No	SmPC Section 4.3 Contraindications
Alanine aminotransferase (ALT/SGPT) levels > 5 x upper limit of normal (ULN)	Liver function test elevations have been observed in patients treated with deferasirox. Post-marketing cases of hepatic failure, sometimes fatal, have been reported in patients treated with deferasirox.	No	The risk of hepatic disorders is appropriately communicated through current labeling: SmPC Section 4.4 Special warnings and precautions for use, Section 4.8 Undesirable Effects and Section 5.2. Physicians and patients are alerted (via label and additional risk minimization measures – educational materials) about this risk and of the importance of regular monitoring of liver tests during treatment with deferasirox. Patients with pre-existing liver disease are specifically more at risk of severe outcomes (as mentioned in Special warnings and precautions for use in SmPC). This patient population should not be considered as missing information in RMP since it is already known that hepatic function may further worsen under deferasirox treatment.
For deferasirox DT: Galactose intolerance, severe lactase	Deferasirox DT contains lactose.	No	This topic is appropriately communicated through current labeling for the DT.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
deficiency, or glucose-galactose malabsorption			SmPC Section 4.4 Special Warnings and precautions for use. Patients with this type of intolerance are expected to have hypersensitivity reactions which will not permit treatment with deferasirox. So, safety is as expected and should not be considered as missing information in the RMP.
History of clinically relevant ocular and/or auditory toxicity related to iron chelation therapy	Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported with deferasirox treatment	No	Hearing loss, Lens opacities, retinal changes and optic neuritis are important identified risks of deferasirox and they are appropriately communicated through current labeling: SmPC Section 4.4 Special Warnings and precautions for use and Section 4.8 Undesirable Effects.
Pregnant or nursing (lactating) women	Standard exclusion criteria in clinical trials	No	There are no safety concerns observed during continued monitoring, and the current label recommendations are appropriately alerting physicians and patients, and it is not expected that any current or feasible future pharmacovigilance (PhV) activities could further characterize the safety profile of the product with respect to safety in pregnancy. For these reasons and based on the Pharmacovigilance Risk Assessment Committee (PRAC) recommendation for the assessment of the Deferasirox EU RMP v 16.0, the MAH agrees that “Safety in pregnant women” is removed from the EU RMP.

Source: SmPC

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure.

During the clinical development program, 8063 patients have been exposed to deferasirox, comparator or placebo cumulatively, in the MAH-sponsored global and local interventional clinical trials as well as in compassionate use programs. Some patients were observed for safety follow-up for up to seven years in the clinical trials, and there were no new adverse drug reactions (ADRs) due to prolonged exposure of more than 12 months.

Deferasirox is not expected to cause ADRs due to its cumulative effect because deferasirox and its metabolites did not show unexpected accumulation in blood and tissues after multiple dosing.

Due to the well-known inherent limitations of clinical trial development programs in general ADRs with a long latency period are often not detected. However, Study CICL670E2422 is currently being conducted to study the long-term safety in pediatric NTDT patients aged 10 to 17 years-old and safety of new formulation (FCT). The sixth Interim Safety Report summarizes the data as of 30-Jun-2019. Forty patients received at least 1 dose of deferasirox as of the cutoff date. The median exposure was 17.0 months (range: 0.1 – 61.6 months). Of the 29 patients treated with DT, the median exposure was 17.5 months (range: 3.0 – 56.6 months), and of the 11 patients treated with FCT, the median exposure was 14.7 months (range 0.1 61.6 months). Four patients overall were treated with DT or FCT (2 patients each) from 48 to ≥ 60 months. The observed AEs in Study CICL670E2422, which is currently ongoing, are in line with the known, most commonly observed AEs in this patient population.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women and breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities: Patients with severe hepatic impairment Patients with moderate to severe renal impairment Patients with cardiovascular impairment (i.e., LVEF < 50%)	Not included in the clinical development program.
Population with relevant different ethnic origin	Refer to Table 4-5.
Other: Pediatric patients aged 2 to less than 6 years of age	In total, 601 pediatric patients aged between 2 and 16 years of age were enrolled in the 5 clinical studies included in the original registration dossier; 52 patients who received deferasirox in the 1-year core phases of these studies were aged 2 to less than 6 years old. In addition, the 5-year observational study, CICL670A2411 was completed, in which 267 children aged 2 to < 6 years (at enrollment) with transfusional hemosiderosis received deferasirox DT.
Pediatric NTDT patients aged 10 to 17 years of age	In total, 21 pediatric patients under 18 years of age were enrolled in clinical trials. Four of these patients were below 12 years of age. Additionally, 40 patients aged 10 to 17 years-old have been treated in the ongoing observational study, CICL670E2422.
Pediatric patients treated with new formulation (FCT or granules)	In completed study, CICL670F2429, 44 children aged 2 to <6 years with transfusional hemosiderosis received crushed deferasirox FCT. There were 21 pediatric patients aged between 10 and 17 years treated in Study CICL670F2201 (10 patients in the DT arm and 11 in the FCT arm). In the ongoing Study CICL670F2202 (core phase analysis completed), as of 18Jan2021, 221 subjects

Type of special population	Exposure
	aged ≥ 2 and < 18 years have been treated, 111 subjects treated with deferasirox DT and 110 with deferasirox granules. Of these 221 subjects, 186 subjects (87 subjects with deferasirox DT and 99 subjects with granules) completed the core phase treatment of the study.

Source: RMP version 20.1-Table 5-2

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

An estimate of patient exposure is calculated based on worldwide sales volume in kilogram (kg) of active substance sold during the reporting interval and the Defined Daily Dose (DDD). The sales volume of deferasirox during the reporting interval was approximately 15994 kg (active ingredient, considering all marketed formulations). The DDD for deferasirox DT is 1000 mg based on an estimated average daily dose of 20 mg/kg and an estimated patient weight of 50 kg. The DDD for deferasirox FCT and granules formulations is 700 mg based on an estimated average daily dose of 14 mg/kg and an estimated patient weight of 50 kg. Many patients receiving deferasirox have a low body weight because they are either children or adults with short stature due to the combined effects of chronic anemia and chronic iron overload.

The estimated exposure was approximately 53990 patient-treatment years (PTY) during the PSUR reporting interval from 01-Nov-2018 to 31-Oct-2019.

The cumulative patient exposure since the International birth date (02-Nov-2005) of the product is estimated to be approximately 515538 PTY.

6.1.2 Part II Module SV.1.2. Exposure

Since the International Birth Date (02-Nov-2005) to 31-Oct-2019, the total cumulative exposure to marketed deferasirox (all marketed formulations) was estimated to be approximately 515538 PTY. Table 6-1 provides an overview by region.

Table 6-1 Cumulative exposure from marketing experience

	EEA (including EU)	CCI	CCI	CCI	ROW
Total exposure in PTY	156574.2	CCI	CCI	CCI	221472.3

EU: European Union; EEA: European Economic Area; LATAM: Latin America; PTY: patient years; ROW: rest of world; USA: United States of America.

Cumulative data obtained from 02-Nov-2005 through 31-Oct-2019.

Source: PSUR (reporting period: 01-Nov-2018 to 31-Oct-2019) Worldwide sales volume, ROW: Rest of the World.

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

There is no evidence that deferasirox has the potential for inducing misuse for illegal purposes.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

8.1.1 Part II Module SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable as the RMP was already approved.

8.1.2 Part II Module SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable as the RMP was already approved.

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

There is no change to the important identified risk, or important potential risk or missing information compared with version 21.2 of the RMP.

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

Safety data in the following risk tables originates as follows:

- For non-transfusion dependent thalassemia, safety data was from the pivotal study for the NTDT indication, Study CICL670A2209 (THALASSA). The data cut-off date for database lock was 27-Jul-2011.
- For transfusional iron overload, safety data was from the pooled data of the 5 studies used for the registration of deferasirox, namely Study CICL670A0105, Study CICL670A0106, Study CICL670A0107, Study CICL670A0108, Study CICL670A0109 (core and extension) as well as the Study CICL670A2402 core study data. Cut-off date applied to the data for this analysis was 28-Sep-2007 for the extension studies, whereas all available data at time of core database lock were used for data from Study CICL670A2402.

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

8.3.1.1 Important Identified Risk: Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome])

Table 8-1 Clinical trial data of renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome])

Renal disorders	Details	
Frequency with 95% CI	**% in all patients (95% CI)**	
	Increased serum creatinine	
	All AEs	10.2 (8.6, 12.0)
	Severe AEs	0.2 (0.0, 0.6)
	Related AEs	8.9 (7.4, 10.6)
	Serious AEs	0.1 (0.0, 0.4)
	AEs leading to disc.	0.3 (0.1, 0.8)
	Acute renal failure	
	All AEs	4.7 (3.6, 6.0)
	Severe AEs	0.4 (0.1, 0.9)
	Related AEs	2.8 (2.0, 3.9)
	Serious AEs	0.4 (0.1, 0.9)
	AEs leading to disc.	0.3 (0.1, 0.8)
	Renal failure	
	All AEs	0.6 (0.3, 1.2)
	Severe AEs	0.2 (0.0, 0.7)
	Related AEs	0.1 (0.0, 0.4)
	Serious AEs	0.2 (0.0, 0.6)
	AEs leading to disc.	0.2 (0.0, 0.7)
	Renal tubular disorders	
	All AEs	0.6 (0.3, 1.2)
	Severe AEs	0.2 (0.0, 0.7)
	Related AEs	0.2 (0.0, 0.7)
	Serious AEs	0.2 (0.0, 0.7)
	AEs leading to disc.	0.1 (0.0, 0.4)

Seriousness/ Outcomes

	Non-transfusion-dependent thalassemia		
Increased serum creatinine	**Deferasirox DT 5 mg / kg N=55**	**Deferasirox DT 10 mg / kg N=55**	**Placebo N=56**
	%	**%**	**%**
All Adverse Events (AEs)	0	3.6	0
Severe AEs	0	0	0
Related AEs	0	1.8	0
Serious AEs (SAEs)	0	0	0
AEs leading to disc.	0	0	0

Acute renal failure (Standardized MedDRA Query [SMQ])

Renal disorders	Details			
	All AEs	3.6	0	0
	Severe AEs	0	0	0
	Related AEs	1.8	0	0
	Serious AEs	0	0	0
	AEs leading to disc.	1.8	0	0
	Renal tubular disorders			
	All AEs	0	0	0
	Severe AEs	0	0	0
	Related AEs	0	0	0
	Serious AEs	0	0	0
	AEs leading to disc.	0	0	0

	Deferasirox	**Placebo**
Lab abnormalities (all age groups combined) (n)	**110**	**56**
Serum creatinine > 2 x upper limit of normal (ULN)	0	0

Other Indications

Increased serum creatinine	**Beta-thal N=1002**	**SCD N=185**	**MDS N=47**	**DBA N=30**	**Other anemia N=22**	**All Patients N=1286**
	%	%	%	%	%	%
All AEs	10.1	6.5	12.8	13.3	36.4	10.2
Severe AEs	0.2	0	0	0	0	0.2
Related AEs	9.2	4.9	8.5	10.0	31.8	8.9
Serious AEs	0.1	0	0	0	0	0.1
AEs leading to disc.	0.2	0	2.1	0	4.5	0.3
Age 2 - < 6 years (n)	**83**	**5**	**0**	**7**	**2**	**97**
All AEs	1.2	0	0	28.6	0	3.1
Related AEs	1.2	0	0	14.3	0	2.1
Age 6 - < 12 years (n)	**221**	**43**	**0**	**5**	**1**	**270**
All AEs	4.1	4.7	0	0	0	4.1
Related AEs	3.6	4.7	0	0	0	3.7
Age 12 - < 16 years (n)	**187**	**42**	**0**	**3**	**2**	**234**
All AEs	7.5	2.4	0	0	0	6.4
Related AEs	6.4	0	0	0	0	5.1
Age 16 - < 65 years (n)	**511**	**95**	**19**	**15**	**14**	**654**
All AEs	15.1	9.5	10.5	13.3	50.0	14.8
Severe AEs	0.4	0	0	0	0	0.3
Related AEs	13.9	7.4	5.3	13.3	42.9	13.3
Serious AEs	0.2	0	0	0	0	0.2
AEs leading to disc.	0.4	0	0	0	7.1	0.5
Age ≥ 65 years (n)	**0**	**0**	**28**	**0**	**3**	**31**
All AEs	0	0	14.3	0	33.3	16.1
Related AEs	0	0	10.7	0	33.3	12.9
AEs leading to disc.	0	0	3.6	0	0	3.2

Renal disorders	Details						
	Lab abnormalities (all age groups combined)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
	Post-baseline serum creatinine > 2 × ULN	2 (0.2)	2 (1.1)	0	0	0	4 (0.3)
	Acute renal failure						
	All AEs	4.5	4.9	6.4	3.3	9.1	4.7
	Severe AEs	0.3	0.5	0	3.3	0	0.4
	Related AEs	3.0	0	6.4	3.3	9.1	2.8
	Serious AEs	0.2	1.6	0	0	0	0.4
	AEs leading to disc.	0.3	0.5	0	0	0	0.3
	Renal Failure						
	All AEs	0.2	0	8.5	0	9.1	0.6
	Severe AEs	0.2	0	2.1	0	0	0.2
	Related AEs	0	0	2.1	0	0	0.1
	Serious AEs	0.2	0	0	0	0	0.2
	AEs leading to disc.	0.1	0	2.1	0	4.5	0.2
	Age 2 - < 6 years (n)	**83**	**5**	**0**	**7**	**2**	**97**
	Acute renal failure						
	All AEs	2.4	0	0	0	0	2.1
	Related AEs	1.2	0	0	0	0	1.0
	Renal failure						
	All AEs	0	0	0	0	0	0
	Age 6 - < 12 years (n)	**221**	**43**	**0**	**5**	**1**	**270**
	Acute renal failure						
	All AEs	5.0	4.7	0	20.0	0	5.2
	Severe AEs	0.9	0	0	20.0	0	1.1
	Related AEs	3.2	0	0	20.0	0	3.0
	Serious AEs	0.5	0	0	0	0	0.4
	AEs leading to disc.	0.9	0	0	0	0	0.7
	Renal failure						
	All AEs	0	0	0	0	0	0
	Age 12 - < 16 years (n)	**187**	**42**	**0**	**3**	**2**	**234**
	Acute renal failure						
	All AEs	6.4	2.4	0	0	0	5.6
	Severe AEs	0.5	0	0	0	0	0.4
	Related AEs	4.3	0	0	0	0	3.4
	Serious AEs	0.5	0	0	0	0	0.4
	AEs leading to disc.	0.5	0	0	0	0	0.4
	Renal failure						
	All AEs	0	0	0	0	0	0
	Age 16 - < 65 years (n)	**511**	**95**	**19**	**15**	**14**	**654**
	Acute renal failure						
	All AEs	3.9	6.3	0	0	14.3	4.3
	Severe AEs	0	1.1	0	0	0	0.2
	Related AEs	2.7	0	0	0	14.3	2.4
	Serious AEs	0	3.2	0	0	0	0.5

Renal disorders	Details						
	AEs leading to disc.	0	1.1	0	0	0	0.2
	Renal failure						
	All AEs	0.4	0	0	0	0	0.3
	Severe AEs	0.4	0	0	0	0	0.3
	Serious AEs	0.4	0	0	0	0	0.3
	AEs leading to disc.	0.2	0	0	0	0	0.2
	Age ≥ 65 years (n)	**0**	**0**	**28**	**0**	**3**	**31**
	Acute renal failure						
	All AEs	0	0	10.7	0	0	9.7
	Related AEs	0	0	10.7	0	0	9.7
	Renal failure						
	All AEs	0	0	14.3	0	66.7	19.4
	Severe AEs	0	0	3.6	0	0	3.2
	Related AEs	0	0	3.6	0	0	3.2
	AEs leading to disc.	0	0	3.6	0	33.3	6.5
	Renal tubular disorders						
	All AEs	0.6	1.1	0	0	0	0.6
	Severe AEs	0.3	0	0	0	0	0.2
	Related AEs	0.3	0	0	0	0	0.2
	Serious AEs	0.2	0.5	0	0	0	0.2
	AEs leading to disc.	0.1	0	0	0	0	0.1
	Age 2 - < 6 years (n)	**83**	**5**	**0**	**7**	**2**	**97**
	All AEs	0	0	0	0	0	0
	Age 6 - < 12 years (n)	**221**	**43**	**0**	**5**	**1**	**270**
	All AEs	0.5	0	0	0	0	0.4
	Severe AEs	0.5	0	0	0	0	0.4
	Serious AEs	0.5	0	0	0	0	0.4
	Age 12 - < 16 years (n)	**187**	**42**	**0**	**3**	**2**	**234**
	All AEs	0.5	0	0	0	0	0.4
	Age 16 - < 65 years (n)	**511**	**95**	**19**	**15**	**14**	**654**
	All AEs	0.8	2.1	0	0	0	0.9
	Severe AEs	0.4	0	0	0	0	0.3
	Related AEs	0.6	0	0	0	0	0.5
	Serious AEs	0.2	1.1	0	0	0	0.3
	AEs leading to disc.	0.2	0	0	0	0	0.2
	Age ≥ 65 years (n)	**0**	**0**	**28**	**0**	**3**	**31**
	All AEs	0	0	0	0	0	0

Source: RMP version 4 Annex 7-PT-Table 2.1a, PT-Table 2.1b, PT-Table 3.1a, PT-Table 3.1b, RMP version 7 Annex 7-Table 1.5-1.1, RMP version 7 Annex 7-Table 1.5-10.1, RMP version 4 Annex 7-PT-Table 2.7a, PT-Table 2.7b, PT-Table 3.7a, PT-Table 3.7b, RMP version 7 Annex 7-Table 1.5-7.1, RMP version 4 Annex 7-PT-Table 2.2a, PT-Table 2.2b, PT-Table 3.2a, PT-Table 3.2b, RMP version 7 Annex 7-Table 1.5-2.1.

Table 8-2 Important Identified Risk Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome]): Other details

Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome])	**Details**
Potential mechanisms	In Study CICL670A2123 deferasirox was associated with a mild reversible hemodynamic effect on renal function in patients receiving short and long-term treatment. The potential mechanism for ARF and renal tubular disorders is unknown.
Evidence source(s) and strength of evidence	In thalassemia patients 0.5% of patients are reported to develop renal tubular dysfunction and 3.1% of patients progressed to dialysis therapy and 8% had a reduced CrCl (Di Iorio et al 2002). Renal tubular abnormalities, including increased urinary excretion of proteins and of tubular enzymes, have been reported in 30% of 250 patients with beta-thalassemia (Aldulak et al 2000; Koliakos et al 2003). Progressive renal insufficiency, generally heralded by the appearance of increasing proteinuria, hypertension and hematuria occurs in 5-18% of patients with SCD and can require hemodialysis or renal transplantation and contributes to 18% of deaths in patients older than 40 years. Acute renal failure has been described as part of a multi-organ failure syndrome that accompanies pain crises in SCD patients and is present in 10% of patients hospitalized with SCD (Scheinman 2003). Renal failure contributes to 18% of deaths in SCD patients older than 40 years (Platt et al 1994). In SCD, 26% of 381 patients were reported to have proteinuria, 13% at or close to the nephritic range. Naqvi et al (2011) reported that 2.3% of MDS patients have renal disorders. Myelodysplastic syndrome patients are generally elderly and have serum creatinine levels that are close to or slightly higher ULN due to the normal aging process.
Characterization of the risk:	**Increased serum creatinine** Increased serum creatinine was reported as an AE in 10.2% of patients overall. The percentage of patients with AEs of increased creatinine increased with age (from 3.1% in children aged 2-< 6 years old to 16.1% in adults aged ≥ 65 years old). The magnitude of the creatinine increases was generally < 50% in comparison to the baseline values. The creatinine levels generally remained within the normal range. Creatinine values > ULN were infrequent and were seen most frequently in elderly patients where baseline creatinine levels were often already close to the ULN. However, the values were generally < 1.5 x ULN. The magnitude of the creatinine elevations to > ULN in comparison to baseline were similar to those in patients in whom the increases remained within the normal range. Very few AEs relating to creatinine increases were severe, were judged to be serious or led to study drug discontinuation. In most patients in whom creatinine increases were reported as an AE, dose reductions of 25% to 33% were performed which resulted in a complete or partial return to baseline levels in about 40% of patients. Creatinine levels remained stable in the remaining patients, albeit at an increased level compared to baseline. In patients in whom treatment with deferasirox was temporarily interrupted, serum creatinine values returned to baseline, generally within a few weeks. In patients receiving deferasirox DT doses > 30 mg/kg, an increased incidence of this AE was not observed. In Study CICL670A2123, deferasirox was associated with a mild reversible hemodynamic effect on renal function in patients receiving short and long term treatment. Renal parameters remained stable between Week 52 and Week 104 indicating no further decline in the renal function over time. The association between the renal parameters could not be discerned when absolute changes from baseline in serum creatinine and CrCl were plotted against glomerular filtration rate, renal plasma flow, and filtration fraction (FF). The findings observed from this study were consistent

Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome])	Details
	with the five year renal data from the pivotal registration study, Study CICL670A0107, indicating no progressive worsening of the renal function over time. **Acute renal failure** Although the overall frequency of patients with at least one of the AE terms included in the standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs) 'Acute renal failure' was 4.7%, ARF was reported as such in only 3 patients, though none of these cases was assessed as related to deferasirox by the Investigator. Proteinuria was the most frequently reported AE and, as discussed under the identified risk 'Renal tubular disorders', there is heavy confounding for this parameter due to a high background incidence of tubular abnormalities in these patients. There was no age-relationship and a low discontinuation rate (primarily due to proteinuria) due to these AEs. This identified risk has been added to the RMP based on post-marketing reports where ARF has been reported, mainly in critically ill patients with multi-organ failure related to complications of the underlying disease. In an additional group of patients, ARF was reported based on quite minor increases in serum creatinine which occurred over the course of several weeks. Although many of the patients with ARF had alternative explanations for the reported findings, it is impossible to exclude a contributory role of deferasirox for all cases. In addition, the fact that there was a positive de-challenge in most patients is suggestive of a contributory role of deferasirox to these events. In patients receiving deferasirox DT doses > 30 mg/kg, an increased incidence of this AE was not observed. **Renal tubular disorders** A nephropathy consisting of renal tubular degeneration, cytoplasmic vacuolization of cortical tubular epithelial cells and tubular necrosis was observed in non-clinical studies with deferasirox in several species. Adverse events related to renal tubular disorders were reported in only a handful of patients in the studies included in these analyses. The abnormalities resolved rapidly (generally within a few days) when deferasirox was interrupted. A single patient discontinued study drug due to the development of a tubulopathy. The numbers of patients with tubular abnormalities are too low to draw any conclusions with respect to a relationship to age. It appears that patients with beta-thalassemia have a high background incidence of tubulopathy. Reports in the literature involving approximately 250 patients in Turkey, Greece and Thailand have documented renal tubular abnormalities, including the increased urinary excretion of proteins and of tubular enzymes, in approximately one third of patients with beta-thalassemia (Aldulak et al 2000, Koliakos et al 2003, Sumboonnanonda et al 1998). The changes were attributed by the respective authors to oxidative damage caused by iron deposits in the kidney. In patients receiving deferasirox DT doses > 30 mg/kg, an increased incidence of this AE was not observed. In Study CICL670A2426, a Prescription Event Monitoring (PEM) study, increased serum creatinine occurred at a lower frequency (n=2, 1.6% of cohort). One event occurred in an adult patient and was assessed as probably related to deferasirox in this study; the serum creatinine at time of event was reported to be above the ULN (value prior to starting was within the normal range). In Study CICL670AFR01T, in all age groups, the mean serum creatinine at baseline in the 5-year follow-up population was 62.2 (±23.3) µmol/l. This value was stable (relative change from baseline of between -33% and +33%) during visits at 2, 3.5 and 5 years. During the last treatment visit, 77% of patients showed a relative change of between -33% and +33% compared to baseline. Only 24 patients had an increase > 33% in their last serum creatinine value while on treatment.

Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome])	**Details**
	In Study CICL670A2301, fourteen (12%) patients had at least one serum creatinine value > 33% above Baseline and the age adjusted ULN in at least two consecutive measurements at least seven days apart. Increased serum creatinine led to drug adjustment or interruption in five (4.3%) patients, and permanent discontinuation of study treatment in four patients. It is also known that factors like underlying disease, certain concomitant medications (such as antibiotics), and underlying medical conditions (such as renal failure) may result in compromised renal function, contributing to higher serum creatinine levels. Eleven (9.4%) patients (all ≥ 18 years) had confirmed CrCl < 60 mL/min on 2 consecutive measurements at least 7 days apart. There were four patients in the overall population who had one value of serum CrCl < 60 mL/min during the study. None of the pediatric patient had a decrease of CrCl to < 60 mL/min. After an initial decrease, CrCl remained stable throughout the study. This is consistent with data from previous studies that have shown an early initial drop in CrCl, followed by stabilization. In Study CICL670A2301, notably, two patients who had at least one serum creatinine with a > 33% change from Baseline and > ULN at 2 consecutives visits at least 7 days apart had renal failure: one patient had a history of chronic renal failure which was an active condition during the study, and the other had one AE of renal failure for a duration of 59 days, which was mild in severity and not suspected to be study drug related.
Risk factors and risk groups	Analyses showed that patients receiving high doses of deferasirox DT (20 or 30 mg/kg) and a low iron intake from infrequent blood transfusions were more likely to develop creatinine increases. Elderly patients were more likely to develop creatinine values > ULN though, as explained above, the magnitude of increase in comparison to baseline was no higher in these patients. Patients with pre-existing renal conditions or patients who are receiving medicinal products that depress renal function may be at higher risk of complications including ARF. In clinical studies a relationship between iron status (liver iron and ferritin concentrations), the rate of iron removal and renal effects has been observed. As with other iron chelator treatment, the risk of toxicity may be increased when inappropriately high doses of deferasirox are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated.
Preventability	It is recommended that serum creatinine be assessed in duplicate before initiating therapy, and monitored monthly thereafter. In patients with pre-existing renal conditions or patients who are receiving medicinal products that depress renal function, weekly monitoring of serum creatinine is recommended in the first month after initiation or modification of therapy, and then monthly thereafter. The SmPC advises dose reduction in patients with CrCl levels <90 mL/min at two consecutive visits. Deferasirox is contraindicated in patients with renal impairment (estimated CrCl < 60 mL/min). The SmPC recommends monthly monitoring for proteinuria. Additional markers of renal tubular function (e.g. glycosuria in non-diabetics and low levels of serum potassium, phosphate, magnesium or urate, phosphaturia, aminoaciduria) may also be monitored. Dose reduction or interruption may be considered if there are abnormalities in levels of tubular markers and/or if clinically indicated. If serum ferritin falls consistently below 500 µg/L, an interruption of treatment should be considered. For NTDT, the SmPC states that chelation therapy should only be initiated when there is evidence of iron overload (LIC ≥ 5 mg Fe/g dry weight or serum ferritin consistently > 800 µg/L). In patients with no LIC assessment, caution should be taken

Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome])	**Details**
	during chelation therapy to minimize the risk of over-chelation. Once a satisfactory body iron level has been achieved (LIC < 3 mg Fe/g dry weight or serum ferritin < 300 µg/L), treatment should be interrupted.
Impact on the benefit-risk balance of the product	Assessment of renal function and urine protein before and at regular intervals during treatment. The impact of increased serum creatinine, in the absence of renal failure, on the quality of life is considered to be low. The impact of ARF and renal tubular disorders, on the quality of life is considered to be significant. It is preventable by monitoring renal function and urine protein and adjusting the dose or holding the dose as indicated in the SmPC.
Public health impact	With regular monitoring and prompt dose adjustment/hold where indicated the public health is considered to be low.
Source: RMP version 20.1-Table 8-2	

8.3.1.2 Important Identified Risk: Increased liver transaminases / Hepatic failure

Table 8-3 Clinical trial data of increased liver transaminases / Hepatic failure

Increased liver transaminases	**Details**			
Frequency with 95% CI		% in all patients (95% CI)		
	All AEs	7.5 (6.2, 9.1)		
	Severe AEs	1.6 (1.0, 2.4)		
	Related AEs	4.6 (3.5, 5.9)		
	Serious AEs	0.9 (0.4, 1.5)		
	AEs leading to disc.	1.2 (0.7, 1.9)		
Seriousness/ Outcomes		Non-transfusion-dependent thalassemia		
		Deferasirox DT 5 mg / kg	Deferasirox DT 10 mg / kg	Placebo
	Increased liver transaminases	N=55 %	N=55 %	N=56 %
	All AEs	1.8	1.8	0
	Severe AEs	0	0	0
	Related AEs	0	1.8	0
	Serious AEs	0	0	0
	AEs leading to disc.	0	0	0
	Lab abnormalities (all age groups combined)	Deferasirox N=110 n (%)	Placebo N=56 n (%)	
Increased liver transaminases	**Details**			
	ALT > 10 x ULN	0	0	
	AST > 10 x ULN	1 (0.9)	0	

		Other Indications					
	Increased liver transaminases	Beta-thal %	SCD %	MDS %	DBA %	Other anemia %	All Patients %
	All AEs	7.9	5.9	0	13.3	13.6	7.5
	Severe AEs	1.1	2.7	0	10.0	4.5	1.6
	Related AEs	4.6	3.8	0	10.0	13.6	4.6
	Serious AEs	0.8	0.5	0	3.3	4.5	0.9
	AEs leading to disc.	1.3	1.1	0	0	0	1.2
	Age 2 - < 6 years (n)	83	5	0	7	2	97
	All AEs	13.3	20.0	0	14.3	0	13.4
	Severe AEs	2.4	20.0	0	14.3	0	4.1
	Related AEs	13.3	0	0	14.3	0	12.4
	Serious AEs	2.4	0	0	14.3	0	3.1
	AEs leading to disc.	3.6	0	0	0	0	3.1
	Age 6 - < 12 years (n)	221	43	0	5	1	270
	All AEs	11.8	7.0	0	40.0	0	11.5
	Severe AEs	0.9	2.3	0	40.0	0	1.9
	Related AEs	8.1	4.7	0	20.0	0	7.8
	Serious AEs	0.9	0	0	0	0	0.7
	AEs leading to disc.	1.4	0	0	0	0	1.1
	Age 12 - < 16 years (n)	187	42	0	3	2	234
	All AEs	7.0	11.9	0	33.3	50.0	8.5
	Severe AEs	1.1	4.8	0	0	0	1.7
	Related AEs	4.3	7.1	0	33.3	50.0	5.6
	Serious AEs	1.1	0	0	0	0	0.9
	AEs leading to disc.	1.1	2.4	0	0	0	1.3
	Age 16 - < 65 years (n)	511	95	0	15	14	654
	All AEs	5.7	2.1	0	0	14.3	5.0
	Severe AEs	1.0	1.1	0	0	7.1	1.1
	Related AEs	1.8	2.1	0	0	14.3	2.0
	Serious AEs	0.4	1.1	0	0	7.1	0.6
	AEs leading to disc.	1.0	1.1	0	0	0	0.9
	Age ≥ 65 years (n)	0	0	28	0	3	31
	All AEs	0	0	0	0	0	0
	Lab abnormalities	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Post-baseline AST > 10x ULN	12 (1.2)	4 (2.2)	0	2 (6.7)	0	18 (1.4)
	Post-baseline ALT > 10x ULN	59 (5.9)	6 (3.2)	0	8 (26.7)	1 (4.5)	74 (5.8)

Hepatic failure	**Details**	
Frequency with 95% CI		% in all patients (95% CI)
	All AEs	1.0 (0.5, 1.7)
	Severe AEs	0.4 (0.1, 0.9)

Hepatic failure	**Details**	
	Related AEs	0.2 (0.0, 0.6)
	Serious AEs	0.5 (0.2, 1.0)

	AEs leading to disc.	0.2 (0.0, 0.7)				
Seriousness/ Outcomes		Non-transfusion-dependent thalassemia				
		Deferasirox DT 5 mg / kg	Deferasirox DT 10 mg / kg	Placebo		
	Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions	N=55	N=55	N=56		
		%	%	%		
	All AEs	1.8	0	0		
	Severe AEs	1.8	0	0		
	Related AEs	1.8	0	0		
	Serious AEs	1.8	0	0		
	AEs leading to disc.	0	0	0		
		Other Indications				
		Beta-thal	SCD	MDS	DBA	Other anemia	All Patients
		N=1002	N=185	N=47	N=30	N=22	N=1286
		%	%	%	%	%	%
	All AEs	0.8	2.2	0	3.3	0	1.0
	Severe AEs	0.2	1.1	0	3.3	0	0.4
	Related AEs	0.2	0	0	0	0	0.2
	Serious AEs	0.2	1.6	0	3.3	0	0.5
	AEs leading to disc.	0.2	0.5	0	0	0	0.2
	Age 2 - < 6 years (n)	83	5	0	7	2	97
	All AEs	0	0	0	0	0	0
	Age 6 - < 12 years (n)	221	43	0	5	1	270
	All AEs	0	0	0	0	0	0
	Age 12 - < 16 years (n)	187	42	0	3	2	234
	All AEs	0.5	0	0	33.3	0	0.9
	Severe AEs	0	0	0	33.3	0	0.4
	Related AEs	0.5	0	0	0	0	0.4
	Serious AEs	0	0	0	33.3	0	0.4
	AEs leading to disc.	0.5	0	0	0	0	0.4
	Age 16 - < 65 years (n)	511	95	19	15	14	654
	All AEs	1.4	4.2	0	0	0	1.7
	Severe AEs	0.4	2.1	0	0	0	0.6
	Related AEs	0.2	0	0	0	0	0.2
	Serious AEs	0.4	3.2	0	0	0	0.8
	AEs leading to disc.	0.2	1.1	0	0	0	0.3
	Age ≥ 65 years (n)	0	0	28	0	3	31
	All AEs	0	0	0	0	0	0

Source: RMP version 4 Annex 7-PT-Table 2.3a, PT-Table 2.3b, PT-Table 3.3a, PT-Table 3.3b, RMP version 7 Annex 7-Table 1.5-3.1, RMP version 7 Annex 7-Table 1.5-10.1.

RMP version 4 Annex 7-PT-Table 2.8a, PT-Table 2.8b, PT-Table 3.8a, PT-Table 3.8b, RMP version 7 Annex 7-Table 1.5-8.1.

Table 8-4 Important Identified Risk Increased liver transaminases / Hepatic failure: Other details

Increased liver transaminases / Hepatic failure	Details
Potential mechanisms	Unknown
Evidence source(s) and strength of evidence	**Increased liver transaminases** Elevated liver transaminases have been correlated with increased LIC in patients with beta-thalassemia. Studies have shown that hepatomegaly is seen in 50% of patients with SCD, hepatitis in 11% of patients, and approximately one third of SCD patients will have a form of hepatic dysfunction (Edwards 2002). **Hepatic failure** In patients aged > 6 years with beta-thalassemia, 4-6% had evidence of liver failure or cirrhosis (Borgna-Pignatti et al 2004; Cunningham et al 2004). Sickle cell disease patients can develop sickle cell crises and sequestration events affecting the liver causing massive hepatic enlargement with hepatic failure occurring in up to 10% of patients. Cirrhosis has been reported in 16 to 29% of SCD patients (Edwards 2002).
Characterization of the risk:	**Increased liver transaminases** Clinical trial data show a consistent correlation between improvements in LIC/serum ferritin and improvements in ALT/aspartate aminotransferase (AST). Transaminase increases was reported as an AE in 7.5% of patients in the studies included in these analyses. There was a decreasing incidence of reports with increasing age (13.4% in children aged 2-< 6 years and 0% in adults aged ≥ 65 years). Transaminase increase was a relatively frequent reason for discontinuation of deferasirox but, the increases in transaminases in some of these patients may have been due to the administration of inappropriately low doses of deferasirox and reflects the associated increase in iron burden due to under-chelation. Increases in liver transaminase levels were reported as an AE with a suspected relationship to study drug in 2.3% of patients treated with deferasirox. Elevations of transaminases > 10 x ULN at ≥ 2 consecutive visits were infrequent (0.5%) though a single elevated value was seen in 5.8% of patients. Transaminase increases were not dose-dependent. Most of these patients had elevated levels prior to receiving deferasirox. The transaminase increases were not accompanied by increases in bilirubin. There were no reports of hepatic failure or hepatic encephalopathy in these studies. A rapid increase in transaminase levels that recurred on re-challenge with deferasirox was seen in one patient with beta-thalassemia in whom the dose of deferasirox DT was increased to 30 mg/kg despite a rapidly falling serum ferritin level. Liver biopsy was compatible with drug-induced liver damage. The patient did not develop hepatic failure and made a full recovery following discontinuation of study drug. A second patient had progressive increases in transaminases during several months on therapy and the liver biopsy findings were compatible with, but not diagnostic of, drug-related hepatotoxicity. The transaminase values remained elevated several years after discontinuation of deferasirox. In Study CICL670A2426, there was one report of ALT levels in the cohort (n=1, 0.8% of cohort), which occurred in an adult patient. There were no reports of ARF, glycosuria or low levels of serum potassium, phosphate, magnesium or urate, phosphaturia or aminoaciduria. There were also no reports of hepatic failure, hepatitis or gall stones. In Study CICL670AFR01T, the AST and ALT assays on inclusion in the study were higher than twice the upper limits of normal (> 80 IU/L) for 12% and 8% respectively of the 127 patients analyzed at follow-up at 5 years. The percentage of patients with assays greater than twice the upper limits of normal never exceeded 17% for AST and 10% for ALT during the 5-year follow-up. AST and ALT remained stable (maximum change of +/- 40 IU/L) for over 80% of the patients throughout the 5-year follow-up. In Study CICL670A2301, one of the primary endpoints was to evaluate the incidence and clinical management of ALT increases in actual practice setting (defined as a patient having ALT above 5 × ULN in at least two consecutive post-Baseline

Increased liver transaminases / Hepatic failure	**Details**
	measurements at least 7 days apart). The proportion of patients which met that condition was 1 (0.9%). One (0.9%) patient had a post-Baseline increase in ALT above 5 x ULN that was confirmed on two consecutive measurements at least 7 days apart, and no patients had post-Baseline increases in ALT above 10 x ULN that were confirmed on two consecutive measurements at least 7 days apart. Two (1.7%) patients (both < 18 years old) had drug adjusted or temporarily interrupted due to elevated ALT and no patients discontinued due to increases in ALT. **Hepatic failure** In toxicology studies with deferasirox, no hepatocellular findings were reported in any species. In the studies included in this analysis, the overall frequency of patients with at least one of the AE terms included in the SMQ 'Hepatic failure, cirrhosis and fibrosis' was 1.0%. Hepatic failure was reported as such in 2 patients. None of these cases was assessed as related to deferasirox by the Investigator. This potential risk has been added to the RMP based mainly on post-marketing reports. Many of the patients with liver failure had severe underlying liver disease, most probably related to severe iron overload, when therapy with deferasirox was initiated, with severe cirrhosis and hepatitis C as the common abnormalities. Most of the patients were critically ill with major life-threatening complications (e.g. sepsis, multi-organ failure) related to their underlying disease. Of note, hepatic failure related to severe liver iron overload is among the leading causes of death in patients with transfusion dependent hemosiderosis. It is not possible to determine whether the subsequent deterioration in liver function in these patients was coincidental, was related to a concomitant medication, or whether deferasirox in some way contributed to liver decompensation. In patients receiving deferasirox DT doses > 30 mg/kg, an increased incidence of this AE was not observed. Of note, clinical trial data show a consistent correlation between improvements in LIC/serum ferritin and improvements in ALT/AST.
Risk factors and risk groups	**Increased liver transaminases** None identified. **Hepatic failure** Patients with pre-existing hepatic impairment.
Preventability	**Increased liver transaminases** The SmPC advises cautious treatment in patients with hepatic impairment. It recommends monitoring of serum transaminases at baseline, after 2 weeks of therapy and monthly thereafter. **Hepatic failure** Apart from the above mentioned step of prevention in the SmPC, interruption of treatment in case of persistent and progressive increase in serum transaminase levels that cannot be attributed to other causes is recommended. Once the cause of the liver function test abnormalities has been clarified or after return to normal levels, cautious re-initiation of treatment at a lower dose followed by gradual dose escalation may be considered.
Impact on the benefit-risk balance of the product	**Increased liver transaminases** Assessment of liver function before and at regular intervals during treatment. The impact of increased liver transaminases on the quality of life, in the absence of hepatic failure, is considered to be low. **Hepatic failure** Assessment of liver function before and at regular intervals during treatment.

Increased liver transaminases / Hepatic failure	**Details**
	The impact of hepatic failure, on the quality of life is considered to be significant but preventable by monitoring clinical signs and symptoms and liver function as indicated in the SmPC.
Public health impact	**Increased liver transaminases and hepatic failure** With regular monitoring and prompt dose adjustment/hold where indicated the public health is considered to be low.
Source: RMP version 20.1-Table 8-4	

8.3.1.3 Important Identified Risk: Gastrointestinal hemorrhage and ulcers; esophagitis

Table 8-5 Clinical trial data of Gastrointestinal hemorrhage and ulcers; esophagitis

GI hemorrhage and ulcers; esophagitis	**Details**	
Frequency with 95% CI	**Gastrointestinal hemorrhage**	**% in all patients (95% CI)**
	All AEs	1.8 (1.1, 2.7)
	Severe AEs	0.2 (0.0, 0.7)
	Related AEs	0.2 (0.0, 0.6)
	Serious AEs	0.5 (0.2, 1.0)
	AEs leading to disc.	0.1 (0.0, 0.4)
	Gastrointestinal ulceration	
	All AEs	2.0 (1.3, 2.9)
	Severe AEs	0.2 (0.0, 0.7)
	Related AEs	0.2 (0.0, 0.6)
	Serious AEs	0.2 (0.0, 0.6)
	Esophagitis	
	All AEs	0.5 (0.2, 1.0)
	Related AEs	0.2 (0.0, 0.6)
	Serious AEs	0.1 (0.0, 0.4)

Seriousness/ Outcomes		**Non-transfusion-dependent thalassemia**		
	Gastrointestinal hemorrhage and ulcers	**Deferasirox DT 5 mg / kg N=55**	**Deferasirox DT 10 mg / kg N=55**	**Placebo N=56**
		%	**%**	**%**
	All AEs	0	1.8	0
	Severe AEs	0	0	0
	Related AEs	0	1.8	0
	Serious AEs	0	0	0
	AEs leading to disc.	0	0	0

		Other indications					
		beta-thal	**SCD**	**MDS**	**DBA**	**Other anemia**	**All Patients**

GI hemorrhage and ulcers; esophagitis	Details						
	GI hemorrhage and ulcers; esophagitis	**N=1002 %**	**N=185 %**	**N=47 %**	**N=30 %**	**N=22 %**	**N=1286 %**
	Gastrointestinal hemorrhage						
	All AEs	1.3	1.1	8.5	10.0	4.5	1.8
	Severe AEs	0	0.5	2.1	3.3	0	0.2
	Related AEs	0.2	0	0	0	0	0.2
	Serious AEs	0.1	1.1	4.3	3.3	0	0.5
	AEs leading to disc.	0	0	0	3.3	0	0.1
	Gastrointestinal ulceration						
	All AEs	2.2	1.6	0	3.3	0	2.0
	Severe AEs	0.3	0	0	0	0	0.2
	Related AEs	0.2	0	0	0	0	0.2
	Serious AEs	0.2	0	0	0	0	0.2
	AEs leading to disc.	0	0	0	0	0	0
	Esophagitis						
	All AEs	0.6	0	0	0	0	0.5
	Severe AEs	0	0	0	0	0	0
	Related AEs	0.2	0	0	0	0	0.2
	Serious AEs	0.1	0	0	0	0	0.1
	AEs leading to disc.	0	0	0	0	0	0
	Age 2 - < 6 years (n)	**83**	**5**	**0**	**7**	**2**	**97**
	Gastrointestinal hemorrhage						
	All AEs	0	0	0	0	0	0
	Gastrointestinal ulceration						
	All AEs	0	0	0	14.3	0	1.0
	Esophagitis						
	All AEs	0	0	0	0	0	0
	Age 6 - < 12 years (n)	**221**	**43**	**0**	**5**	**1**	**270**
	Gastrointestinal hemorrhage						
	All AEs	0.5	0	0	0	0	0.4
	Gastrointestinal ulceration						
	All AEs	1.8	2.3	0	0	0	1.9
	Severe AEs	0.5	0	0	0	0	0.4
	Related AEs	0.9	0	0	0	0	0.7
	Serious AEs	0.5	0	0	0	0	0.4
	Esophagitis						
	All AEs	0.5	0	0	0	0	0.4
	Related AEs	0.5	0	0	0	0	0.4
	Age 12 - < 16 years (n)	**187**	**42**	**0**	**3**	**2**	**234**
	Gastrointestinal hemorrhage						
	All AEs	1.1	0	0	33.3	0	1.3
	Severe AEs	0	0	0	33.3	0	0.4
	Related AEs	0.5	0	0	0	0	0.4
	Serious AEs	0.5	0	0	33.3	0	0.9

GI hemorrhage and ulcers; esophagitis	Details						
	AEs leading to disc.	0	0	0	33.3	0	0.4
	Gastrointestinal ulceration						
	All AEs	1.1	2.4	0	0	0	1.3
	Esophagitis						
	All AEs	0	0	0	0	0	0
	Age 16 - < 65 years (n)	**511**	**95**	**19**	**15**	**14**	**654**
	Gastrointestinal hemorrhage						
	All AEs	2.0	2.1	10.5	13.3	7.1	2.6
	Severe AEs	0	1.1	0	0	0	0.2
	Related AEs	0.2	0	0	0	0	0.2
	Serious AEs	0	2.1	5.3	0	0	0.5
	Gastrointestinal ulceration						
	All AEs	3.1	1.1	0	0	0	2.6
	Severe AEs	0.4	0	0	0	0	0.3
	Serious AEs	0.2	0	0	0	0	0.2
	Esophagitis						
	All AEs	1.0	0	0	0	0	0.8
	Related AEs	0.2	0	0	0	0	0.2
	Serious AEs	0.2	0	0	0	0	0.2
	Age ≥ 65 years (n)	**0**	**0**	**28**	**0**	**3**	**31**
	Gastrointestinal hemorrhage						
	All AEs	0	0	7.1	0	0	6.5
	Severe AEs	0	0	3.6	0	0	3.2
	Related AEs	0	0	3.6	0	0	3.2
	Serious AEs	0	0	3.6	0	0	3.2
	Gastrointestinal ulceration						
	All AEs	0	0	0	0	0	0
	Esophagitis						
	All AEs	0	0	0	0	0	0

Source: RMP version 4 Annex 7-PT-Table 2.6a, PT-Table 2.6b, PT-Table 3.6a, PT-Table 3.6b, RMP version 7 Annex 7 - Table 1.5-6.1.

Table 8-6 Important Identified Risk Gastrointestinal hemorrhage and ulcers; esophagitis: Other details

Gastrointestinal hemorrhage and ulcers; esophagitis	Details
Potential mechanisms	Unknown
Evidence source(s) and strength of evidence	Gastrointestinal hemorrhage and ulcers (including GI perforation) and esophagitis have been observed in humans.
Characterization of the risk:	The overall incidence of GI hemorrhage, ulceration, perforation and esophagitis in the studies included was low. The numbers of events were too low to draw conclusions about a possible age-relationship. This identified risk is based mainly on a review of all cases (clinical trial and spontaneous reports) since marketing approval, as discussed

Gastrointestinal hemorrhage and ulcers; esophagitis	**Details**
	below. A review of the safety database up to 31-Oct-2007 identified a total of 35 patients with GI hemorrhage, gastric ulcer, duodenal ulcer, or combinations of these events. The likelihood that deferasirox at least contributed to some of the events is based on the following considerations: • Nausea, vomiting, and/or abdominal pain were reported in approximately 27% of patients treated in the 1-year registration studies. Although these symptoms settled spontaneously in most patients, this symptom complex is suggestive of upper GI irritation. • The presence of multiple ulcers was mentioned in 4 reports of patients with gastric ulcer. • Five reports involved pediatric patients (aged 7-16 years). A review of the literature identified no reports of GI hemorrhage and ulceration in children outside the setting of patients in intensive care units. • Upper GI ulceration was seen in pre-clinical studies in mice and rats. • Some of the patients were taking concomitant medications that are known to predispose to GI hemorrhage and ulceration (NSAIDs, corticosteroids, anticoagulants, or oral bisphosphonates) and some had severe thrombocytopenia. However, these confounding factors could have played an additive role, rather than being an alternative explanation for the GI AEs. The safety database also identified 11 reports of esophagitis.
Risk factors and risk groups	Patients who are taking deferasirox in combination with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids or oral bisphosphonates, and in patients receiving anticoagulants.
Preventability	Physicians and patients should remain alert for signs and symptoms of gastrointestinal ulceration and haemorrhage during deferasirox therapy. In case of gastrointestinal ulceration or haemorrhage, deferasirox should be discontinued and additional evaluation and treatment must be promptly initiated.
Impact on the benefit-risk balance of the product	The impact of gastrointestinal hemorrhage, gastric ulcer, GI perforation and esophagitis, on the quality of life is considered to be significant. It is preventable by monitoring for signs of symptoms of these conditions and initiating treatment promptly.
Public health impact	With regular monitoring and prompt dose adjustment/hold where indicated the public health is considered to be low.
Source: RMP version 20.1-Table 8-6	

8.3.1.4 Important Identified Risk: Hearing loss

Table 8-7 Clinical trial data of hearing loss

Hearing loss	**Details**	
Frequency with 95% CI	**Hearing losses**	**% in all patients (95% CI)**
	All AEs	3.4 (2.5, 4.6)
	Severe AEs	0.2 (0.0, 0.6)
	Related AEs	1.0 (0.5, 1.7)
	Serious AEs	0.1 (0.0, 0.4)
	AEs leading to disc.	0.2 (0.0, 0.6)
	Auditory function diagnostic procedures	
	All AEs	0.1 (0.0, 0.4)

Hearing loss	Details						
Seriousness/ Outcomes		Non-transfusion-dependent thalassemia					
		Deferasirox DT 5 mg / kg	Deferasirox DT 10 mg / kg	Placebo			
		N=55	N=55	N=56			
	Hearing Losses	%	%	%			
	All AEs	0	0	1.8			
	Severe AEs	0	0	0			
	Related AEs	0	0	1.8			
	Serious AEs	0	0	0			
	AEs leading to disc.	0	0	0			
		Other indication					
		beta-thal	SCD	MDS	DBA	Other anemia	All Patients
		N=1002	N=185	N=47	N=30	N=22	N=1286
		%	%	%	%	%	%
	Hearing losses						
	All AEs	2.9	4.3	6.4	6.7	9.1	3.4
	Severe AEs	0.2	0	0	0	0	0.2
	Related AEs	0.8	0.5	4.3	3.3	4.5	1.0
	Serious AEs	0	0	2.1	0	0	0.1
	AEs leading to disc.	0.2	0	0	0	0	0.2
	Auditory function diagnostic procedures						
	All AEs	0	0.5	0	0	0	0.1
	Hearing losses						
	Age 2 - < 6 years (n)	**83**	**5**	**0**	**7**	**2**	**97**
	All AEs	1.2	0	0	0	0	1.0
	Age 6 - < 12 years (n)	**221**	**43**	**0**	**5**	**1**	**270**
	All AEs	1.4	7.0	0	0	0	2.2
	Severe AEs	0.5	0	0	0	0	0.4
	Related AEs	0.5	0	0	0	0	0.4
	AEs leading to disc.	0.5	0	0	0	0	0.4
	Age 12 - < 16 years (n)	**187**	**42**	**0**	**3**	**2**	**234**
	All AEs	2.7	7.1	0	0	0	3.4
	Related AEs	0.5	0	0	0	0	0.4
	AEs leading to disc.	0.5	0	0	0	0	0.4
	Age 16 - < 65 years (n)	**511**	**95**	**19**	**15**	**14**	**654**
	All AEs	3.9	2.1	5.3	13.3	14.3	4.1
	Severe AEs	0.2	0	0	0	0	0.2
	Related AEs	1.2	1.1	0	6.7	7.1	1.4
	Age ≥ 65 years (n)	**0**	**0**	**28**	**0**	**3**	**31**
	All AEs	0	0	7.1	0	0	6.5
	Related AEs	0	0	7.1	0	0	6.5
	Serious AEs	0	0	3.6	0	0	3.2
	Auditory function diagnostic procedures						
	Age 12 - < 16 years						
	All AEs	0	2.4	0	0	0	0.4

Hearing loss	Details

Source: RMP version 4 Annex 7-PT-Table 2.4a, PT-Table 2.4b, PT-Table 3.4a, PT-Table 3.4b, RMP version 7 Annex 7-Table 1.5-4.1.

Table 8-8 Important Identified Risk Hearing loss: Other details

Hearing loss	Details
Potential mechanisms	From the experience with DFO, high frequency hearing impairment appears to be the main finding related to chelation therapy and this was confirmed in only a minority of patients with hearing loss during therapy both with deferasirox and DFO. A low serum ferritin has also been reported to predispose to deafness in patients treated with DFO. However, there was no clear relationship to serum ferritin levels in patients reporting deafness as an AE whether treated with deferasirox or DFO. The relationship of these audiometry findings to deferasirox is currently uncertain.
Evidence source(s) and strength of evidence	Hearing loss not attributed to chelation therapy has been reported in 28% of patients with beta-thalassemia (Chiodo et al 1997). A study of 75 adults with SCD demonstrated that the prevalence of hearing loss was 41% and was higher than that of the general population (Crawford et al 1991).
Characterization of the risk:	Adverse events relating to hearing loss were reported irrespective of relationship to deferasirox in 3.4% of patients but in only 1% of patients with a suspected relationship to study drug. The percentage of patients with AEs related to deafness increased with age (from 1.0% in children aged 2-< 6 years to 6.5% in adults aged ≥ 65 years). Only 2 patients discontinued deferasirox due to hearing loss. Of the 353 patients treated with deferoxamine in Study CICL670A0107 and Study CICL670A0109, 10 patients developed hearing loss which was assessed as drug-related in five cases. From the experience with DFO, high frequency hearing impairment appears to be the main finding related to chelation therapy and this was confirmed in only a minority of patients with hearing loss during therapy both with deferasirox and DFO. A low serum ferritin has also been reported to predispose to deafness in patients treated with DFO. However, there was no clear relationship to serum ferritin levels in patients reporting deafness as an AE whether treated with deferasirox or DFO. The relationship of these audiometry findings to deferasirox is currently uncertain. In patients receiving deferasirox DT doses >30 mg/kg, an increased incidence of this AE was not observed. In Study CICL670A2411, 15 (5.7%) patients in total experienced at least 1 AE belonging to the ear and labyrinth disorders SOC. The most commonly reported PT was conductive deafness (8 patients; 3.1%) followed by ear pain (3 patients, 1.1%). These were transitory in nature and usually associated with upper respiratory or middle ear infections. There were 21 (8.0%) patients with evidence of hearing impairment in at least one ear. None of these events were assessed as having a suspected relationship to drug by the Investigator. Auditory evaluations did not reveal the appearance of new clinically relevant abnormalities during deferasirox treatment in this study.
Risk factors and risk groups	As with other iron chelator treatment, the risk of toxicity may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated.
Preventability	Auditory testing is recommended before the start of deferasirox treatment and at regular intervals thereafter (every 12 months). If disturbances are noted, dose reduction or interruption may be considered.
Impact on the benefit-risk balance of the product	Auditory testing before and at regular intervals during treatment. The impact of hearing impairment on the quality of life is considered to be significant. It is preventable by monitoring for signs of symptoms of hearing loss and initiating treatment promptly.
Public health impact	Low
Source: RMP version 20.1-Table 8-8	

8.3.1.5 Important Identified Risk: Lens opacities, retinal changes and optic neuritis

Table 8-9 Clinical trial data of lens opacities, retinal changes and optic neuritis

Lens opacities, retinal changes and optic neuritis	Details			
Frequency with 95% CI	**Cataract conditions**	**% in all patients (95% CI)**		
	All AEs	1.2 (0.7, 2.0)		
	Severe AEs	0.2 (0.0, 0.6)		
	Related AEs	0.5 (0.2, 1.0)		
	Serious AEs	0.4 (0.1, 0.9)		
	AEs leading to disc.	0.2 (0.0, 0.7)		
	Retinal structural change, deposit and degeneration			
	All AEs	0.9 (0.4, 1.5)		
	Severe AEs	0.1 (0.0, 0.4)		
	Related AEs	0.1 (0.0, 0.4)		
		% in all patients (95% CI)		
	Retinal bleeding and vascular disorders			
	All AEs	0.1 (0.0, 0.4)		
	Retinopathies			
	All AEs	0.3 (0.1, 0.8)		
	AEs leading to disc.	0		
Seriousness/ Outcomes		**Non-transfusion-dependent thalassemia**		
		Deferasirox DT 5 mg / kg	**Deferasirox DT 10 mg / kg**	**Placebo**
		N=55	**N=55**	**N=56**
		%	**%**	**%**
	Cataract conditions			
	All AEs	1.8	0	0
	Severe AEs	1.8	0	0
	Related AEs	0	0	0
	Serious AEs	1.8	0	0
	AEs leading to disc.	0	0	0
	Optic neuritis			
	All AEs	0	0	1.8
	Severe AEs	0	0	1.8
	Related AEs	0	0	0
	Serious AEs	0	0	1.8
	AEs leading to disc.	0	0	1.8
		Other indications		

Lens opacities, retinal changes and optic neuritis	Details						
		beta-thal	SCD	MDS	DBA	Other anemia	All Patients
		N=1002	N=185	N=47	N=30	N=22	N=1286
		%	%	%	%	%	%
	Cataract conditions						
	All AEs	0.9	1.6	4.3	0	9.1	1.2
	Severe AEs	0.2	0	0	0	0	0.2
	Related AEs	0.3	1.6	0	0	0	0.5
	Serious AEs	0.3	0	2.1	0	4.5	0.4
	AEs leading to disc.	0.3	0	0	0	0	0.2
		beta-thal	SCD	MDS	DBA	Other anemia	All Patients
		N=1002	N=185	N=47	N=30	N=22	N=1286
		%	%	%	%	%	%
	Retinal structural change, deposit and degeneration						
	All AEs	1.0	0.5	0	0	0	0.9
	Severe AEs	0.1	0	0	0	0	0.1
	Related AEs	0.1	0	0	0	0	0.1
	Serious AEs	0	0	0	0	0	0
	AEs leading to disc.	0	0	0	0	0	0
	Retinal bleeding and vascular disorders						
	All AEs	0	0.5	0	0	0	0.1
	Retinopathies						
	All AEs	0.2	1.1	0	0	0	0.3
	Retinal, choroids and vitreous infections and inflammations						
	All AEs	0	0	0	0	0	0
	Optic neuritis						
	All AEs	0	0	0	0	0	0
	Age 2 - < 6 years (n)	83	5	0	7	2	97
	Cataract conditions						
	All AEs	1.2	0	0	0	0	1.0
	Severe AEs	1.2	0	0	0	0	1.0
	Related AEs	1.2	0	0	0	0	1.0
	Serious AEs	1.2	0	0	0	0	1.0
	AEs leading to disc.	1.2	0	0	0	0	1.0
	Retinal structural change, deposit and degeneration						
	All AEs	0	0	0	0	0	0
	Retinal bleeding and vascular disorders						
	All AEs	0	0	0	0	0	0
	Retinopathies						
	All AEs	0	0	0	0	0	0
	Age 6 - < 12	**221**	**43**	**0**	**5**	**1**	**270**

Lens opacities, retinal changes and optic neuritis	Details						
	years (n)						
	Cataract conditions						
	All AEs	0	2.3	0	0	0	0.4
	Related AEs	0	2.3	0	0	0	0.4
	Retinal structural change, deposit and degeneration						
	All AEs	0.5	0	0	0	0	0.4
	Retinal bleeding and vascular disorders						
	All AEs	0	2.3	0	0	0	0.4
	Retinopathies						
	All AEs	0	2.3	0	0	0	0.4
	Age 12 - < 16 years (n)	**187**	**42**	**0**	**3**	**2**	**234**
	Cataract conditions						
	All AEs	0	0	0	0	0	0
	Retinal structural change, deposit and degeneration						
	All AEs	0.5	0	0	0	0	0.4
	Retinal bleeding and vascular disorders						
	All AEs	0	0	0	0	0	0
	Retinopathies						
	All AEs	0.5	0	0	0	0	0.4
	Age 16 - < 65 years (n)	**511**	**95**	**19**	**15**	**14**	**654**
	Cataract conditions						
	All AEs	1.6	2.1	5.3	0	7.1	1.8
	Severe AEs	0.2	0	0	0	0	0.2
	Related AEs	0.4	2.1	0	0	0	0.6
	Serious AEs	0.4	0	5.3	0	0	0.5
	AEs leading to disc.	0.4	0	0	0	0	0.3
	Retinal structural change, deposit and degeneration						
	All AEs	1.6	1.1	0	0	0	1.4
	Severe AEs	0.2	0	0	0	0	0.2
	Related AEs	0.2	0	0	0	0	0.2
	Retinal bleeding and vascular disorders						
	All AEs	0	0	0	0	0	0
	Retinopathies						
	All AEs	0.2	1.1	0	0	0	0.3
	Age ≥ 65 years (n)	**0**	**0**	**28**	**0**	**3**	**31**
	Cataract conditions						
	All AEs	0	0	3.6	0	33.3	6.5
	Serious AEs	0	0	0	0	33.3	3.2
	Retinal structural change, deposit and degeneration						

Lens opacities, retinal changes and optic neuritis	Details						
	All AEs	0	0	0	0	0	0
	Retinal bleeding and vascular disorders						
	All AEs	0	0	0	0	0	0
	Retinopathies						
	All AEs	0	0	0	0	0	0

Source: RMP version 4 Annex 7-PT-Table 2.5a, PT-Table 2.5b, PT-Table 3.5a, PT-Table 3.5b, RMP version 7 Annex 7-Table 1.5-5.1.

Table 8-10 Important Identified Risk Lens opacities, retinal changes and optic neuritis: Other details

Lens opacities, retinal changes and optic neuritis	Details
Potential mechanisms	Unknown
Evidence source(s) and strength of evidence	The background incidence of eye abnormalities in patients with beta-thalassemia is poorly documented. However, several reports document patients with lenticular opacities who have never received chelation therapy though the overall incidence was not provided (Bloomfield et al 1978, Gartaganis et al 1989, Rinaldi et al 1993). Cataracts have not been reported in patients with SCD. In the predominantly elderly patients with MDS, senile cataracts are a relatively frequent event.
Characterization of the risk:	Cataracts/lenticular opacities were observed in non-clinical studies with deferasirox. Adverse events relating to eye abnormalities were reported irrespective of relationship to deferasirox in 1.2% of patients and in 0.5% of patients with a suspected relationship to study drug. The incidence of cataracts/lenticular opacities was relatively high in patients aged ≥ 65 years (at 6.5%) but this was based on low numbers of patients treated with deferasirox. None of these events was assessed as related to study drug, suggesting that the investigators believed these to be 'senile' cataracts. Three patients with thalassemia discontinued deferasirox due to cataracts/lenticular opacities. Of the 353 patients treated with DFO in Study CICL670A0107 and Study CICL670A0109, five developed lens opacities, which were assessed to be drug-related in four cases. A low serum ferritin has been reported to predispose to eye abnormalities in patients treated with DFO. Although three patients discontinued deferasirox due to ocular findings, none had low serum ferritins and therefore an excessive removal of iron appears to be an unlikely explanation for the findings in these individuals. The relationship of the eye abnormalities to deferasirox is currently uncertain. In patients receiving deferasirox DT doses > 30 mg/kg, an increased incidence of this AE was not observed. In Study CICL670A2411, 12/261 (4.6%) patients in total reported events in the eye disorder system organ class (SOC) during the study. An abnormal ophthalmological examination was reported in two patients (hyperopic astigmatism in one patient and subcapsular cataract in another patient). Study drug was not adjusted or interrupted. The patients completed the study and were continuing deferasirox when the study closed. There was one more patient in addition for which blurred vision was reported repeatedly although no abnormal ophthalmological assessment was available. No severe potentially irreversible disorders of the retina were reported during this study. In summary, repeated visual evaluations did not reveal the appearance of new clinically relevant abnormalities during deferasirox treatment in this study.
Risk factors and risk groups	As with other iron chelator treatments, the risk of toxicity may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated.

Lens opacities, retinal changes and optic neuritis	Details
Preventability	Ophthalmic testing (including fundoscopy) is recommended before the start of treatment and at regular intervals thereafter (every 12 months). If disturbances are noted, dose reduction or interruption may be considered.
Impact on the benefit-risk balance of the product	Ophthalmic testing before and at regular intervals during treatment. The impact of lens opacities, retinal changes and optic neuritis on the quality of life is considered to be significant. It is preventable by monitoring for signs of symptoms of lens opacities, retinal changes and optic neuritis and initiating treatment promptly.
Public health impact	With regular monitoring, prompt dose adjustment/hold and treatment where indicated the public health impact is considered to be low.
Source: RMP version 20.1-Table 8-10	

8.3.1.6 Important Potential Risk: Compliance with posology and biological monitoring

Table 8-11 Important Potential Risk: Compliance with posology and biological monitoring: Other details

Compliance with posology and biological monitoring	**Details**
Potential mechanisms	Compliance with posology: prescription error Compliance with biological monitoring: Lack of awareness of developing AEs if monthly monitoring is not performed.
Evidence source(s) and strength of evidence	Not applicable
Characterization of the risk:	Compliance with posology and biological monitoring (LIC, serum ferritin, renal and hepatic function, urine protein, ocular and hearing screening at baseline and during treatment) requirements in the SmPC is an important routine risk minimization measure. Study CICL670A2425 A total of 209 eligible respondents completed the Physician survey in 2015. The results suggest that the respondents had a modest understanding of the appropriate dosing and biological monitoring (serum ferritin, renal and hepatic laboratory parameters). Overall, dissemination of information about the appropriate use of deferasirox has been moderately effective in making prescribers aware of the appropriate dosing and biological monitoring requirements for deferasirox. Italy and Spain generally demonstrated a higher level of understanding with a high proportion (above 90%) of prescribers in these two countries reporting having received information from MAH sales representatives and a low proportion from the mailing of education materials (less than 6%). Seriousness and outcome of noncompliance depend on the degree of noncompliance. Physician survey (Survey NO6987) This physician survey aimed to assess the impact of educational materials and the existing label on the physicians' awareness of doses and biological monitoring recommendations and the awareness and appropriate use of both Exjade DT and FCT formulations. A total of 375 eligible respondents completed the survey in 2018. For posology questions common to both the 2015 and 2018 surveys, the 2015 respondents had an overall higher correct response rate for administration and dosing questions (62.2%) versus the 2018 respondents (55.9%). For biological monitoring questions common to both the 2015 and 2018 surveys, the total correct response rates were similar (73% in

Compliance with posology and biological monitoring	Details
	both surveys), indicating a continuity in the physician's knowledge of the complex biological monitoring, and which remains so after several years on the market. Overall, there was generally a high level of awareness for deferasirox in: mode of FCT dosing administration; starting dose difference when switching from DT to FCT; initial daily dose of FCTs and DTs following transfusion or with transfusional iron overload; dose escalation; proper clinical parameters assessed before starting therapy; monitoring of serum creatinine; monitoring of serum ferritin; recommendations in case of persistent and progressive increase in serum transaminase levels; and the risk of complications for patients with pre-existing renal conditions. An overview of effectiveness of this Physician survey also indicated that physicians have acquired relevant knowledge around switching between the different dosing forms. Taken into consideration the increased complexity during the 2018 survey, (2 pharmaceutical forms [DT and FCT] were in the market during the 2018 survey and only 1 [DT] during the 2015 survey), the overall results of the 2018 are on par with those of the 2015 survey (65.05% vs 67.89%). Study CICL670A2429 This is a survey to assess physician's knowledge of Exjade posology and biological monitoring recommendations as described in the Educational Materials. The survey data for this study was collected in 8 EU countries and the United Kingdom from 12-Jan-2024 to 15-Feb-2024. The main objective of the study was to assess whether sufficient levels of knowledge of posology and biological monitoring recommendations as described in the Exjade EU Summary of Product Characteristics (SmPC) can be attained among prescribers of Exjade/deferasirox, through the provision of Exjade EMs (which includes a Physician's reference checklist) developed by Novartis. To that end, the survey consisted of two sections assessing knowledge of the following: • Section A) Posology of Exjade (deferasirox) • Section B) Biological monitoring associated with the prescribing of Exjade (deferasirox) A total of 400 eligible respondents completed the survey. The overall average across questions from both sections was 71.2%. The overall average percentage of correct responses for the administration and dosing questions (Section A) was 66.6%, while the overall average percentage of correct responses for the biological monitoring questions (Section B) was 74.5%. More survey participants confirmed reading the Educational Materials (53.8%) than receiving the educational materials (46.3%) since January 2021. The overall average results in those who self-reported that they had received and read the educational materials was slightly higher (75.8%) than in those who either reported they had not received, or not read, the educational materials (68.7%;). Only 8.8% of respondents indicated that the educational materials are their primary source of information. By far the most popular primary sources physicians use to learn about dosing and biological monitoring for Exjade are the EU SmPC (24.5%) EMA website (18.3%). Among total respondents, results from Section A for the administration and dosing questions were slightly below the established threshold of 70% for the average correct response rate (66.6%). Regarding the biological monitoring questions in section B, the threshold of 70% was exceeded (74.9%). The survey also suggests that educational materials play a very minor role as primary source of information for physicians (8.8%).
Risk factors and risk groups	Patients who are non-compliant with posology and biological monitoring requirements in the SmPC.
Preventability	The risk of non-compliance with posology and biological monitoring requirements in the SmPC can be reduced through appropriate labeling information and educational materials for physicians and patients for all the formulations and for all indications.

Compliance with posology and biological monitoring	Details
Impact on the benefit-risk balance of the product	Medium
Public health impact	The potential public health impact depends on the seriousness and outcome of AEs patients may experience as a consequence of non-compliance with posology and biological monitoring requirements.
Source: RMP version 20.1-Table 8-11	

8.3.1.7 Important Potential Risk: Medication errors due to switching between Exjade FCT/granules and generic versions of deferasirox DT

Table 8-12 Important Potential Risk: Medication errors due to switching between Exjade FCT/granules and generic versions of deferasirox DT: Other details

Medication errors due to switching between Exjade FCT/granules and generic versions of deferasirox DT	Details
Potential mechanisms	Prescription error
Evidence source(s) and strength of evidence	Not applicable
Characterization of the risk:	Prescription errors due to lack of awareness of dosing adjustments necessary during switch between FCT/granules and generic versions of DT, available on the market by different MAHs and as appropriate depending on the coexistence of these formulations at a national level, which could lead to potential over/under-dosing. Potential for overdose or underdose as a result of medication errors. Physician survey (Survey NO6987) This Physician survey aimed to assess the impact of educational materials and the existing label on the physicians' awareness of doses and biological monitoring recommendations and the awareness and appropriate use of both Exjade DT and FCT formulations. A total of 375 eligible respondents completed the survey. The results of the Physician survey indicated that there was generally a good level of awareness for deferasirox in: mode of FCT dosing administration; starting dose difference when switching from DT to FCT; initial daily dose of FCTs and DTs following transfusion or with transfusional iron overload; dose escalation; proper clinical parameters assessed before starting therapy; monitoring of serum creatinine; monitoring of serum ferritin; recommendations in case of persistent and progressive increase in serum transaminase levels; and the risk of complications for patients with pre-existing renal conditions.
Risk factors and risk groups	Patients may be at risk of medication errors during switch between Exjade FCT/granules and generic versions of deferasirox DT available on the market by different MAHs and as appropriate depending on the coexistence of these formulations at a national level.
Preventability	Brand names labelling and packaging differentiation between formulations. Educational materials for physicians and patients for formulations of FCT and granules with reference about corresponding doses of Exjade DT for all indications and availability of generic versions of deferasirox DT available in the market by different MAH.
Impact on the benefit-risk balance of the product	Medium

Medication errors due to switching between Exjade FCT/granules and generic versions of deferasirox DT	Details
Public health impact	The potential public health impact depends on the seriousness and outcome of AEs patients may experience as a consequence of medication errors.
Source: RMP version 20.1-Table 8-12	

8.3.2 Part II Module SVII.3.2. Presentation of the missing information

Table 8-13 Missing information: Long term safety in pediatric NTDT patients aged 10 to 17 years

Long term safety in pediatric NTDT patients aged 10 to 17 years	Details
Evidence source	**Population in need of further characterization:** The ongoing dedicated study (Study CICL670E2422) is aiming to characterize the safety in this patient population. **Anticipated risk/consequence of the missing information:** The anticipated risk cannot be characterized due to limited information.

Table 8-14 Missing information: Safety of new formulation (FCT)

Safety of new formulation (FCT)	Details
Evidence source	**Population in need of further characterization:** Currently, Study CICL670E2422 (with DT and FCT formulations) is being conducted to further study the safety of FCT formulations. **Anticipated risk/consequence of the missing information:** The FCT is a more recent formulation of deferasirox and has been studied in fewer patients compared to the conventional DT. Therefore, the understanding of the safety profile of the FCT formulation is considered limited.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Table Part II 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 due to switching between Exjade FCT/granules and generic versions of deferasirox DT
Missing information	• Long term safety in pediatric NTDT patients aged 10 to 17 years • Safety of new formulation (FCT)

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists:

Specific adverse event follow-up checklists are used to collect further data to help characterize and/or closely monitor each of the respective safety concerns specified below:

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

These checklists are provided in Annex 4 of the RMP.

Other forms of routine pharmacovigilance activities for risks:

No other forms of routine PhV activities for risks were proposed.

10.2 Part III.2. Additional pharmacovigilance activities

One PhV study/activity is ongoing; CICL670E2422, details of which are provided below.

Study CICL670E2422 - An observational, multi-center study to evaluate the safety of deferasirox in the treatment of pediatric patients with non-transfusion-dependent iron overload

Study short name and title:

An observational, multi-center study to evaluate the safety of deferasirox in the treatment of pediatric patients with non-transfusion-dependent iron overload.

Rationale and study objectives:

The purpose of this observational study is to provide further assessment of the safety of deferasirox in NTDT pediatric patients with documented iron overload as defined in a local product label. The primary objective is to characterize the long term safety profile of deferasirox in pediatric patients with NTDT with exposure up to 5 years.

Study design:

This study is a registry of pediatric patients with non-transfusion dependent thalassemia conducted in response to a post-approval commitment to the United States (US) Food and Drug Administration (FDA) for an observational study in this population in order to assess long-term exposure and safety of deferasirox. (PMR 1994-4: "Establish a registry of children [aged 10 to

< 18 years old at enrollment] with NTDT and treated with deferasirox for documented iron overload. Study CICL670E2422 will follow at least 40 children for up to 5 years to assess and analyze the long-term safety of treatment with deferasirox, including an assessment of growth, compared to children on a regular transfusion program receiving deferasirox [based on historical data]").

This study is non-interventional and does not impose a therapy protocol, diagnostic/therapeutic interventions or a visit schedule. However, a minimum of quarterly visits are suggested. Patients will be treated with deferasirox in accordance with the local (country-specific) deferasirox prescribing information.

Study population:

This is a non-interventional study which plans to enroll a minimum of 40 patients. No formal sample size calculation based on the primary endpoint of long-term safety is performed.

Milestones:

Protocol submission: Nov-2013 (Actual)

Final CSR: Jul-2025 (Planned)

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
CICL670E2422 Non-interventional An observational, multi-center study to evaluate the safety of deferasirox in the treatment of pediatric patients with non-transfusion-dependent iron overload Ongoing	To assess the safety of deferasirox DT and FCT in pediatric NTDT patients (10 to 17 years old)	Long term safety in pediatric NTDT patients aged 10 to 17 years-old; Safety of new formulation (FCT)	Protocol submission	Nov-2013 (Actual)
			Final CSR	Jul-2025 (Planned)
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
None				

11 Part IV: Plans for post-authorization efficacy studies

There are no post-authorization efficacy studies.

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

Risk Minimization Plan

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important Identified Risks	
Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome])	**Routine risk communication:** SmPC Section 4.2 Section 4.3 Section 4.4 Section 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** This item is appropriately communicated through current labeling: SmPC Section 4.2 Posology and method of administration, Section 4.3 Contraindications, and Section 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs Section 4.8 Undesirable effects. **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine, to be used by experienced physicians in the approved indications.
Increased liver transaminases / Hepatic failure	**Routine risk communication:** SmPC Section 4.2 Section 4.4 Section 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** This item is appropriately communicated through current labeling: SmPC Section 4.2 Posology and method of administration, Section 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs Section 4.8 Undesirable effects. **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine, to be used by experienced physicians in the approved indications.
Gastrointestinal hemorrhage and ulcers; esophagitis	**Routine risk communication:** SmPC Section 4.4 Section 4.5 Section 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** This item is appropriately communicated through current labeling: SmPC Section 4.4 Special warnings and precautions for use, and Section 4.5 Interaction with other medicinal products and other forms of interaction. Relevant terms are included as ADRs in SPC Section 4.8 Undesirable effects. **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine, to be used by experienced physicians in the approved indications.

Safety concern	Routine risk minimization activities
Hearing loss	**Routine risk communication:** SmPC Section 4.4 Section 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** This item is appropriately communicated through current labeling: SmPC Section 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs in Section 4.8 Undesirable effects. **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine, to be used by experienced physicians in the approved indications.
Lens opacities, retinal changes and optic neuritis	**Routine risk communication:** SmPC Section 4.4 Section 4.8 Section 5.3 **Routine risk minimization activities recommending specific clinical measures to address the risk:** This item is appropriately communicated through current labeling: SmPC Section 4.4 Special warnings and precautions for use, 5.3 Preclinical safety data. Relevant terms are included as ADRs in Section 4.8 Undesirable effects. **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine, to be used by experienced physicians in the approved indications.
Important Potential Risks	
Compliance with posology and biological monitoring	**Routine risk communication:** SmPC Section 4.2 Section 4.4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** This item is appropriately communicated through current labeling: SmPC Section 4.2 Posology and method of administration and Section 4.4 Special warnings and precautions for use. **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine, to be used by experienced physicians in the approved indications.
Medication errors due to switching between Exjade FCT/granules and generic versions of deferasirox DT	**Routine risk communication:** SmPC Section 4.2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** This item is appropriately communicated through current labeling: SmPC Section 4.2 Posology and method of administration. **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine, to be used by experienced physicians in the approved indications.
Missing Information	
Long term safety in pediatric NTDT patients aged 10 to 17 years	**Routine risk communication:** SmPC Section 4.2 Section 4.4 **Routine risk minimization activities recommending specific clinical measures to address the risk:**

Safety concern	Routine risk minimization activities
	This item is appropriately communicated through current labeling: SmPC Section 4.2 Posology and method of administration, and Section 4.4 Special warnings and precautions for use. **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine, to be used by experienced physicians in the approved indications.
Safety of new formulation (FCT)	**Routine risk communication:** SmPC Section 4.2 Section 5.2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** This item is communicated through labeling: SmPC Section 4.2 and 5.2 and Patient Leaflet. **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine, to be used by experienced physicians in the approved indications.

12.2 Part V.2. Additional Risk minimization measures

Educational material:

Objectives:

Aimed to inform healthcare professionals and patients to minimise the risks related to:

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

Rationale for the additional risk minimization activity:

- To educate prescribers and patients about the appropriate dosing (including dose adjustment requirements in case of switch between Exjade FCT/granules and generic versions of deferasirox DT) and biological monitoring.
- To provide a prescribing decision tool for physicians to support calculation of appropriate posology and tracking of biological monitoring (physicians' checklist).

Target audience and planned distribution path:

Prescribers and patients.

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

The effectiveness of risk minimization measures for the safety concern will be measured on the basis of ongoing routine PhV activities and assessment of new data in PSURs.

12.3 Part V.3. Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

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

Safety concern	Risk minimization measures	Pharmacovigilance activities
Lens opacities, retinal changes, and optic neuritis	**Routine risk minimization measures:** SmPC Section 4.4 Special warnings and precautions for use, 5.3 Preclinical safety data. Relevant terms are included as ADRs in Section 4.8 Undesirable effects.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up using a targeted checklist. **Additional pharmacovigilance activities:** None
Important potential risks		
Compliance with posology and biological monitoring	**Routine risk minimization measures:** SmPC Section 4.2 Posology and method of administration and 4.4 Special warnings and precautions for use. **Additional risk minimization measures:** Educational materials for physicians (which also includes a physicians' checklist) and patients regardless of indication.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:**None
Medication errors due to switching between Exjade FCT/granules and generic versions of deferasirox DT	**Routine risk minimization measures:** SmPC Section 4.2 Posology and method of administration. **Additional risk minimization measures:** Educational materials for physicians (which also includes a physicians' checklist) and patients clarifying the dose adjustment requirements in case of switch between Exjade FCT/granules and generic versions of deferasirox DT.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Missing information		
Long term safety in pediatric NTDT patients aged 10 to 17 years	**Routine risk minimization measures:** SmPC Section 4.2 Posology and method of administration, 4.4 Special warning and precautions for use **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Review of data from Study CICL670E2422
Safety of new formulation (FCT)	**Routine risk minimization measures:** SmPC Section 4.2 and 5.2 and the Patient Leaflet **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
		None **Additional pharmacovigilance activities:** Review of data from the study CICL670E2422

13 Part VI: Summary of the risk management plan for deferasirox (ICL670)

This is a summary of the RMP for deferasirox. The RMP details important risks of deferasirox, how these risks can be minimized, and how more information will be obtained about deferasirox's risks and uncertainties (missing information).

Deferasirox's SmPC and its package leaflet give essential information to healthcare professionals and patients on how deferasirox should be used.

This summary of the RMP for deferasirox 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 the European Public Assessment Report (EPAR).

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

13.1 Part VI: I. The medicine and what it is used for

Deferasirox is N-substituted bis-hydroxyphenyl-triazole. It is a tridentate ligand that binds ferric iron with high affinity in a 2:1 ratio and promotes excretion of iron, primarily in the feces. Deferasirox is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients with thalassemia, SCD, MDS or other rare anemias, and for the treatment of chronic iron overload in patients with NTDT syndromes.

For transfusional iron overload, recommended initial daily dose for FCT/granules is 14 mg/kg body weight (initial doses of 7 mg/kg or 21 mg/kg may be considered depending on transfusion intensity and treatment goal). Dose adjustments in steps of 3.5-7 mg/kg/day may be considered every 3-6 months. Doses above 28 mg/kg are not recommended because there is only limited experience with doses above this level.

For patients with NTDT syndromes, recommended initial daily dose for FCT/granules is 7 mg/kg body weight. Dose adjustments in steps of 3.5-7 mg/kg/day may be considered every 36 months. Doses above 14 mg/kg are not recommended because there is no experience with doses above this level . In patients in whom LIC was not assessed and serum ferritin is ≤ 2000 µg/L, as well as in pediatric patients, 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 ≤ 2000 µg/L.

Exjade Dispersible Tablet (DT) has been discontinued in the EU markets and is therefore no longer available for patients. However, generic versions of deferasirox DT may be available.

In case of switching patients between Exjade FCT/granules and generic versions of deferasirox DT, the dose of the Exjade FCT/granules should be adjusted. As a reference, the corresponding doses for Exjade FCT/granules and Exjade DT are shown in the tables below.

Transfusional iron overload:

	Exjade film-coated tablets/granules	**Exjade Dispersible tablets**
Starting dose	14 mg/kg/day	20 mg/kg/day

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

NTDT syndromes:

	Exjade film-coated tablets/granules	**Exjade 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

Further information about the evaluation of deferasirox's benefits can be found in deferasirox's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage link to product's EPAR summary landing page on the EMA webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/exjade

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of deferasirox, together with measures to minimize such risks and the proposed studies for learning more about deferasirox's risks, are outlined below.

Measures to minimize 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 minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of deferasirox, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, in Table 13-7 and Table 13-8, below.

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

If important information that may affect the safe use of deferasirox is not yet available, it is listed under 'missing information' in Table 13-9 and Table 13-10, below.

13.2.1 Part VI - II.A: List of important risks and missing information

Important risks of deferasirox are risks that need special risk management activities to further investigate or minimize 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. 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).

Table 13-1 List of important risks and missing information

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 due to switching between Exjade FCT/granules and generic versions of deferasirox DT
Missing information	• Long term safety in pediatric NTDT patients aged 10 to 17 years • Safety of new formulation (FCT)

13.2.2 Part VI - II.B: Summary of important risks

Table 13-2 Important identified: Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome])

Evidence for linking the risk to the medicine	In thalassemia patients 0.5% of patients are reported to develop renal tubular dysfunction and 3.1% of patients progressed to dialysis therapy and 8% had a reduced CrCl. Renal tubular abnormalities, including increased urinary excretion of proteins and of tubular enzymes, have been reported in 30% of 250 patients with β-thalassemia. Progressive renal insufficiency, generally heralded by the appearance of increasing proteinuria, hypertension and hematuria occurs in 5-18% of patients with SCD and can require hemodialysis or renal transplantation and contributes to 18% of deaths in patients older than 40 years. Acute renal failure has been described as part of a multi-organ failure syndrome that accompanies pain crises in SCD patients and is present in 10% of patients hospitalized with SCD. Renal failure contributes to 18% of deaths in SCD patients older than 40 years. In SCD, 26% of 381 patients were reported to have proteinuria, 13% at or close to the nephritic range. It was reported that 2.3% of MDS patients have renal disorders. Myelodysplastic syndrome patients are generally elderly and have serum creatinine levels that are close to or slightly > ULN due to the normal aging process.
Risk factors and risk groups	Analyses showed that patients receiving high doses of deferasirox DT (20 or 30 mg/kg) and a low iron intake from infrequent blood transfusions were more likely to develop creatinine increases. Elderly patients were more likely to

	develop creatinine values > ULN though, as explained above, the magnitude of increase in comparison to baseline was no higher in these patients. Patients with pre-existing renal conditions or patients who are receiving medicinal products that depress renal function may be at higher risk of complications including ARF. In clinical studies a relationship between iron status (liver iron and ferritin concentrations), the rate of iron removal and renal effects has been observed. As with other iron chelator treatment, the risk of toxicity may be increased when inappropriately high doses of deferasirox are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.2 Posology and method of administration, 4.3 Contraindications, and 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs Section 4.8 Undesirable effects. **Additional risk minimization measures** None

Table 13-3 Important identified risk: Increased liver transaminases / Hepatic failure

Evidence for linking the risk to the medicine	**Increased liver transaminases** Elevated liver transaminases have been correlated with increased LIC in patients with β-thalassemia. Studies have shown that hepatomegaly is seen in 50% of patients with SCD, hepatitis in 11% of patients, and approximately one third of SCD patients will have a form of hepatic dysfunction. **Hepatic failure** In patients aged > 6 years with beta-thalassemia, 4-6% had evidence of liver failure or cirrhosis. SCD patients can develop sickle cell crises and sequestration events affecting the liver causing massive hepatic enlargement with hepatic failure occurring in up to 10% of patients. Cirrhosis has been reported in 16 to 29% of SCD patients.
Risk factors and risk groups	**Increased liver transaminases** None identified **Hepatic failure** Patients with pre-existing hepatic impairment.
Risk minimization measures	**Increased liver transaminases / Hepatic failure** **Routine risk minimization measures** SmPC Section 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs Section 4.8 Undesirable effects. **Additional risk minimization measures** None

Table 13-4 Important identified risk: Gastrointestinal hemorrhage and ulcers; esophagitis

Evidence for linking the risk to the medicine	No information was found regarding the incidence of this event in the unexposed population.
Risk factors and risk groups	Patients who are taking deferasirox in combination with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids or oral bisphosphonates, and in patients receiving anticoagulants.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.4 Special warnings and precautions for use, and 4.5 Interaction with other medicinal products and other forms of interaction. Relevant terms are included as ADRs in SmPC Section 4.8 Undesirable effects. **Additional risk minimization measures**

	None

Table 13-5 Important identified risk: Hearing loss

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

Table 13-6 Important identified risk: Lens opacities, retinal changes and optic neuritis

Evidence for linking the risk to the medicine	The background incidence of eye abnormalities in patients with beta-thalassemia is poorly documented. However, several reports document patients with lenticular opacities who have never received chelation therapy though the overall incidence was not provided. Cataracts have not been reported in patients with SCD. In the predominantly elderly patients with MDS, senile cataracts are a relatively frequent event.
Risk factors and risk groups	As with other iron chelator treatments, the risk of toxicity may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.4 Special warnings and precautions for use, 5.3 Preclinical safety data. Relevant terms are included as ADRs in Section 4.8 Undesirable effects. **Additional risk minimization measures** None

Table 13-7 Important potential risk: Compliance with posology and biological monitoring

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

Table 13-8 Important potential risk: Medication errors due to switching between Exjade FCT/granules and generic versions of deferasirox DT

Evidence for linking the risk to the medicine	Not applicable

Risk factors and risk groups	Patients may be at risk of medication errors during switch between Exjade FCT/granules and generic versions of deferasirox DT available on the market by different MAHs and as appropriate depending on the coexistence of these formulations at a national level.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.2 Posology and method of administration. **Additional risk minimization measures** Educational materials for physicians (which also includes a physicians' checklist) and patients clarifying the dose adjustment requirements in case of switch between Exjade FCT/granules and generic versions of deferasirox DT.

Table 13-9 Missing information: Long term safety in pediatric NTDT patients aged 10 to 17 years

Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use **Additional risk minimization measures** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CICL670E2422: An observational, multi-center study to evaluate the safety of deferasirox in the treatment of pediatric patients with non-transfusion-dependent iron overload.

Table 13-10 Missing information: Safety of new formulation (FCT)

Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.2 and 5.2 and Patient Leaflet **Additional risk minimization measures** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CICL670E2422: An observational, multi-center study to evaluate the safety of deferasirox in the treatment of pediatric patients with non-transfusion-dependent iron overload.

13.2.3 Part VI: II.C: Post-authorization development plan

13.2.3.1 II.C.1. Studies which are conditions of the marketing authorization

Table 13-11 Studies which are conditions of the marketing authorization

Study short name	Purpose of the study:
CICL670E2422 (Observational study)	An observational, multicenter study to evaluate the safety of deferasirox DT and FCT in pediatric NTDT patients aged 10 to 17-years old.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

There are no studies required for Exjade.

14 Part VII: Annexes

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, renal tubular disorders [acquired Fanconi's syndrome])
- Increased liver transaminases and hepatic failure
- Gastrointestinal hemorrhage, ulcer, and esophagitis
- Hearing loss
- Lens opacities, retinal changes and optic neuritis

Targeted follow-up checklists:

- **Exjade Serum Creatinine Increase/Renal impairment (Version 4.0 Jul-2022)**

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

Information on Dose of Exjade:

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 Exjade discontinued?

☐ **Yes** - Date of Exjade discontinuation: ___/___/____ (dd/mm/yyyy)
- Has serum creatinine returned to baseline after discontinuation? ☐ **Yes** ☐ **No** ☐ **Unknown**
- Has Exjade been restarted? ☐ **Yes** ☐ **No**
If **Yes,** restart date:___/___/____ (dd/mm/yyyy), Dose:_____
Re-occurrence of serum creatinine increase?☐ **Yes** ☐ **No** ☐ **Unknown**

☐ **No** - Has Exjade dose been reduced? ☐ **Yes** ☐ **No**
If **Yes,** reduction date:___/___/____ (dd/mm/yyyy), Dose:_____
- Has serum creatinine returned to baseline after reduction? ☐ **Yes** ☐ **No** ☐ **Unknown**

2) Measurement of serum creatinine:

	Date	**Serum creatinine values**	**Unit**	**Reference Range**
[@ treatment start, if available]				
[during treatment #1, if available]				

[during treatment #2, if available]				
[@ time of event]				
*[follow-up measurement @ **+30d**]*				
*[follow-up measurement @ **+60d**]*				

3)Renal biopsy:
Has a renal biopsy been performed? ☐ **Yes** ☐ **No**
If **Yes**, please provide results

4) Measurement of serum ferritin:

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

Event Description:

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

☐ Fever
☐ Dehydration
☐ Nausea/vomiting
☐ Pain around costovertebral angle
☐ Urinary urgency
☐ Infections
☐ Change in size of urine stream
☐ Trouble sleeping
☐ Increased urinary output
☐ Hematuria/red or cola colored urine
☐ Loss of Appetite
☐ Edema
☐ Lethargy
☐ Confusion
☐ Burning sensation upon urinating
☐ Difficulty starting or maintaining urine stream
☐ Pain upon urinating
☐ Arthralgia
☐ Muscle Cramps
☐ Skin rash
☐ Flank pain
☐ Dry/itchy skin
☐ Shortness of breath
☐ Decreased urinary output
☐ Bradycardia
☐ Tachycardia
☐ Hypotension
☐ Hypertension
☐ 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
☐ BUN
☐ Serum creatinine
☐ Hemoglobin
☐ CPK
☐ Urinalysis (including microscopic)
☐ Complement studies
☐ Urine protein/Urine creatinine
☐ Albumin
☐ Serum total protein
☐ Myoglobin
☐ Electrolytes
☐ Glomerular filtration rate (estimated/measured)
☐ Chest x-ray
☐ Kidney biopsy
☐ CT scan
☐ Renal ultrasound
☐ Cystoscopy
☐ Echocardiogram
☐ Pulmonary angiography

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

Relevant medical history (concurrent and pre-existing conditions)

(Please specify medical condition and date of onset)

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

☐ Congestive heart failure ☐Multiple myeloma ☐ Exposure to chemical dyes
☐ Diabetes mellitus (Type I or Type II) ☐ Urinary tract infection ☐ Myocardial infarction
☐ Reflux nephropathy ☐ Thromboembolic disease ☐ Coronary artery disease
☐ Renal disease (including nephrolithiasis) ☐ Obstructive uropathy ☐ Hypercalcemia
☐ Autoimmune disease (specify) ☐ Sickle cell disease ☐ History of renal transplant
☐ Hypertension ☐ Hyperuricemia ☐ Hepatorenal syndrome
☐ Trauma/ burns ☐ Renal artery obstruction ☐ Hemolytic uremic syndrome
☐ Kidney or bladder problems/Stones ☐ Drug allergies *(please specify)* ☐ Dehydration
☐ Disease of the prostate ☐ Rhabdomyolysis
☐ Intravenous contrast ☐ Hemorrhage ☐ Cystic kidney disease
☐ Other relevant history *(please specify)* ☐ None of the above ☐ History of dialysis

_____
_____
_____
_____

Relevant family history

☐ Chronic kidney disease ☐Hearing loss/deafness ☐ Kidney cancer
☐ kidney genetic abnormalities

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

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

- **Liver Injury (Version 3.0 May-2021)**

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

Event Description:

1. Diagnosis and date of diagnosis_____

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

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

3. Were any of the following diagnostic tests performed?

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

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

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

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

5. 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

- **Exjade Gastrointestinal Ulcers & Bleeds (Version 3 November-2020)**

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 Exjade, time of occurrence during the day in relation to Exjade ingestion, severity, and frequency, if applicable**

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

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

At time of bleed _____

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

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

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

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

☐ Other – please specify: _____ ___/___/____ (dd/mm/yyyy) Results: _____

☐ None of the above

Patient History:

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

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

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

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

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

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

- **Exjade Hearing Loss (Version 2.1 November-2020)**

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 Exjade discontinued?**

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

☐ **No** - Has Exjade 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]				

- **Exjade Lens Opacities / Cataracts (Version 2.1 May-2021)**

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 Exjade discontinued?

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

☐ **No** - Has Exjade 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 minimization activities (if applicable)

Organization of material

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

The educational programme is aimed to inform healthcare professionals and patients to minimize the risks related to:

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

The risk of medication error is due to switching between Exjade FCT/granules and generic deferasirox DT formulations available on the market by different MAHs and as appropriate depending on the coexistence of these formulations at a national level. The MAH shall ensure that, in each Member State where EXJADE is marketed, all healthcare professionals and patients who are expected to prescribe, dispense and use EXJADE are provided with the following educational package for all available formulations (EXJADE film-coated tablets and EXJADE granules) for all indications:

- Physician education material and
- Patient information pack

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

The MAH shall use distinct outer cartons, blisters and tablets for all formulation (film-coated tablets and granules).

Objective

The objectives and goals of the educational materials are to provide further detailed information to prescribers of deferasirox and their patients to minimize the potential safety risk of compliance with posology and biological monitoring and medication errors due to switching between Exjade FCT/granules and generic versions of deferasirox DT, and to ensure more effective dissemination of the information of the key safety elements.

Furthermore, the educational material aims to provide a prescribing decision tool for physicians to support calculation of appropriate posology and tracking of biological monitoring, through the provision of a physicians' checklist.

Details of proposed educational program

The physician educational material should contain elements:

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

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

- Description of available deferasirox formulation (EXJADE film-coated tablets and granules) in the EU markets
  - Different posology regimen
  - Different conditions of administration
- Dose conversion table of Exjade FCT/granules and Exjade DT as a reference when switching between Exjade FCT/granules and generic versions of deferasirox DT
- 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
    a. On two occasions prior to initiation of treatment
    b. Every week during the first month of initiation of treatment or after therapy modification
    c. Monthly thereafter
  - The need to reduce by 7 mg/kg the dose if serum creatinine rises:
    a. Adults: >33% above baseline and creatinine clearance <Lower limit of normal (LLN) (90 ml/min)
    b. Pediatrics: 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:
    a. Adults and Pediatrics: remain >33% above baseline or creatinine clearance <LLN (90 ml/min)
  - The need to consider renal biopsy:
    a. When serum creatinine is elevated and if another abnormality has been detected (e.g. proteinuria, signs of Fanconi's 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 pediatric population
  - A warning on the currently unknown safety consequences of long-term treatment in the pediatric population

The patient information pack should contain:

- Package 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 formulation (i.e., generic version of deferasirox 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)