RISK MANAGEMENT PLAN

Ferriprox® (deferiprone)

Version 13.5

Date of report: 08 September 2022

Chiesi Farmaceutici SpA
26/A, Via Palermo, 43122 Parma, Italy

RMP version to be assessed as part of this application:

RMP Version number:	13.5
Data lock point for this RMP:	31 May 2022
Date of final sign off:	26 September 2022

Rationale for submitting an updated RMP: Consequential changes related to SWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug (EMA/CHMP/SWP/74077/2020)

Summary of significant changes in this RMP:

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- Change of Marketing Authorization Holder (MAH) from Apotex B.V. to Chiesi Farmaceutici S.p.A.
- SV.1.2: exposure data updated to DLP of 31 May 2022
- SVII.3.1.: section updated to reflect changes in section 4.3 and 4.6 of SmPC
- II.B: section updated to reflect changes in section 4.3 and 4.6 of SmPC
- Implementation of additional changes as per PRAC AR (10 August 2022)
    - Clarification of the age of the paediatric population (8 years) for which Ferriprox is approved in the US throughout the relevant sections of RMP.
    - Alignment of the content of RMP Part 2 module VII and Part 6 with the product information.
    - Alignment of the content of RMP annex 6 and PI annex IID
- Minor wording change in Annex 6 (patient card)

Other RMP versions under evaluation: None

Details of the currently approved RMP:

Version number:	13.2
Approved with procedure:	EMEA/H/C/000236/II/0126/G
Date of approval (opinion date):	31 Jan 2019

APPROVAL

Chiesi Farmaceutici S.p.A.

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PART I: PRODUCT OVERVIEW

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	deferiprone
Pharmacotherapeutic group(s) (ATC Code)	V03AC02
Marketing Authorisation Holder	Chiesi Farmaceutici S.p.A. (Hereafter referred to as Chiesi)
Medicinal products to which this RMP refers	Ferriprox®
Invented name(s) in the European Economic Area (EEA)	Ferriprox®
Marketing authorisation procedure	Central
Brief description of the product	Deferiprone is an Iron Chelator, ATC code V03AC02. Deferiprone (3-hydroxy-1, 2-dimethylpyridin-4-one), a bidentate ligand which binds to iron in a 3:1 ratio.
Hyperlink to the Product Information	*Include a link or reference to the proposed product information (PI) in the eCTD sequence, as appropriate. If no updated PI is submitted with the procedure, the link should direct to the latest approved PI.*
Indication(s) in the EEA	Current: Ferriprox monotherapy is indicated for the treatment of iron overload in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate. Ferriprox in combination with another chelator is indicated in patients with thalassaemia major when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction.
	Proposed (if applicable): Not applicable

Dosage in the EEA	Current: Deferiprone is usually given as 25 mg/kg body weight, orally, three times a day for a total daily dose of 75 mg/kg body weight. Dose per kilogram body weight should be calculated to the nearest half tablet. Doses above 100 mg/kg/day are not recommended because of the potentially increased risk of adverse reactions. Dose adjustments during monotherapy Dose adjustments should be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). Dose adjustments when used with other iron chelators In patients for whom monotherapy is inadequate, Ferriprox may be used with deferoxamine at the standard dose (75 mg/kg/day) but should not exceed 100 mg/kg/day. In the case of iron-induced heart failure, Ferriprox at 75-100 mg/kg/day should be added to deferoxamine therapy. The product information of deferoxamine should be consulted. Concurrent use of iron chelators is not recommended in patients whose serum ferritin falls below 500 µg/l due to the risk of excessive iron removal.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current: 500 mg and 1000 mg film-coated tablets each divisible in half 100 mg/mL oral solution
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

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

Beta-thalassaemias are a group of hereditary blood disorders characterized by anomalies in the synthesis of the beta chains of haemoglobin resulting in variable phenotypes ranging from severe anaemia to clinically asymptomatic individuals.

Three main forms of Beta-thalassaemia have been described: thalassaemia major (variably referred to as "Cooley's Anemia" and "Mediterranean Anemia"), thalassaemia intermedia and thalassaemia minor (also called "beta-thalassaemia carrier", "beta-thalassaemia trait" or "heterozygous beta-thalassaemia"). Individuals with thalassaemia major usually present within the first two years of life with severe anaemia, requiring regular red blood cell (RBC) transfusions for their survival. Findings in untreated or poorly transfused individuals with thalassaemia major, as seen in some developing countries, are growth retardation, pallor, jaundice, poor musculature, hepatosplenomegaly, leg ulcers, development of masses from extramedullary hematopoiesis, and skeletal changes that result from expansion of the bone marrow. Regular transfusion therapy leads to iron overload-related complications including endocrine dysfunction such as growth retardation, failure of sexual maturation, cardiac failure, diabetes mellitus, and insufficiency of the parathyroid, thyroid, pituitary, adrenal glands, dilated myocardiopathy, liver fibrosis and cirrhosis and premature death.

Patients with thalassaemia intermedia present later in life with moderate anaemia and do not require regular transfusions. The main clinical features in these patients are hypertrophy of erythroid marrow with medullary and extramedullary excessive hematopoiesis and its complications (osteoporosis, masses of erythropoietic tissue that primarily affect the spleen, liver, lymph nodes, chest and spine, and bone deformities and typical facial changes), gallstones, painful leg ulcers and increased predisposition to thrombosis. Thalassaemia minor is clinically asymptomatic but some subjects may have mild or moderate anaemia.

Beta-thalassaemia is prevalent in Mediterranean countries, the Middle East, Central Asia, India, Southern China, and the Far East as well as countries along the north coast of Africa. The highest carrier frequency is reported in Cyprus (14%), Sardinia (10.3%), and Southeast Asia.[3, 27, 64] It has been estimated that about 1.5% of the global population (80 to 90 million people) are carriers of beta-thalassaemia, with about 60,000 symptomatic individuals born annually, the great majority in the developing world. Prevalence of symptomatic individuals is estimated at 0.4 per 10,000 people in the European Union. However, accurate data on carrier rates in many populations are lacking, particularly in areas of the world known or expected to be heavily affected.[64] According to the Thalassemia International Federation, about 200,000 patients with thalassemia major are alive and registered as receiving regular treatment around the world.[61]

Table 1 Epidemiology of indication in patients with thalassaemia major in the EU

Thalassaemia major	
Incidence of target indication	1.0 per 10,000
Prevalence of target indication	0.4 per 10,000
Mortality in target indication	The life expectancy of patients with thalassaemia major has significantly increased in recent years, as reported by several groups in different countries.[11] In Italy, 50% of patients born before 1970 died before age of 12 years old. Regular blood transfusions and iron chelation have changed the prognosis of the disease.[12] With those measures, the survival rate at age 25 years for patients born in or after 1970 increased to between 81 and 92%.[11, 12] The main cause of death in those patients remains iron-induced cardiac disease. Since the development of magnetic resonance imaging techniques that measure the cardiac iron content and the availability of Ferriprox, which is superior to deferoxamine in removing excess cardiac iron, there has been a significant decline in the number of deaths due to iron overload in patients with thalassaemia major.[11, 14, 35, 41, 44, 51, 52, 60] These survival data are recognized by the EMA (refer to section 5.1 of the Ferriprox SmPC).

Potential health risk	Individuals with thalassaemia major usually present within the first two years of life with severe anaemia, requiring regular red blood cell (RBC) transfusions.
	Regular transfusion therapy leads to iron overload-related complications:
	- Cardiomyopathy
	- Liver fibrosis and cirrhosis
	- Endocrine complications:
	  - Growth retardation
	  - Failure of sexual maturation
	  - Diabetes mellitus
	  - Insufficiency of the parathyroid, thyroid, pituitary, and less commonly, adrenal glands

Demographic profile of target population	<u>Race</u> Beta-thalassaemia genes are reported throughout the world, although more frequently in Mediterranean, African, and Southeast Asian populations. • The genetic defect in Mediterranean populations is caused most commonly by (1) a mutation creating an abnormal splicing site or (2) a mutation creating a premature translation

	termination codon. • Southeast Asian populations also have a significant prevalence of Hb E and alpha thalassaemia. • African populations more commonly have genetic defects leading to alpha thalassaemia. <u>Gender</u> This genetic disorder is caused by abnormalities in the beta-globin gene, located on chromosome 11. It is not a sex-linked genetic trait. <u>Age</u> The manifestations of the disease may not be apparent until a complete switch from fetal to adult Hb synthesis occurs. This switch typically is completed by the sixth month after birth.

Important co-morbidities in patients with thalassaemia major: cardiac dysfunction, hepatic dysfunction, endocrinopathies (diabetes, hypothyroidism, hypogonadism).

There is no active mechanism for the excretion of iron by the human body. Thus, the iron content of blood transfusions inevitably will accumulate in transfusion-dependent patients and cause tissue iron overload. Ferriprox is intended to control iron overload and to prevent associated complications.

In the EU, Ferriprox is labelled as a second-line treatment, to be used in patients for whom deferoxamine is contraindicated or inadequate. However, data from the published literature are consistent with the results from the Chiesi studies, demonstrating less heart disease and/or increased survival in Ferriprox-treated patients than in those treated with deferoxamine.[11, 14, 35, 41, 44, 51, 52, 60]

Module SII: Non-clinical part of the safety specification

The following findings have been observed in laboratory animals during toxicology studies. It is not known whether these effects may be relevant to human safety, because those that might be detectable or inferred from signs in the course of a clinical trial or clinical practice have not been reported as occurring.

Non-clinical toxicology studies were conducted in naïve (not iron-loaded) and iron-loaded mice, rats, and monkeys. The effects of deferiprone generally were dose- and time-dependent, and occurred at doses around or in excess of 150 mg/kg/day in non-iron-loaded animals, and at doses around or exceeding 200 mg/kg/day in iron-loaded animals, thus indicating that iron loading affords some degree of protection. The potential relevance of these findings to human usage is summarized below.

Table 2 Important safety findings from non-clinical studies

KEY SAFETY FINDINGS (from non-clinical studies)	RELEVANCE TO HUMAN USAGE
Bone Marrow Effects - Bone marrow suppression with concurrent decreases in peripheral red cell, white cell (without evident preference for neutrophils), and/or platelet counts have been reported in various laboratory animal species. These effects were readily monitored through routine peripheral blood counts and were reversible upon cessation of treatment.	Decreases in all blood cell counts (erythrocytes, leukocytes and platelets) such as those noted in laboratory animals given deferiprone, and that would be secondary to bone marrow suppression, have not been noted in clinical practice. Effects in patients are generally limited to episodes of neutropenia and, less frequently, of idiosyncratic occurrences of agranulocytosis, that have no correlate in animals. Therefore, effects seen in laboratory animals are not considered relevant to humans.
Genotoxicity/Carcinogenicity - Deferiprone was not mutagenic in a bacterial reverse mutation assay using several *S. typhimurium* tester strains. It was clastogenic in *in vitro* and *in vivo* assays at concentrations exceeding those reported in clinical practice. Dose- or concentration-response profiles suggest the possibility of an indirect mechanism through enzyme inhibition-mediated effect.	In view of the positive clastogenicity results, a carcinogenic potential of deferiprone cannot be excluded, although there are no human data suggestive of such effects being attributable to or associated with deferiprone.
Atrophy of thymus, spleen- These effects have been observed in laboratory rats given daily supratherapeutic doses of deferiprone and were frequently associated with decreases in peripheral lymphocyte counts, moribundity and/or mortality. They may result from treatment-associated stress and/or lymphocyte depletion.	No evidence suggestive of such effects has been noted in clinical practice.
Atrophy of the male mammary gland and hyperplasia of the female mammary gland - These effects were observed in laboratory rats sub-chronically and chronically exposed to deferiprone. The mammary hyperplasia was reversible upon cessation of dosing.	No such effects were noted in studies with non-human primates, and no symptomatic evidence suggestive of such effects has been noted in clinical practice.
Thyroid follicular hypertrophy with diffuse colloidal basophilia - Thyroid follicular hypertrophy with diffuse colloidal basophilia was observed in rats dosed chronically with deferiprone.	No such effects were noted in studies with non-human primates, and no evidence suggestive of thyroidal changes has been noted in clinical practice.

KEY SAFETY FINDINGS (from non-clinical studies)	RELEVANCE TO HUMAN USAGE
Embryotoxicity/Fetotoxicity - Deferiprone was teratogenic and embryotoxic in reproductive studies in non-iron-loaded rats and rabbits at doses as low as 10 and 25 mg/kg/day, respectively. The mechanisms involved are unknown, but may be related to interference with availability of iron to the growing fetus and/or from inhibition of ribonucleotide reductase or other iron-dependent enzymes involved in DNA synthesis or management.	In view of the positive results in non-clinical studies, developmental effects of deferiprone on the embryo and/or fetus cannot be excluded.
Reproductive Toxicity - No effects on fertility or early embryonic development were noted in non-iron-loaded male and female rats that received deferiprone orally for 28 days (males) or 2 weeks (females) prior to mating and until termination (males) or through early gestation (females). In females, an effect on the estrous cycle (delayed time to confirmed mating) was noted at all doses tested.	The risk to humans is unknown, but likely to be low based on the absence of significant reproductive and early embryonic effects in rats.

Module SIII: Clinical trial exposure

The cumulative exposure of subjects in Chiesi -sponsored clinical trials is presented in Tables 3-6. A total of 1,723 subjects were exposed to at least one dose of Ferriprox for a total of 2,249.18 subject-years. Two Chiesi-sponsored clinical trials, LA39-0412 and LA40-0412, evaluated the use of Ferriprox in subjects with impaired renal function and subjects with impaired hepatic function respectively. Chiesi-sponsored clinical trial LA44-0114 evaluated the use of Ferriprox in HIV-positive subjects. The cumulative exposure of special populations to Ferriprox from these three trials is presented in section SIV.3.

Table 3 Clinical trial exposure, by duration

Estimated duration of exposure (at least)	Number of Subjects	Subject-Time (subject-years)
≥ 3 months	986	2229.82
≥ 6 months	855	2180.35
≥ 1 year	656	2023.14
≥ 3 years	222	1123.15

Estimated duration of exposure (at least)	Number of Subjects	Subject-Time (subject-years)
≥ 5 years	108	690.43
≥ 10 years	6	99.18
≥ 15 years	4	75.10

Table 4 Clinical trial exposure, by dose

Dose	Number of Subjects*	Subject-Time* (subject-years)
< 50 mg/kg/day	605	283.69
50 mg/kg/day	102	38.20
75 mg/kg/day	577	1243.28
100 mg/kg/day	439	684.01
Total	**1723**	**2249.18**

*Number of subjects and subject exposure from completed and ongoing clinical studies.
Note: Dose is taken as the maximum dose. Doses between 50 and < than 62.5 are put into the 50 category, doses ≥62.5 up to 87.5 into the 75 category and those greater than 87.5 into the 100 category.

Table 5 Cumulative subject exposure to investigational drug from completed clinical trials, by age and gender

Subject Age*	Number of Subjects			Subject-Time (subject-years)		
	Male	Female	Total	Male	Female	Total
Pre-term newborn infants	0	0	0	0	0	0
Term newborn infants (0 - 27 days)	0	0	0	0	0	0
28 days - 23 months	4	0	4	7.59	0	7.59
2 - 11 years	126	114	240	217.17	207.41	424.58
12 - 16 years	98	83	181	248.97	158.87	407.84
17 - 18 years	59	52	111	128.75	120.48	249.23

Subject Age*	Number of Subjects			Subject-Time (subject-years)		
	Male	Female	Total	Male	Female	Total
19 - 64 years	632	467	1099	498.84	585.30	1084.15
65 - 74 years	14	7	21	8.54	4.65	13.19
75 - 84 years	5	2	7	2.54	0.46	3.00
≥ 85 years	0	0	0	0	0	0
Total	**938**	**725**	**1663**	**1112.4**	**1077.17**	**2189.57**

* For subjects in more than one trial, the age at first exposure to investigational drug.

Table 6 Cumulative subject exposure to investigational drug from completed clinical trials, by racial origin

Racial Group	Number of Subjects	Subject-Time (subject-years)
Caucasian/White	1290	1621.41
Asian	151	287.31
Black/African American/Coloured	131	66.14
Unknown	60	174.32
Multi-Racial	27	37.73
Other	3	0.02
Native American	1	2.65
Total	**1663**	**2189.57**

Module SIV: Populations not studied in clinical trials

The clinical studies conducted on deferiprone are considered to be representative of the target population in the approved indication. The identified sub-populations which were not studied, or which were studied to a limited degree, are described in Table 10. With the exception of paediatric patients, for whom there are now data on the safety and efficacy of Ferriprox, each of these sub-populations correlates to a safety concern included in this RMP as an important identified risk (agranulocytosis) or as missing information (off-label use and in

immunocompromised patients). Based on the information obtained during 18 years of post-marketing experience, the adverse reactions detected during clinical trials are representative of the events reported from the target population.

Table 7 Populations not studied in clinical trials

Population not studied in clinical trials	Reflection in SmPC	Comment
Patients with systemic iron overload other than thalassaemia major	Section 4.1 "Therapeutic indication" states the following: Ferriprox monotherapy is indicated for the treatment of iron overload in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate. Ferriprox in combination with another chelator (see section 4.4) is indicated in patients with thalassaemia major when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction (see section 4.1).	Chiesi has conducted a study (LA38-0411) to evaluate the efficacy and safety of Ferriprox® for the treatment of transfusional iron overload in patients with sickle cell disease or other anemias. The study was concluded on 20 APR 2019 and the study report was finalized on 20 September 2019.
Paediatric patients	Section 4.2 "Posology and method of administration" states the following: There are limited data on the use of deferiprone in children between 6 and 10 years of age, and no data on deferiprone use in children under 6 years of age.	In the pre-authorisation phase Ferriprox had been studied in a limited number of children between the age of 6 years and 10 years and in no children under the age of 6 years. Since the time of authorisation, a number of studies have included paediatric patients and there are now safety and efficacy data in 462 children (<18 years of age at first exposure to deferiprone) participating in clinical trials, including 75 children less than 6 years old. The total drug exposure of this cohort is 898.88 patient-years.
Use in immunocompromised	Section 4.4 "Special warnings and precautions for use" states the	Chiesi conducted a short-term study to evaluate the safety and tolerability

Population not studied in clinical trials	Reflection in SmPC	Comment
patients	following: No data are available on the use of deferiprone in HIV positive or in other immunocompromised patients. Given that deferiprone can be associated with neutropenia and agranulocytosis, therapy in immunocompromised patients should not be initiated unless potential benefits outweigh potential risks.	of orally administered high doses of deferiprone (33 or 50 mg tid) in 14 patients with HIV; however, insufficient data on immune-compromised patients exposed to long-term use of Ferriprox is available to fully evaluate the risk of Ferriprox use in immunocompromised patients. A proof of concept study evaluating the safety, antiretroviral activity and pharmacokinetics of an intravenously administered deferiprone in treatment-naïve HIV patients was completed on 30 Mar 2016. All participants received twice-daily (b.i.d.) treatment for 10 days, consisting of two 1-hour infusions administered approximately 10 hours apart. There were two sequential cohorts, with Cohort 1 receiving 1500 mg IV DFP (n=10) or matching placebo (n=5), and Cohort 2 receiving 2500 mg IV DFP (n=10) or matching placebo (n=5). There were no significant differences between the treatment groups in the rate of any AEs, the intensity of any AEs, or the rate of ADRs.

Population not studied in clinical trials	Reflection in SmPC	Comment
Patients who develop agranulocytosis following deferiprone therapy	Section 4.4 "Special warnings and precautions for use" states the following: Limited information is available regarding rechallenge. Therefore, in the event of neutropenia, rechallenge is not recommended. In the event of agranulocytosis, rechallenge is contraindicated.	Three patients from Chiesi's clinical trials (data collected between 1993 and 31 August 2014) were rechallenged following an event of agranulocytosis. Agranulocytosis recurred in two patients. Neutropenia occurred in the third patient. Fifteen reports of rechallenge, following an event of agranulocytosis, have been reported from post-marketing surveillance. Follow-up data is available in 12 of the 15 reports. Recurrence was observed in 9 (75%).[63] Registries of patients who experienced agranulocytosis during post marketing use of Ferriprox in the United States of America (USA) and in Canada are in place. The analysis of registry data in the USA and Canada is expected to be completed in October 2018 and in March 2020, respectively. It should be noted that all reported cases of agranulocytosis from worldwide sources are included in the analysis.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

This version of the RMP is not the initial RMP submission as Ferriprox was registered in the European Union on 25 Aug 1999. The summary of populations not studied in clinical trials is presented above in Table 7.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme 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 or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 8 Clinical trial exposure of special populations from completed clinical trials

Special population	Number of Subjects	Subject-Time (subject-years)
Pregnant women	0	0
Lactating women	0	0
Renal impairment	24	0.07
Hepatic impairment	14	0.04
Cardiac impairment	0	0
Subpopulations with genetic polymorphism	0	0
Immunocompromised*	34	0.73

* Patients were asymptomatic and HIV-positive.

Module SV: Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Post-authorisation exposure to Ferriprox has been calculated following the methodology used in previous PSURs, i.e., derived from the cumulative worldwide sales and a defined daily dose of 75 mg/kg. For tablet formulations (500 and 1000 mg), one patient-year of exposure is considered equivalent to1,643,625 mg of sales, as follows: at an average patient weight of 60 kg and the defined daily dose of 75 mg/kg, the daily dose requirement is 4500 mg, taken 365.25 days per year. For the oral solution (100 mg/mL), one patient-year of exposure is considered equivalent to 1,095,750 mg of sales; since it is expected that most use of this formulation is by paediatric patients, a lower average patient weight is used than for the tablet formulations, as follows: at an average patient weight of 40 kg and the defined daily dose of 75 mg/kg, the daily dose requirement is 3000 mg, taken 365.25 days per year. It should be noted that the cumulative estimate of exposure is based upon sales since Apr 2001, as this is the date of earliest reliable data.

SV.1.2 Exposure

As of 31 May 2022, there had been an estimated 100.869,82 patient-years of exposure to Ferriprox (inclusive of all formulations) in the post-authorization setting. Additional information on the cumulative post-authorisation exposure to Ferriprox is presented in Table 11. Of the cumulative 100.869,82 patient-years of exposure to Ferriprox in the post-authorization setting, 64.925,35 patient-years occurred in the EU and 35.944,47 in Extra-EU countries.

It is not possible to estimate the absolute number of patients exposed to Ferriprox in the EU post-marketing setting, or to stratify exposure data based on patients' primary diagnosis, age, sex or dose prescribed, as no patient registry is maintained. The provision of overall estimates of post-authorisation exposure in patient-years, based upon a defined daily dose (as described above), remains as the most accurate alternative approach.

Table SV.1: Exposure table by indication by region

Table 9 Cumulative exposure from marketing experience, by region or country expressed in patient-years

Indication	Sex			Age (years)					Dose (mg/kg/day)				Form		Region	
	Male	Female	Unknown	0 - 2	>2 - 16	> 16-65	> 65	Unknown	< 75	75-100	> 100	Unknown	Tablet	Oral solution	EU	Non-EU
All	Not available			Not available					Not available				92.611,37	8.258,45	64.925,35	35.944,47

Post-authorisation use in populations not studied in clinical trials

Data on the post-authorisation use of Ferriprox in special populations is not available to Chiesi Farmaceutici S.p.A.. Chiesi Farmaceutici S.p.A.. has not become aware of any pattern of use of Ferriprox that is considered important to the interpretation of safety data, or which has indicated a safety signal.

Post-authorisation off-label use

In the EU, Ferriprox 500 mg and 1000 mg film-coated tablets and Ferriprox 100 mg/mL oral solution are indicated for the treatment of iron overload in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate'. Ferriprox in combination with another chelator is indicated in patients with thalassaemia major when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction. In Turkey and Kuwait, Ferriprox is indicated as a first-line treatment for iron overload in patients with thalassaemia major and thalassaemia, respectively. In the USA and Canada, Ferriprox film coated tabletsis indicated for the treatment of transfusional iron overload in adult and pediatric patients 8 years of age and older with thalassemia syndromes, sickle cell disease or other anemias, whereas the oral solution has the same indications but in a population of pediatric patients 3 years of age and older. .. In the territories where Ferriprox is approved as second-line therapy, first-line therapy with Ferriprox would constitute off-label use. It is thought that such first-line use does occur, but there is no reason to anticipate that this would be associated with increased risk compared with second-line use.

In some countries (e.g. US, Turkey, Brazil) Ferriprox is approved for treating iron overload in other associated conditions including sickle cell disease and myelodysplastic syndrome, or in patients with hereditary (primary) haemochromatosis.

Deferoxamine is indicated for use in aluminum overload of end-stage renal failure. This off-label use of Ferriprox is considered possible, but there have been no reports implicating the use of Ferriprox in patients with this condition.

Prescribers have access to the regulatory-approved product label, which should be used to make well-informed prescribing decisions based on the best available estimate of the benefit/risk ratio.

It is not possible to estimate the absolute number of patients exposed to Ferriprox in the post-marketing setting, by indication (including first/second line use information), as no patient registry is maintained outside of the USA and Canada. Based on current knowledge of patterns of off-label use, no significant impact on public health safety is anticipated.

Module SVI: Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Ferriprox at its recommended therapeutic dose is thought to have no potential for abuse.

Module SVII: Identified and potential risks

Potential for harm from overdose

For patients with a body weight of 40 kg, the maximum recommended therapeutic dose is eight 500 mg tablets, or four 1000 mg tablets, or 40 mL oral solution per day. For a body weight of 60 kg, this increases to twelve tablets, six tablets or 60 mL a day, respectively. The likelihood of a significant inadvertent overdose seems small when so many tablets need to be taken therapeutically. In small children, the large size of the tablets makes accidental overdosing unlikely, and sucking the tablets will rapidly produce an unpleasant taste, limiting the risks from inadvertent exposure.

The introduction of the liquid presentation might have increased the risk of accidental overdose, and this would be a particular consideration for young children. However, the bitter taste of the oral solution is also considered a limiting factor for inadvertent overdose.

There is no specific antidote to Ferriprox overdose

As of 31 May 2022 and during the 20 plus years that Ferriprox has been commercially available, Chiesi has received reports of a total of twelve cases of overdose involving patients receiving greater than the maximum recommended dose of 100 mg/kg/day or their prescribed dose. Six of them were not associated with any adverse events. Five of these six cases were reported in adult patients. One patient took Ferriprox at a dose of 6000 mg/day for one month instead of the correct dose of 3000 mg/day. The second patient accidentally took one extra dose of 2000 mg on one day; the prescribed dose was 73 mg/kg/day (6000 mg/day in three divided doses). The total dose in this patient was 98 mg/kg on that single day, i.e., the accidental extra dose did not result in the patient exceeding the maximum approved dose of 100 mg/kg/day. The third case concerned an adult patient (69 kg body weight), who consumed [redacted] of Ferriprox (equivalent to a dose of [redacted]) in an attempt to commit suicide after experiencing a psychotic episode due to an intense argument with her partner. The patient was admitted to the hospital, where gastric lavage was performed. The patient did not experience any clinical symptoms while in the hospital. The fourth case was in an adult patient, prescribed a dose of 91 mg/kg/day (3750 mg/day in 3 divided doses). The patient accidentally took a single additional dose of Ferriprox on one day; instead of 3 doses, the patient took 4 doses. On the following day, the patient skipped the morning and the afternoon dose , the patient continued taking Ferriprox as prescribed. The patient did not experience any adverse reactions associated with the accidental overdose.

In the fifth case, the parents accidentally administered double the prescribed dose to their child. The prescribed dose was not specified at the time of the report. In the sixth case the patient was referred to have taken Ferriprox ad a dose higher than the maximum indicated as per label, although no additional details were provided. Regardless, the event was not associated with any adverse event.

Of the remaining six cases of overdose:

Two patients were children who had been voluntarily prescribed approximately 2.5 times the maximum recommended dose for up to more than 1 year. Neurological disorders (such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, hand movements and axial hypotonia) were observed in both children. The neurological disorders progressively regressed after Ferriprox discontinuation.

One adult patient, prescribed a dose of 4,500 mg/day (as three doses of 1,500 mg), had incorrectly taken 4,500 mg three times daily (for a total dose of 13,500 mg/day or 255 mg/kg/day) for approximately one month, when the patient experienced agranulocytosis and elevated ALT. The events resolved upon discontinuation of Ferriprox. The patient was subsequently re-challenged with the correct dose and agranulocytosis reoccurred.

Another adult patient, reported to have taken a total daily dose of 16,000 mg/day (186 mg/kg/day) for an unknown period of time, experienced fatigue and somnolence. The dose was corrected and decreased to 70 mg/kg/day on an unspecified date. The outcome of the events was unknown at the time of the last follow-up report.

In an adult patient Ferriprox was prescribed at a dose of of 170 mg/kg. In this case the event was indicated also as a medication error; however, the circumstances leading to the error, and whether the dose was administered as a single dose or a daily dose were not reported clearly. The patient experienced neutropenia (ANC values not reported) on the same day the patient received the first (single) dose of Ferriprox. The event resolved following Ferriprox therapy interruption. While neutropenia is observed during Ferriprox use, its causality to Ferriprox has been questioned given the observed frequency of neutropenia in patients not treated with Ferriprox. No previous cases of neutropenia have been reported after a single dose of Ferriprox. In the twelfth and last case, an adult male patient experienced a severe case of kidney stones (kidney stones), cold symptoms, after taking Ferriprox at higher than the maximum recommended dose (drug overdose). The event resolved without further complications for the patient.

Potential for transmission of infectious agents

There is no potential for transmission of infectious agents. In particular, neither of the two tablet formulations nor the liquid formulation contains protein or protein-derived active or excipients, nor any material of bovine origin.

Potential for medication errors

There is minimal to no potential for medication errors.

Potential for off-label use

In the EU, Ferriprox 500 mg and 1000 mg film-coated tablets and Ferriprox 100 mg/mL oral solution are indicated as monotherapy for the treatment of iron overload in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate. Ferriprox in

combination with another chelator is indicated in patients with thalassaemia major when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction. In Turkey and Kuwait, Ferriprox is indicated as a first-line treatment for iron overload in patients with thalassaemia major and thalassaemia, respectively.

In the USA and Canada, Ferriprox film coated tabletsis indicated for the treatment of transfusional iron overload in adult and pediatric patients 8 years of age and older with thalassemia syndromes, sickle cell disease or other anemias, whereas the oral solution has the same indications but in a population of pediatric patients 3 years of age and older. In the territories where Ferriprox is approved as second-line therapy, first-line therapy with Ferriprox would constitute off-label use. It is thought that such first-line use does occur, but there is no reason to anticipate that this would be associated with increased risk compared with second-line use.

In some countries (e.g. US, Turkey, Brazil) Ferriprox is approved for treating iron overload in other associated conditions including sickle cell disease and myelodysplastic syndrome, or in patients with hereditary (primary) haemochromatosis.

A pilot study of deferiprone in patients with Friedreich's Ataxia (FRDA) showed significant reductions in brain iron and a modest improvement in neurological symptoms.[10] Based on the results of this study and on non-clinical data indicating that deferiprone might be a therapeutic option for patients with FRDA, ApoPharma has conducted a clinical development program to determine the safety and efficacy of deferiprone for the treatment of these patients. Results from this study indicate that deferiprone at 20 or 40 mg/kg/day taken b.i.d. (two equal doses at each intake) was tolerated by both adult and minor subjects with FRDA. Deferiprone at 60 mg/kg/day was associated with worsening ataxia in some patients, which improved upon discontinuation of the drug. It is possible that, Ferriprox might be used off-label in patients with FRDA. For this patient population, in addition to the risks associated with the use of Ferriprox in patients with thalassaemia, it is possible that its use might be associated with a dose-dependent decline in endogenous iron levels, leading to iron-deficiency anaemia. It is anticipated that the anaemia and iron deficiency would be reversible upon discontinuation of Ferriprox therapy.

The drug might also be used for treatment of neurological disorders associated with regional or localized brain iron accumulation, such as pantothenate kinase-associated neurodegeneration (PKAN), superficial siderosis and Parkinson's disease. Based upon spontaneous reports of AEs, there is no reason to suggest that the use of deferiprone in these conditions is associated with identified or important potential risk other than those for patients with thalassaemia.

Clinical trials are ongoing to determine the benefit/risk ratio of deferiprone for the treatment of: iron overload in patients with sickle cell disease or other anaemias, patients with PKAN (a condition of localized iron accumulation), and patients with Parkinson's disease.

It is also possible that Ferriprox might be used in patients with acute iron poisoning and chronic poisoning with other metals. It might also be used for aluminum overload of end-stage renal failure, as this is an indication for use of deferoxamine. These off-label use of Ferriprox are considered possible, but there have been no reports indicating that Ferriprox has been used in patients with these conditions.

Prescribers have access to the regulatory-approved product label, which should be used to make well-informed prescribing decisions based on the best available estimate of the benefit/risk ratio.

Specific paediatric issues

Issues identified in paediatric investigation plans

Not applicable

Potential for paediatric off-label use

Ferriprox is not contra-indicated in the paediatric population, and at the time of approval, patients as young as 6 years of age had been studied in company-sponsored clinical trials. Although the SmPC specifically states that Ferriprox has not been studied in children under 6 years of age, several studies by ApoPharma and by independent investigators have now evaluated the safety and efficacy of deferiprone for the treatment of iron overload in paediatric patients as young as 1 year old.[5, 16, 39, 40, 42, 65] Data from 222 paediatric patients participating in clinical trials, including 61 children less than 6 years old were analysed, and the results are discussed below.

ApoPharma conducted analysis comparing the proportion of patients in the adult and paediatric groups experiencing at least one AE and at least one ADR. The mean length of follow-up for adults is 2.0 years, which is similar to that for paediatrics (2.2 years). The proportions of patients in the adult and paediatric groups experiencing at least one AE are 85.5% (359/420) and 80.6% (179/222), respectively. They are not significantly different (p=0.1163). Similarly, the proportions of patients in the adult and paediatric groups experiencing at least one ADR are 55.5% (233/420) and 54.1% (120/222), respectively. They are not significantly different (p=0.7394).

The rate of AEs for adults is 6.0/patient-year and for paediatrics it is 4.0/patient-year; they are statistically significantly different (p<0.0001). The rate of ADRs for adults is 1.3/patient-year and for paediatrics is 0.90/patient-year and they are statistically significantly different (p<0.0001).

The overall conclusion is that the occurrence of AEs or ADRs in paediatric patients is not more frequent than in adults.

Furthermore, based on a PK study of deferiprone in children under 6 years of age, a dosing regimen of 25 mg/kg t.i.d. is recommended in children aged <6 years, with the possibility of titration up to 33.3 mg/kg t.i.d.[7]

Pharmacological class effects

There are no known pharmacological class effects of iron chelators. In RMP v 7.0, the information available on the risks of interaction with Vitamin C, lactation toxicity and use in pregnancy was described as insufficient to determine whether the risk is common among the pharmacological class. The lack of sufficient evidence was discussed in RMP 7.0.

Increased liver function test values have been reported in some patients taking deferiprone. There is no clear evidence of the increased alanine aminotransferase (ALT) being dose dependent. In the majority of these patients, the increase was asymptomatic and transient, and returned to baseline without discontinuation or decreasing the dose of deferiprone. Liver function test elevations have been observed in some patients taking deferasirox; however, deferoxamine is not associated with an increase in serum liver enzymes. Increased liver enzymes is, therefore, not considered a pharmacological class effect.

The risks of allergic reactions and skin disorders were the two risks included as common to all three available iron chelators (deferiprone, deferasirox and deferoxamine) in RMP 7.0, RMP 8.0 and RMP 8.1; both these risks are included in this RMP (Table10) and are listed as important identified risks of Ferriprox. Blood disorders may also be a pharmacological class risk, but different disorders have been reported during use of each iron chelator (e.g., neutropenia and agranulocytosis during use of deferiprone; thrombocytopenia and leukopenia during use of deferoxamine; and thrombocytopenia, leukopenia and pancytopenia during use of deferasirox); the specific risks of agranulocytosis and neutropenia are not class effects.

Table 10 Pharmacological class effects included as important identified risks of Ferriprox therapy

Risk	Frequency seen in clinical trials of deferiprone (DFP)	Frequency seen with other iron chelating agents (deferoxamine (DFO) and deferasirox (DFX))	Comment
Allergic reactions	1.2%	DFO: Anaphylactic shock, anaphylactic reactions, angioneurotic oedema and allergic reaction are very rare (≤1/10,000)	DFO: There is a contraindication for hypersensitivity to desferrioxamine mesilate unless the patients can be desensitised. DFX: Hypersensitivity reactions (including

Risk	Frequency seen in clinical trials of deferiprone (DFP)	Frequency seen with other iron chelating agents (deferoxamine (DFO) and deferasirox (DFX))	Comment
		DFX: Not known	anaphylaxis and angioedema) have been reported during post marketing experience. There is a contraindication for hypersensitivity to the active substance or to any of the excipients. As with the other iron chelators, there is a contraindication to Ferriprox use for hypersensitivity to the active substance or to any of the excipients. Based on the available information, allergic reactions are observed with each member of the pharmacological class, but it is unclear if they are a pharmacological class effect.
Skin disorders	12.4%	DFO: Rash generalised is very rare (≤1/10,000) DFX: Rash, pruritus are common (≥ 1/100 to < 1/10), skin rash reported in about 7% of patients; pigmentation disorder is uncommon (≥ 1/1,000 to < 1/100); and the frequencies of other skin and subcutaneous tissue disorders are not known	DFX: Skin rashes may appear during treatment. The rashes resolve spontaneously in most cases. Leukocytoclastic vasculitis, urticarial, erythema multiforme, and alopecia have also been reported during post marketing experience. Based on the available information, skin reactions are observed with each member of the pharmacological class but it is unclear if they are a pharmacological class effect.

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

This version of the RMP is not the initial RMP submission as Ferriprox was registered in the European Union on 25 Aug 1999. The summary of safety concerns is tabulated in section SVIII. Details of important identified risks, important potential risks, and missing information are presented in section SVII.3.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Since the last update there were no safety concerns that were newly identified, removed, or re-classified.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

The characteristics of each important identified risk, based on cumulative data are presented in Table 11 through Table 13. Details of the unique Preferred Terms included in the reporting frequencies of each risk are presented in Annex 7.1.

Table 11 Important identified risk: Agranulocytosis (absolute neutrophil count less than 0.5 x 10^9/L)

Frequency	273 events (24 events from clinical trials and 249 ADRs from post-marketing sources)
Extent of use	100.869,82 The extent of use has been estimated as the total exposure to Ferriprox in clinical trials and marketing experience, as described in Modules SIII and SV.
Estimate of relative risk (RR)	Unknown The rate of agranulocytosis in a population with untreated thalassaemia major has not been described in the published literature.
Estimate of absolute risk (R)	0.25/100 patient-years Note that an estimate of the absolute rate is provided, as the number of individual patients exposed to Ferriprox is not available from global marketing experience. A limitation of this approach is that it does not account for possible differences in reporting rates between clinical trials and post-marketing. This rate is consistent with the rate presented in the analysis of data obtained from 1999 to 31 August 2014 by Tricta et al[63], which described that the rate of agranulocytosis was 1.1 per 100 patient-years of drug exposure in clinical trials and 0.24 per 100 patient-years of post-marketing exposure.
Risk period	No data regarding the duration of Ferriprox use by individual patients are available from worldwide post-marketing data. However, based on all available data, the risk of Ferriprox-induced agranulocytosis is greatest during the first year of therapy, and particularly during the first six months. In the analysis by Tricta et al, 61% of agranulocytosis cases occurred during the first 6 months of therapy and 78% during the first year. Median time to occurrence of agranulocytosis was 5 months (9 days–17 years) from the start of therapy. The incidence of agranulocytosis declined with increasing duration of therapy[63].

Impact on the individual patient	Agranulocytosis is the most serious and important identified risk associated with Ferriprox treatment. Although events generally resolve upon interruption of therapy, without early detection and appropriate management potentially fatal complications of agranulocytosis can occur. Mortality is due to infections that complicate agranulocytosis. The reported agranulocytosis fatality rate was 0% in clinical trials versus 10.5% (15/143) in the post-marketing setting.[14]
Public health impact	Due to the limited size of the patient population treated and the low incidence of the condition among patients treated with Ferriprox, there is no significant public health impact.
Risk factors	The risk of Ferriprox-induced agranulocytosis is greatest during the first year of therapy, and particularly during the first six months of therapy. Although no formal studies have been conducted in patients with Diamond-Blackfan anaemia, the available data suggest that Ferriprox-induced agranulocytosis may be more frequent and severe in these patients than in patients with other transfusion-dependent iron overload conditions. Clinical findings suggest that Ferriprox-induced agranulocytosis is idiosyncratic and is not dose-related. The results of a 2010 survey did not indicate statistically significant differences in the incidence or rate of agranulocytosis between paediatric and adult patients with thalassaemia administered Ferriprox in the EU. Tricta et al. 2016 evaluated age as a risk factor. Analysis of data obtained from 1999 to 31 August 2014 showed that 7 (2.7%) of 263 paediatric patients (<16 years old) experienced agranulocytosis versus 10 (1.2%) of 864 adults treated with deferiprone in CT (P =0.08).[63] It was also demonstrated that agranulocytosis occurred three times more often in females than in males.[63]
Preventability	There are no measures to predict those patients who will experience agranulocytosis during Ferriprox therapy. Although global prescribing information (including the current SmPC) recommends discontinuation of Ferriprox at the earliest sign of neutropenia, continued therapy during episodes of mild neutropenia has not been associated with progression to agranulocytosis. Periodic monitoring of the ANC may allow prompt detection of the asymptomatic onset of agranulocytosis and reduction of the occurrence of potentially fatal complications but does not prevent agranulocytosis from occurring.

Reversibility	Agranulocytosis events generally resolve within a median time of 11 days upon interruption of Ferriprox therapy. Of the 21 events of agranulocytosis reported from clinical trials as of 31 Aug 2017, 19 (90.5%) were noted as having recovered upon interruption of deferiprone therapy. The mean duration until recovery (recovery date is when ANC $\geq 1.5x10^9$/L) was 14.7 days (min: 4 days; max: 83 days). The mean duration until an ANC of $\geq 0.5x10^9$/L was achieved was 5.7 days (min: 1 day; max: 13 days).
Potential mechanism	The mechanism of development of agranulocytosis during therapy with Ferriprox remains obscure.
Evidence source(s) and strengths	Information about the risk of agranulocytosis is available from clinical trials, post-marketing experience and scientific literature. Although there are remaining gaps in knowledge about the characteristics of this risk, the above information is supported by strong evidence. 1. European Agranulocytosis Survey Final Report, 2011. 2. Data on file, studies LA30-0307 and LA35-PM. 3. Arneborn P, Palmblad J. Drug-induced neutropenia – A survey for Stockholm 1973-1978. Acta Med Scand. 1982; 212: 289-92.(4) 4. Cohen AR, Galanello R, Piga A, DiPalma A, Vullo C, Tricta F. Safety profile of the oral iron chelator deferiprone: a multicentre study. Br J Haematol. 2000; 108: 305-12.(18) 5. Palmblad J. Drug-induced neutropenias: now and then. Arch Int Med. 1999; 159: 2745.(49) 6. Tricta F, Uetrecht J, Galanello R, Connelly J, Rozova A, Spino M, Palmblad J. Deferiprone-induced agranulocytosis: 20 years of clinical observations. Am J Hematol. 2016 Oct;91(10):1026-31(63)

Table 12 Important identified risk: Neutropenia (absolute neutrophil count less than 1.5 x 10^9/L but not less than 0.5 x 10^9/L)

Frequency	540 events (111 events from clinical trials (including 2 on blinded therapy) and 429 ADRs from post-marketing sources)
Extent of use	100.869,82 The extent of use has been estimated as the total exposure to Ferriprox in clinical trials and marketing experience, as described in Modules SIII and SV.
Estimate of relative risk (RR)	Unknown Neutropenia is a common event in thalassaemia patients, particularly in those with hypersplenism. Comparable rates of neutropenia were reported in Ferriprox- and deferoxamine-treated subjects in ApoPharma clinical trials (3.2 and 4.2/100 patient-years, respectively), despite more frequent monitoring of neutrophil counts during Ferriprox therapy which would have detected more episodes of transient neutropenia. The periodic monitoring of the neutrophil counts increases the probability of detecting transient episodes of mild or moderate neutropenia, which often would have been undetected with less frequent monitoring.
Estimate of absolute risk (R)	0.44/100 patient-years Note that an estimate of the absolute rate is provided, as the number of individual patients exposed to Ferriprox is not available from marketing experience. A limitation of this approach is that it does not account for possible differences in reporting rates between clinical trials and post-marketing; however, the data required to do this are not available.
Risk period	No data regarding the duration of Ferriprox use by individual patients are available. However, in clinical trials, the majority of neutropenia cases occurred within the first two years of therapy, which could be the product of the weekly monitoring of the neutrophil count upon initiation of deferiprone and of discontinuation of therapy upon diagnosis of an episode of neutropenia.
Impact on the individual patient	Neutropenia is generally transient and resolves despite continued deferiprone therapy. Neutropenia is usually not associated with morbidity unless the absolute neutrophil count drops to a level classified as agranulocytosis (see agranulocytosis). Although discontinuation of Ferriprox at the earliest sign of neutropenia is recommended, continued therapy during episodes of mild neutropenia has not been associated with progression to agranulocytosis.

Public health impact	Due to the limited size of the patient population treated and the low incidence of the condition among patients treated with Ferriprox, the risk has a negligible impact on overall public health.
Risk factors	In clinical trials, the majority of neutropenia cases occurred within the first two years of therapy. Clinical findings suggest that some of the neutropenia episodes observed during Ferriprox therapy are not drug-related. Neutropenia occurred at comparable rates in deferiprone- and deferoxamine-treated subjects in ApoPharma clinical trials. The results of a 2010 survey did not indicate statistically significant differences in the incidence or rate of neutropenia between paediatric and adult patients with thalassaemia administered Ferriprox in the EU. Analysis by Tricta et al revealed that neutropenia incidence in CT suggested age dependency: 24 (9.1%) of 263 paediatric patients compared to 38 (4.4%) of 864 adults (P=0.003)[63], which is consistent with the higher occurrence of neutropenia in healthy children than in adults.[31]
Preventability	Periodic monitoring of the ANC may allow prompt detection of neutropenia. The patient's absolute neutrophil count (ANC) should be monitored every week during the first year of therapy. For patients whose Ferriprox has not been interrupted during the first year of therapy due to any decrease in the neutrophil count, the frequency of ANC monitoring may be extended to the patient's blood transfusion interval (every 2-4 weeks) after one year of deferiprone therapy. The change from weekly ANC monitoring to at the time of transfusion visits after 12 months of Ferriprox therapy, should be considered on an individual patient basis, according to the physician's assessment of the patient's understanding of the risk minimization measures required during therapy. Neutropenia in patients treated with Ferriprox or deferoxamine occurs significantly more often in non-splenectomized patients than in patients who have undergone splenectomy. Splenectomy, which used to be frequently performed in thalassaemia major patients, prevents development of hypersplenism and reduces the occurrence of neutropenia and thrombocytopenia.
Reversibility	Neutropenic events generally resolve despite continued Ferriprox therapy.[25]
Potential mechanism	The mechanism of development of neutropenia during therapy with Ferriprox remains obscure.

Evidence source(s) and strengths	Information about the risk of neutropenia is available from clinical trials, post-marketing experience and scientific literature. Although there are remaining gaps in knowledge about the characteristics of this risk, the above information is supported by strong evidence. 1. European Agranulocytosis Survey Final Report, 2011. 2. Data on file. 3. Arneborn P, Palmblad J. Drug-induced neutropenia – A survey for Stockholm 1973-1978. Acta Med Scand. 1982; 212: 289-92.(4) 4. Cohen AR, Galanello R, Piga A, DiPalma A, Vullo C, Tricta F. Safety profile of the oral iron chelator deferiprone: a multicentre study. Br J Haematol. 2000; 108: 305-12.(18) 5. Orkin SH, Nathan DG. The thalassemias. In: Nathan DG, Orkin SH, editors. Hematology of infancy and childhood. Philadelphia. W.B. Saunders Company; 1998.(47) 6. Palmblad J. Drug-induced neutropenias: now and then. Arch Int Med. 1999; 159: 2745.(49) 7. El-Beshlawy A.M., El-Alfy M.S., Sari T.T., Chan L.L., Tricta F. Continuation of deferiprone therapy in patients with mild neutropenia may not lead to a more severe drop in neutrophil count. Eur J Haematol. 2014 Apr;92(4):337-40. (25) 8. Tricta F, Uetrecht J, Galanello R, Connelly J, Rozova A, Spino M, Palmblad J. Deferiprone-induced agranulocytosis: 20 years of clinical observations. Am J Hematol. 2016 Oct;91(10):1026-31.(63) 9. Hsieh MM, Everhart JE, Byrd-Holt DD, Tisdale JF, Rodgers GP. Prevalence of neutropenia in the U.S. population: age, sex, smoking status, and ethnic differences. Ann Intern Med. 2007 Apr 3;146(7):486-92.(31)

Table 13 Important identified risk: Use in pregnancy

Frequency	50 cases of pregnancies (6 pregnancies resulted in spontaneous abortion, 2 pregnancies resulted in an infant with anomalies*) 10 cases of pregnancies of partners of male patients treated with Ferriprox (1 pregnancy resulted in intrauterine death of twins, 1 pregnancy resulted in an infant with hypospadias)
Extent of use	100.869,82 The extent of use has been estimated as the total exposure to Ferriprox in clinical trials and marketing experience, as described in Modules SIII and SV.
Estimate of relative risk (RR)	Unknown Until recently, pregnancies in patients with thalassaemia major

	were uncommon due to iron-induced hypogonadism. Limited information is available on the rate of abnormal pregnancies in a population with untreated thalassaemia major.
Estimate of absolute risk (R)	Unknown Demographic information about individual patients exposed to Ferriprox is not available from marketing experience. It is, therefore, not possible to estimate the absolute risk in the at-risk population.
Risk period	The risk period is limited to the duration of *in utero* exposure to Ferriprox in female patients.
Impact on the individual patient	At present, a limited amount of data from the use of Ferriprox in pregnant women is available. Embryotoxicity and teratogenicity in non-iron-loaded animals suggest that deferiprone may cause fetal harm when administered to a pregnant woman. Based on data from animal studies, deferiprone use during pregnancy may affect fetal growth or development. In addition, endocrine and cardiac complications of iron overload may cause pregnancy complications in women with thalassaemia.
Public health impact	Due to the limited size of the patient population treated and the low number of pregnancies among patients treated with Ferriprox, the risk has a negligible impact on overall public health.
Risk factors	Females of childbearing age. Hypogonadotrophic hypogonadism is common in young adults with thalassaemia major and it thought to contribute to low fertility in this population. Due to the genotoxic potential of deferiprone, women of childbearing potential are recommended to use effective contraceptive measures while being treated with Ferriprox and for 6 months following the completion of treatment. Men are recommended to use effective contraceptive measures and to not father a child while receiving Ferriprox and for 3 months following the completion of treatment.
Preventability	Since the risk to humans is unknown, Ferriprox use is contraindicated during pregnancy or breastfeeding. Pregnant women must be advised to immediately stop taking Ferriprox. Women of child-bearing potential are recommended to use effective contraceptive measures and avoid becoming pregnant while being treated with Ferriprox and for 6 months following the

	completion of treatment. Men are recommended to use effective contraceptive measures and to not father a child while receiving Ferriprox and for 3 months following the completion of treatment.
Reversibility	Not Applicable
Potential mechanism	Based on data from animal studies, deferiprone use during pregnancy may affect fetal growth or development. The mechanism of these effects has not been clearly established.
Evidence source(s) and strengths	Information about the risk of deferiprone use during pregnancy is collected from non-clinical studies, clinical trials, post-marketing experience and scientific literature. 1. Data on file. 2. Cunningham MJ, Macklin EA, Muraca G, Neufeld EJ. Successful pregnancy in thalassemia major women in the Thalassemia Clinical Research Network. Paediatr Res. 2004; 55(4 Suppl S): 294A.(20) 3. De Sanctis V, Perera D, Katz M, Fortini M, Gamberini MR. Spermatozoal DNA damage in patients with B Thalassaemia Syndromes. Pediatr Endocrinol Rev. 2008 Oct;6 Suppl 1:185-9.(21) 4. Karagiorga-Lagana M. Fertility in thalassemia: the Greek experience. J Pediatr Endocrinol Metab. 1998; 11(Suppl 3): 945-51.(32) 5. Pafumi C, Farina M, Pernicone G, Bandiera S, Russo A, Mangiafico L, et al. At term pregnancies in transfusion-dependent beta-thalassemic women. Clin Exp Obstet Gynecol. 2000; 27: 185-7.(48) 6. Skordis N, Christou S, Koliou M, Pavlides N, Angastiniotis M. Fertility in female patients with thalassemia. J Pediatr Endocrinol Metab. 1998; 11 (Suppl 3): 935-43.(58) 7. Cassinerio E, Baldini IM, Alameddine RS, Marcon A, Borroni R, Ossola W, Taher A, Cappellini MD. Pregnancy in patients with thalassemia major: a cohort study and conclusions for an adequate care management approach. Ann Hematol. 2017 Jun;96(6):1015-1021. doi: 10.1007/s00277-017-2979-9.(13)

* Infant with anal atresia, nephroptosis, ventricular septal defect, hemivertebra and urethral fistula.

SVII.3.2. Presentation of the missing information

None.

Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Important identified risks	• Agranulocytosis • Neutropenia • Use in pregnancy

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for agranulocytosis and neutropenia:

Chiesi utilizes a specific questionnaire to collect detailed information about each reported event of agranulocytosis and neutropenia. A copy of this questionnaire is provided in Annex 4.

Other forms of routine pharmacovigilance activities:

The objective of the routine pharmacovigilance program conducted by the Pharmacovigilance Department at Chiesi is to systematically review post-marketing safety data from multiple sources to detect and evaluate changes suggestive of new safety concerns. Standard pharmacovigilance practices include the following:

Real-time reviews of single cases.

Scheduled reviews of aggregate data from ARGUS (safety database used by Chiesi) to identify relevant changes in reporting frequency or patterns of adverse events.

Aggregate reviews, at pre-specified intervals, of product quality complaint cases with associated adverse events and lot numbers, to identify safety signals related to product quality and manufacturing.

Analysis of the MAH's non-clinical, clinical and epidemiological study results.

Both medically confirmed and medically unconfirmed reports are included in these reviews.

The system, processes and procedures for routine pharmacovigilance used by Chiesi are provided in detail in Chiesi – Pharmacovigilance System Master File (data on file). This includes a description of the quality system that is in place. It covers the mechanisms for receipt, handling, recording and evaluation of individual case safety reports and the processes for expedited reporting in accordance with prevailing regulations. The description of the pharmacovigilance system also provides an account of literature screening, the applicable routine signal detection and review activities and the oversight function afforded by the European Qualified Person for Pharmacovigilance. The processes for preparation, review and submission of periodic safety update reports are summarized.

III.2 Additional pharmacovigilance activities

Studies that are currently underway to evaluate particular safety concerns are described in Table III.3. The protocols for these additional pharmacovigilance activities are provided in Annex 3.

PMR 1828-2: Registry for enhanced pharmacovigilance of agranulocytosis in patients treated with Ferriprox®

Study short name and title:

PMR 1828-2: Registry for enhanced pharmacovigilance of agranulocytosis in patients treated with Ferriprox®

Rationale and study objectives:

This study was initiated as per FDA's requirement in its approval of Ferriprox. The objective of the study is to collect and analyse cases of agranulocytosis as well as neutropenia or infections that were fatal or led to hospitalization in patients treated with Ferriprox.

Study design:

A registry of Ferriprox prescribers and users.

Study population:

All US and Canadian patients receiving a Ferriprox prescription within the program period will be part of the registry.

Milestones:

US FDA:

Report	Data lock point	Report submission
Annual Interim Report #1	31 March 2013	30 April 2013
Annual Interim Report #2	31 March 2014	30 April 2014
Annual Interim Report #3	31 March 2015	30 April 2015
Annual Interim Report #4	31 March 2016	30 April 2016
Annual Interim Report #5	31 March 2017	30 April 2017
Annual Interim Report #6	31 March 2018	30 April 2018
Final Report	31 October 2018	30 April 2019

Health Canada:

Report	Data lock point	Report submission
Annual Interim Report #1	31 March 2016	30 April 2016
Annual Interim Report #2	31 March 2017	30 April 2017
Annual Interim Report #3	31 August 2018	09 November 2018
Annual Interim Report #4	31 August 2019	09 November 2019
Final Report	31 August 2020	09 November 2020

A genotype analysis will be initiated after samples are obtained from at least 20 patients that developed agranulocytosis during Ferriprox use. Samples may be obtained from patients receiving Ferriprox in the post-marketing setting in the USA and Canada and those enrolled in Chiesi-sponsored clinical trials worldwide. The Registry was closed on October 2021.

LA40-0412: An open-label study to compare the pharmacokinetic profiles of a single dose of Ferriprox® in subjects with impaired hepatic function and healthy volunteers

Study short name and title:

LA40-0412: An open-label study to compare the pharmacokinetic profiles of a single dose of Ferriprox® in subjects with impaired hepatic function and healthy volunteers.

Rationale and study objectives:

Primary Objective: To determine the effect of impaired hepatic function on the PK of deferiprone and its 3-O-glucuronide metabolite following a single oral 33 mg/kg dose of Ferriprox® in subjects with hepatic impairment as compared to healthy volunteers.

Secondary Objective: To evaluate the safety and tolerability of Ferriprox® in subjects with hepatic impairment.

Study design:

A Phase IV, multicenter, non-randomized, open-label, single-dose, parallel group study to determine the effect of impaired hepatic function on the PK of deferiprone and its 3-O-glucuronide metabolite following a single oral dose of 33 mg/kg deferiprone in subjects with mild or moderate hepatic impairment as compared to healthy volunteers.

Study population:

A total of 21 participants: 7 subjects with mild hepatic impairment, 7 subjects with moderate hepatic impairment, and 7 healthy volunteers.

Milestones:

Last subject: Mar 2014
Final study report completion: Jul 2014 Amended Jan 2015
Final data submitted to US FDA: 31 Jul 2014

LA39-0412: An open-label study to compare the pharmacokinetic profiles of a single dose of Ferriprox® in subjects with impaired renal function and healthy volunteers

Study short name and title:

LA39-0412: An open-label study to compare the pharmacokinetic profiles of a single dose of Ferriprox® in subjects with impaired renal function and healthy volunteers

Rationale and study objectives:

Primary Objective: To determine the effect of impaired renal function on the pharmacokinetics of deferiprone and its 3-*O*-glucuronide metabolite following a single oral 33 mg/kg dose of Ferriprox in subjects with renal impairment, as compared to healthy volunteers.

Secondary Objective: To evaluate the safety and tolerability of Ferriprox in subjects with renal impairment.

Study design:

A Phase IV, multicenter, non-randomized, open-label, single-dose, parallel group study to compare the pharmacokinetics and safety of Ferriprox in subjects with renal impairment and healthy volunteers.

Study population:

Healthy adult male and female volunteers and subjects with mild, moderate, or severe renal impairment.

Milestones:

Last subject: Jul 2013
Final study report completion: Mar 2014 Amended Dec 2014
Final data submitted to US FDA: 15 Apr 2014

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: On-going 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				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
of the marketing authorisation				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Category 3 - Required additional pharmacovigilance activities				
PMR 1828-2: Registry for enhanced pharmacovigilance of agranulocytosis in patients treated with Ferriprox® *Study was closed on October 2021*	Collect and analyse cases of agranulocytosis to understand agranulocytosis associated with use of Ferriprox®	Agranulocytosis	Annual Interim Reports #1-6 to US FDA	Report 1: 30 Apr 2013 (submitted) Report 2: 30 Apr 2014 (submitted) Report 3: 30 Apr 2015 (submitted) Report 4: 30 Apr 2016 (submitted) Report 5: 30 Apr 2017 (submitted) Report 6: 30 Apr 2018
			Final report to US FDA	30 Apr 2019
			Annual Interim Reports #1-5 to Health Canada	Report 1: 30 Apr 2016 (submitted) Report 2: 30 Apr 2017 (submitted) Report 3: 09 Nov 2018 Report 4: 09 Nov 2019
			Final Report to Health Canada	09 Nov 2020

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no requirements for post-authorisation efficacy studies of Ferriprox and none are planned to investigate efficacy in the approved indication.

Summary of existing efficacy data

Chronic blood transfusion programs lead to progressive iron accumulation (transfusional siderosis) with damage to, particularly, the heart, liver, and endocrine organs. Without effective chelation, death commonly occurs in the second or third decade of transfusions, predominantly due to iron-induced cardiac disease. Two other iron chelators, deferoxamine (Desferal®) and deferasirox (Exjade®; Jadenu™), are available for the treatment of iron overload; both are marketed by Novartis and both active pharmaceutical ingredients involved (deferoxamine and deferasirox) have limitations related to efficacy and toxicity.

Data generated during ApoPharma-sponsored clinical trials and published over the last decade reveal that the benefits of Ferriprox therapy, particularly those relating to heart disease and its outcome, outweigh its potential risks. Furthermore, these data show that Ferriprox fills an unmet need in transfused patients with iron overload. Ferriprox provides an important advantage over deferoxamine in the amelioration of the most significant cause of morbidity and mortality in transfusion-dependent subjects, namely iron-induced cardiac disease and early mortality.[6] Ferriprox use has been associated with decreased cardiac disease and improved survival in transfused patients in Europe.[11, 14, 35, 41, 44, 51, 52, 60]

The following is a summary of the evidence of benefits of Ferriprox for transfusion-dependent thalassaemia patients with systemic iron overload:

Decrease in serum ferritin: Studies LA16-0102, LA-01, and LA08-9701 found the efficacy of Ferriprox to be equivalent to that of deferoxamine in promoting a net stabilisation or reduction of body iron load despite continuous transfusional iron intake.

Onset of cardiac disease: Study LA12-9907 compared 129 patients with thalassaemia major treated for at least 4 years with Ferriprox or deferoxamine. Of patients who were cardiac disease-free at the first assessment, newly diagnosed cardiac dysfunction occurred in 13 (20.6%) deferoxamine-treated patients compared to 2 (4.3%) Ferriprox-treated patients (p=0.013).

Progression of existing cardiac disease: Also in study LA12-9907, of patients who had cardiac dysfunction at first assessment, none treated with Ferriprox (0%) compared with 4 (33%) treated with deferoxamine had worsening of their cardiac status (p=0.245). Overall, fewer Ferriprox-treated patients than deferoxamine-treated patients showed a worsening of cardiac dysfunction from first assessment to last assessment (4% vs. 20%, p=0.007).

Decrease in cardiac iron: Study LA16-0102, in which patients with cardiac iron overload who were being treated with deferoxamine were randomized to either continue on deferoxamine or switch to Ferriprox, found an improvement over 12 months in cardiac T2* of more than 3 ms in patients treated with Ferriprox compared with about 1 ms in patients treated with deferoxamine.

Improvement in survival: Data from the published literature are consistent with the results from the ApoPharma studies, demonstrating less heart disease and/or increased survival in Ferriprox-treated patients than in those treated with deferoxamine.[11, 14, 35, 41, 44, 51, 52, 60]

Improvement in cardiac function as measured by LVEF: Study LA16-0102 also found that LVEF increased from baseline by 3.07 ± 3.58 absolute units (%) in the Ferriprox group and by 0.32 ± 3.38 absolute units (%) in the deferoxamine group (p=0.003).

Improvement in cardiac function as measured by RVEF: A recent study that re-analysed imaging data from two earlier trials found Ferriprox to be effective in improving RVEF.[2] Patients with mild or moderate cardiac iron overload who had been treated with a combination Ferriprox and deferoxamine regimen for 12 months showed a significant increase in RVEF, while no significant increase was seen in the group that received deferoxamine only. Patients with severe cardiac iron overload who received combination therapy for 12 months showed a significant improvement from baseline in RVEF.

Combination with another chelator: An investigator-led study evaluated the effects of combination therapy with Ferriprox and deferoxamine in 65 patients with thalassaemia major who were on deferoxamine monotherapy and had mild to moderate cardiac iron overload.[59] All participants continued on deferoxamine 5 days per week, and were randomized to additionally receive daily Ferriprox at a dosage of 75 mg/kg/day (N=32) or matching placebo (N=33). After one year, patients on the concurrent chelation regimen showed significantly greater reductions in serum ferritin, myocardial iron, and liver iron concentration compared to the patients who had remained on deferoxamine monotherapy.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

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

Safety concern	Routine risk minimisation activities
Agranulocytosis	Routine risk communication: Contraindications and warnings in SmPC sections 4.3 and 4.4, respectively
Neutropenia	Routine risk communication: Contraindications and warnings in SmPC sections 4.3 and 4.4, respectively
Use in pregnancy	Routine risk communication: Contraindications, warnings, and preclinical safety data in SmPC sections 4.3, 4.6, and 5.3, respectively

V.2. Additional Risk Minimisation Measures

Distribution of a Dear Health Care Professional Letter to Ferriprox prescribers in the European Community

Objectives:

Risks addressed are agranulocytosis and neutropenia.

- To emphasize to health care professionals the recommendations concerning monitoring of blood cell counts of patients taking Ferriprox
- To emphasize to health care professionals the recommendations concerning early discontinuation of Ferriprox at the first sign of neutropenia

Rationale for the additional risk minimisation activity:

If health care professionals are reminded of the risks of Ferriprox therapy and of methods of preventing agranulocytosis and neutropenia, adherence to the recommendations in the SmPC may improve, reducing the severity of cases of neutropenia and agranulocytosis and the number of those cases with complications.

Target audience and planned distribution path:

Target audience are health care professionals.

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

Evaluation of effectiveness:

- Awareness of recommendations in the SmPC, as determined by a survey
- Reported rates of agranulocytosis
- Reported rates of fatal cases of agranulocytosis

Milestones for evaluation and reporting:

Review of this activity has taken place. After implementation of this activity in 2006 (as well as the patient/carer reminder cards), survey results indicated awareness of prevention and treatment measures for neutropenia and agranulocytosis among health care professionals. Although the reported rate of agranulocytosis remained consistent, there was a decline in the reported rate of fatal cases of agranulocytosis from 0.07 to 0.01 episodes/100 patient-years, which coincided with the implementation of these risk minimization activities.

Inclusion of a wallet-sized, tear-away, patient card within the Labelling and Packaging Leaflet (Annex III)

Objectives:

Risks addressed are agranulocytosis and neutropenia.

- To increase patient awareness of the importance of regular monitoring of the neutrophil count during treatment with Ferriprox
- To increase patient awareness of the significance of any symptoms of infection while taking Ferriprox

Rationale for the additional risk minimisation activity:

If patients understand the risks of Ferriprox therapy and are aware of the important of monitoring for agranulocytosis and neutropenia, adherence to the monitoring and treatment recommendations in the SmPC may improve, reducing the risk of complications secondary to neutropenia and agranulocytosis.

Target audience and planned distribution path:

The target audience are patients. Cards are within the labelling and packaging leaflet (Annex III).

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

Evaluation of effectiveness:

- Reported rates of neutropenia and agranulocytosis
- Reported rates of fatal cases of agranulocytosis

Milestones for evaluation and reporting:

Review of this activity has already taken place. Although the reported rate of agranulocytosis remained consistent after the implementation of this activity in 2006 (as well as the patient/carer reminder cards), there was a decline in the reported rate of fatal cases of agranulocytosis from 0.07 to 0.01 episodes/100 patient-years, which coincided with the implementation of these risk minimization activities.

Removal of additional risk minimisation activities: Not applicable

V.3 Summary of risk minimisation measures

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Agranulocytosis	Routine risk minimisation measures: • SmPC sections 4.3 and 4.4 Additional risk minimisation measures: • Dear Health Care Professional Letter to Ferriprox prescribers in the European Community (sent out 2006) • Patientcard (part of the Labelling and Package Leaflet, Annex III) (ongoing)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up form for agranulocytosis and neutropenia. • Real-time reviews of single cases. • Scheduled reviews of aggregate data from ARGUS to identify relevant changes in reporting frequency or patterns of adverse events. • Aggregate reviews, at pre-specified intervals, of product quality complaint cases with associated adverse events and lot numbers, to identify safety signals related to product quality and manufacturing. • Analysis of the MAH's non-clinical, clinical and epidemiological study

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		results. Additional pharmacovigilance activities: • PMR 1828-2: Registry for enhanced pharmacovigilance of agranulocytosis in patients treated with Ferriprox®
Neutropenia	Routine risk minimisation measures: • SmPC sections 4.3 and 4.4 Additional risk minimisation measures: • Dear Health Care Professional Letter to Ferriprox prescribers in the European Community (sent out in 2006) • Patient card (part of the Labelling and Package Leaflet, Annex III (ongoing)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up form for agranuloctytosis and neutropenia. • Real-time reviews of single cases. • Scheduled reviews of aggregate data from ARGUS to identify relevant changes in reporting frequency or patterns of adverse events. • Aggregate reviews, at pre-specified intervals, of product quality complaint cases with associated adverse events and lot numbers, to identify safety signals related to product quality and manufacturing. • Analysis of the MAH's non-clinical, clinical and epidemiological study results. Additional pharmacovigilance activities: • PMR 1828-2: Registry for

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		enhanced pharmacovigilance of agranulocytosis in patients treated with Ferriprox® • Deferiprone-induced agranulocytosis: 20 years of clinical observations , a retrospective cohort study of agranulocytosis and neutropenia associated with use of Ferriprox® (63)
Use in pregnancy	• Routine risk minimisation measure: SmPC sections 4.3, 4.6, 5.3 Additional risk minimisation measure: • Patientcard (part of the Labelling and Package Leaflet, Annex III) (ongoing)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Real-time reviews of single cases. • Scheduled reviews of aggregate data from ARGUS to identify relevant changes in reporting frequency or patterns of adverse events. • Aggregate reviews, at pre-specified intervals, of product quality complaint cases with associated adverse events and lot numbers, to identify safety signals related to product quality and manufacturing. • Analysis of the MAH's non-clinical, clinical and epidemiological study results. Additional pharmacovigilance activities: None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Ferriprox® (deferiprone)
This is a summary of the risk management plan (RMP) for Ferriprox. The RMP details important risks of Ferriprox, how these risks can be minimised, and how more information will be obtained about Ferriprox' risks and uncertainties (missing information).

Ferriprox' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ferriprox should be used.

This summary of the RMP for Ferriprox 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 Ferriprox' RMP.

I. The medicine and what it is used for

Ferriprox is authorised for the treatment of iron overload in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate.

Ferriprox in combination with another chelator is indicated in patients with thalassaemia major when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction (see SmPC for the full indication). It contains deferiprone as the active substance and it is given by 500 mg and 1000 mg film-coated tablets each divisible in half and 100 mg/mL oral solution.

Further information about the evaluation of Ferriprox' benefits can be found in Ferriprox' EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: *http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000236/WC500022044.pdf*

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

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

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

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

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

In the case of Ferriprox, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

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

If important information that may affect the safe use of Ferriprox is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Ferriprox are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ferriprox. 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.

List of important risks	
Important identified risks	• Agranulocytosis • Neutropenia • Use in pregnancy

II.B Summary of important risks and missing information

Important identified risk: Agranulocytosis	
Evidence for linking the risk to the medicine	Information about the risk of agranulocytosis is available from clinical trials, post-marketing experience and scientific literature.

	Although there are remaining gaps in knowledge about the characteristics of this risk, the above information is supported by strong evidence. 1. European Agranulocytosis Survey Final Report, 2011. 2. Data on file, studies LA30-0307 and LA35-PM. 3. Arneborn P, Palmblad J. Drug-induced neutropenia – A survey for Stockholm 1973-1978. Acta Med Scand. 1982; 212: 289-92.(4) 4. Cohen AR, Galanello R, Piga A, DiPalma A, Vullo C, Tricta F. Safety profile of the oral iron chelator deferiprone: a multicentre study. Br J Haematol. 2000; 108: 305-12.(18) 5. Palmblad J. Drug-induced neutropenias: now and then. Arch Int Med. 1999; 159: 2745.(49) 6. Tricta F, Uetrecht J, Galanello R, Connelly J, Rozova A, Spino M, Palmblad J. Deferiprone-induced agranulocytosis: 20 years of clinical observations. Am J Hematol. 2016 Oct;91(10):1026-31(63)
Risk factors and risk groups	The risk of Ferriprox-induced agranulocytosis is greatest during the first year of therapy, and particularly during the first six months of therapy. Although no formal studies have been conducted in patients with Diamond-Blackfan anaemia, the available data suggest that Ferriprox-induced agranulocytosis may be more frequent and severe in these patients than in patients with other transfusion-dependent iron overload conditions. Clinical findings suggest that Ferriprox-induced agranulocytosis is idiosyncratic and is not dose-related. The results of a 2010 survey did not indicate statistically significant differences in the incidence or rate of agranulocytosis between paediatric and adult patients with thalassaemia administered Ferriprox in the EU. Tricta et al. 2016 evaluated age as a risk factor. Analysis of data obtained from 1999 to 31 August 2014 showed that 7 (2.7%) of 263 paediatric patients (<16 years old) experienced agranulocytosis versus 10 (1.2%) of 864 adults treated with deferiprone in CT (P =0.08).(63)
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.3 and 4.4

	Additional risk minimisation measures: • Dear Health Care Professional Letter to Ferriprox prescribers in the European Community (2006) • Patient/card (part of the Labelling and Package Leaflet, Annex III) (ongoing)
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PMR 1828-2: Registry for enhanced pharmacovigilance of agranulocytosis in patients treated with Ferriprox® See section II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: Neutropenia	
Evidence for linking the risk to the medicine	Information about the risk of neutropenia is available from clinical trials, post-marketing experience and scientific literature. Although there are remaining gaps in knowledge about the characteristics of this risk, the above information is supported by strong evidence. 1. European Agranulocytosis Survey Final Report, 2011. 2. Data on file. 3. Arneborn P, Palmblad J. Drug-induced neutropenia – A survey for Stockholm 1973-1978. Acta Med Scand. 1982; 212: 289-92.(4) 4. Cohen AR, Galanello R, Piga A, DiPalma A, Vullo C, Tricta F. Safety profile of the oral iron chelator deferiprone: a multicentre study. Br J Haematol. 2000; 108: 305-12.(18) 5. Orkin SH, Nathan DG. The thalassemias. In: Nathan DG, Orkin SH, editors. Hematology of infancy and childhood. Philadelphia. W.B. Saunders Company; 1998.(47) 6. Palmblad J. Drug-induced neutropenias: now and then. Arch Int Med. 1999; 159: 2745.(49) 7. El-Beshlawy A.M., El-Alfy M.S., Sari T.T., Chan L.L., Tricta F. Continuation of deferiprone therapy in patients with mild neutropenia may not lead to a more severe drop in neutrophil count. Eur J Haematol. 2014 Apr;92(4):337-40. (25) 8. Tricta F, Uetrecht J, Galanello R, Connelly J, Rozova A,

	Spino M, Palmblad J. Deferiprone-induced agranulocytosis: 20 years of clinical observations. Am J Hematol. 2016 Oct;91(10):1026-31.(63) 9. Hsieh MM, Everhart JE, Byrd-Holt DD, Tisdale JF, Rodgers GP. Prevalence of neutropenia in the U.S. population: age, sex, smoking status, and ethnic differences. Ann Intern Med. 2007 Apr 3;146(7):486-92.(31)
Risk factors and risk groups	In clinical trials, the majority of neutropenia cases occurred within the first two years of therapy. Clinical findings suggest that some of the neutropenia episodes observed during Ferriprox therapy are not drug-related. Neutropenia occurred at comparable rates in deferiprone- and deferoxamine-treated subjects in ApoPharma clinical trials. The results of a 2010 survey did not indicate statistically significant differences in the incidence or rate of neutropenia between paediatric and adult patients with thalassaemia administered Ferriprox in the EU. Analysis by Tricta et al revealed that neutropenia incidence in CT suggested age dependency: 24 (9.1%) of 263 paediatric patients compared to 38 (4.4%) of 864 adults (P=0.003)(63), which is consistent with the higher occurrence of neutropenia in healthy children than in adults.(31)
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.3 and 4.4 Additional risk minimisation measures: • Dear Health Care Professional Letter to Ferriprox prescribers in the European Community (2006) • Patientcard (part of the Labelling and Package Leaflet, Annex III (ongoing)
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PMR 1828-2: Registry for enhanced pharmacovigilance of agranulocytosis in patients treated with Ferriprox® See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Use in pregnancy	
Evidence for linking the risk to the medicine	Information about the risk of deferiprone use during pregnancy is collected from non-clinical studies, clinical trials, post-marketing experience and scientific literature. 1. Data on file. 2. Cunningham MJ, Macklin EA, Muraca G, Neufeld EJ. Successful pregnancy in thalassemia major women in the Thalassemia Clinical Research Network. Paediatr Res. 2004; 55(4 Suppl S): 294A.(20) 3. De Sanctis V, Perera D, Katz M, Fortini M, Gamberini MR. Spermatozoal DNA damage in patients with B Thalassaemia Syndromes. Pediatr Endocrinol Rev. 2008 Oct;6 Suppl 1:185-9.(21) 4. Karagiorga-Lagana M. Fertility in thalassemia: the Greek experience. J Pediatr Endocrinol Metab. 1998; 11(Suppl 3): 945-51.(32) 5. Pafumi C, Farina M, Pernicone G, Bandiera S, Russo A, Mangiafico L, et al. At term pregnancies in transfusion-dependent beta-thalassemic women. Clin Exp Obstet Gynecol. 2000; 27: 185-7.(48) 6. Skordis N, Christou S, Koliou M, Pavlides N, Angastiniotis M. Fertility in female patients with thalassemia. J Pediatr Endocrinol Metab. 1998; 11 (Suppl 3): 935-43.(58) 7. Cassinerio E, Baldini IM, Alameddine RS, Marcon A, Borroni R, Ossola W, Taher A, Cappellini MD. Pregnancy in patients with thalassemia major: a cohort study and conclusions for an adequate care management approach. Ann Hematol. 2017 Jun;96(6):1015-1021. doi: 10.1007/s00277-017-2979-9.(13)
Risk factors and risk groups	<u>Women of childbearing potential/contraception in men and women</u> Due to the genotoxic potential of deferiprone (see section 5.3), women of childbearing potential are recommended to use effective contraceptive measures while being treated with Ferriprox and for 6 months following the completion of treatment. Pregnant women must be advised to immediately stop taking Ferriprox (see section 4.3). Men are recommended to use effective contraceptive measures and to not father a child while receiving Ferriprox and

	for 3 months following the completion of treatment.
Risk minimisation measures	Routine risk minimisation measure: • SmPC sections 4.3, 4.6, 5.3 Additional risk minimisation measure: • Patientcard (part of the Labelling and Package Leaflet, Annex III) (ongoing)

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligations applying to Ferriprox.

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

PMR 1828-2: Registry for enhanced pharmacovigilance of agranulocytosis in patients treated with Ferriprox®

Study short name and title:

PMR 1828-2: Registry for enhanced pharmacovigilance of agranulocytosis in patients treated with Ferriprox®

Rationale and study objectives:

This study was initiated as per FDA's requirement in its approval of Ferriprox. The objective of the study is collect and analyse cases of agranulocytosis as well as neutropenia or infections that were fatal or led to hospitalization in patients treated with Ferriprox.

LA40-0412: An open-label study to compare the pharmacokinetic profiles of a single dose of Ferriprox® in subjects with impaired hepatic function and healthy volunteers

Study short name and title:

LA40-0412: An open-label study to compare the pharmacokinetic profiles of a single dose of Ferriprox® in subjects with impaired hepatic function and healthy volunteers.

Rationale and study objectives:

Primary Objective: To determine the effect of impaired hepatic function on the PK of deferiprone and its 3-O-glucuronide metabolite following a single oral 33 mg/kg dose of Ferriprox® in subjects with hepatic impairment as compared to healthy volunteers.

Secondary Objective: To evaluate the safety and tolerability of Ferriprox® in subjects with hepatic impairment.

LA39-0412: An open-label study to compare the pharmacokinetic profiles of a single dose of Ferriprox® in subjects with impaired renal function and healthy volunteers

Study short name and title:

LA39-0412: An open-label study to compare the pharmacokinetic profiles of a single dose of Ferriprox® in subjects with impaired renal function and healthy volunteers

Rationale and study objectives:

Primary Objective: To determine the effect of impaired renal function on the pharmacokinetics of deferiprone and its 3-O-glucuronide metabolite following a single oral 33 mg/kg dose of Ferriprox in subjects with renal impairment, as compared to healthy volunteers.

Secondary Objective: To evaluate the safety and tolerability of Ferriprox in subjects with renal impairment.

Annex 4 Specific adverse drug reaction follow-up forms

- Agranulocytosis and neutropenia case report form

Annex 6 Details of proposed additional risk minimisation activities

Approved key messages of the additional risk minimisation measures

The patient information pack:

- Patient information leaflet

A patient card:

- To increase patient awareness of the importance of regular monitoring of the neutrophil count during treatment with deferiprone
- To increase patient awareness of the significance of any symptoms of infection while taking deferiprone
- To warn women of childbearing age to not become pregnant because deferiprone may seriously harm the unborn baby.