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. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• 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. 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. 5. Palmblad J. Drug-induced neutropenias: now and then. Arch Int Med. 1999; 159: 2745. 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
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 thalassemia 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).
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/carer reminder 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® • Deferiprone-induced agranulocytosis: 20 years of clinical observations, a retrospective cohort study of agranulocytosis and neutropenia associated with use of 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. 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. 5. Orkin SH, Nathan DG. The thalassemias. In: Nathan DG, Orkin SH, editors. Hematology of infancy and childhood. Philadelphia. W.B. Saunders Company; 1998. 6. Palmblad J. Drug-induced neutropenias: now and then. Arch Int Med. 1999; 159: 2745. 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. 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. 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.

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 thalassemia 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), which is consistent with the higher occurrence of neutropenia in healthy children than in adults.
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/carer reminder 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® • Deferiprone-induced agranulocytosis: 20 years of clinical observations , a retrospective cohort study of agranulocytosis and neutropenia associated with use of 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. 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. 4. Karagiorga-Lagana M. Fertility in thalassemia: the Greek experience. J Pediatr Endocrinol Metab. 1998; 11(Suppl 3): 945-51. 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. 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. 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.
Risk factors and risk groups	Females of childbearing age. Hypogonadotrophic hypogonadism is common in young adults with thalassemia major and it thought to contribute to low fertility in this population.
Risk minimisation measures	Routine risk minimisation measure: • SmPC sections 4.3, 4.6, 5.3 Additional risk minimisation measure: • Patient/carer reminder card (part of the Labelling and Package Leaflet, Annex III) (ongoing)
Important identified risk: Arthropathy (including arthralgia)	
Evidence for linking the risk to the medicine	Information about the risk of arthropathy 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. Data on file.

	2. Berkovitch M, Laxer RM, Inman R, Koren G, Pritzker KPH, Fritzler MJ, et al. Arthropathy in thalassemia patients receiving deferiprone. Lancet. 1994; 343: 1471-2. 3. Devanur LD, Neubert H, Hider RC. The fenton activity of iron(III) in the presence of deferiprone. J Pharm Sci. 2007. 4. Esposito BP, Breuer W, Sirunkapracha P, Pootrakul P, Hershko C, Cabantchik ZI. Labile plasma iron in iron overload: redox activity and susceptibility to chelation. Blood. 2003; 102(7): 2670-77.
Risk factors and risk groups	Unknown
Risk minimisation measures	Routine risk minimisation measure: • SmPC section 4.8
Important identified risk: Increased liver function test values	
Evidence for linking the risk to the medicine	Information about the risk of increased liver function test values is available from clinical trials, post-marketing experience and scientific literature. 1. Data on file.
Risk factors and risk groups	An increase in serum liver enzymes levels is most frequently observed during the first three months of Ferriprox therapy. Thalassemia patients often present with increased ALT levels, mainly due to hepatic iron overload and concomitant transfusional hepatitis. In ApoPharma studies, roughly half of the subjects who were evaluated for ALT had abnormal values at baseline. Hepatitis C status (positive at baseline) was found to be a confounding factor in more than 50% of subjects with elevated ALT values (greater than two, three, or five times the upper limit of normal (ULN)) for two or more consecutive visits. No clear trends are apparent as a function of Ferriprox dose level on the proportion of subjects with ALT values exceeding two or three times ULN at two or more consecutive visits.
Risk minimisation measures	Routine risk minimisation measure: • SmPC sections 4.4, 4.8
Important identified risk: Skin disorders	
Evidence for linking the risk to the medicine	Information about the risk of skin disorders is available from clinical trials, post-marketing experience and scientific literature. 1. Data on file.

	2. Dogramaci AC, Savas N, Ozer B, Duran N. Skin diseases in patients with β-thalassemia major. Int J Dermatol. 2009; 48: 1057-61.
Risk factors and risk groups	Unknown
Risk minimisation measures	Routine risk minimisation measure: • SmPC section 4.8
Important identified risk: Allergic reactions	
Evidence for linking the risk to the medicine	Information about the risk of allergic reactions is available from clinical trials and post-marketing experience. 1. Data on file.
Risk factors and risk groups	Unknown
Risk minimisation measures	Routine risk minimisation measure: • SmPC section 4.8
Important potential risk: Carcinogenicity	
Evidence for linking the risk to the medicine	Information about the potential risk of carcinogenicity is available from non-clinical toxicology studies. 1. Data on file. 2. Chung W.S., Lin C.L., Lin C.L., Kao C.H. Thalassaemia and risk of cancer: a population-based cohort study. J Epidemiol Community Health 2015;69:1066–1070. 3. Repousi E. Moraki M. Kyriakopoulou D. Delaporta P. Kafourou A. Kattamis A. Increasing incidence of malignancies in aging thalassemic patients: A single institution's longitudinal experience. Haematologica (2017) 102 Supplement 2 (137-138).
Risk factors and risk groups	A study conducted in Taiwan investigated the epidemiological relationship between thalassemia and cancers. The study compared the incidence and risk of cancer in 2655 patients diagnosed with thalassemia between 1998 and 2010 by using data from the Taiwan Longitudinal Health Insurance Database. The comparison cohort comprised 10 620 people from the general population without thalassemia. The overall incidence of cancer was 52% higher in the thalassemia cohort than in the comparison cohort, with an adjusted HR (aHR) of 1.54 (95% CI 1.15 to 2.07). Patients with thalassemia had a considerably higher risk of hematological malignancy (aHR=5.32, 95% CI 2.18 to 13.0) and abdominal cancer (aHR=1.96, 95% CI 1.22 to 3.15) than did the comparison cohort. Furthermore, patients with thalassemia with transfusion exhibited a 9.31-fold risk for developing hematological

	malignancy and a 9.12-fold risk for developing abdominal cancer compared with those who did not receive transfusion. Repousi et al. conducted a retrospective study and found an increased incidence of malignancies in thalassemia patients in Greece, which is at least partially related to the aging of this population.
Risk minimisation measures	Routine risk minimisation measure: • SmPC section 4.4
Missing Information: Lactation toxicity	
Risk minimisation measures	No risk minimisation measures
Missing information: Off-label use	
Risk minimisation measures	No risk minimisation measures
Missing Information: Long-term safety data	
Risk minimisation measures	No risk minimisation measures
Missing information: Risk in immunocompromised patients	
Risk minimisation measures	No risk minimisation measures

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

Tricta F, Uetrecht J, Galanello R, Connelly J, Rozova A, Spino M, et al. Deferiprone-induced agranulocytosis: 20 years of clinical observations. Am J Hematol. 2016;91(10):1026-31.>

Study short name and title:

Tricta F, Uetrecht J, Galanello R, Connelly J, Rozova A, Spino M, et al. Deferiprone-induced agranulocytosis: 20 years of clinical observations. Am J Hematol. 2016;91(10):1026-31

Rationale and study objectives:

To identify risk factors for agranulocytosis during deferiprone therapy, the effectiveness of weekly ANC monitoring in avoiding its consequences, and the rate of its recurrence upon rechallenge. This article summarizes the data reviewed and the conclusions and recommendations offered by a panel of experts in thalassemia and drug-induced agranulocytosis convened to evaluate fulfillment of those needs.

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.