28 April 2016
EMA/ 591403/2015
Committee for Medicinal Products for Human use (CHMP)

Assessment report

Invented name: Ferriprox

International non-proprietary name/Common name: DEFERIPRONE

Procedure No. EMEA/H/C/000236/II/0103

Marketing authorisation holder (MAH): Apotex Europe BV

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

b-TM	b-Thalassemia major
DFO	deferoxamine (Desferal)
DFP	deferiprone (Ferriprox)
DFX	deferasirox (Exjade)
LEFV	Left ventricular ejection fraction
MAH	Marketing Authorisation Holder
MRI	magnetic resonance imaging
PD	Pharmacodynamics
PK	Pharmacokinetics
TDT	Transfusion Dependent Thalassaemia

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Apotex Europe BV submitted to the European Medicines Agency on 21 August 2015 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include a new indication for Ferriprox in combination with another chelator.
As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.
In addition, the Marketing authorisation holder (MAH) took the opportunity of this procedure to update the Product Information in compliance with the QRD template version 9.1 and combine the SmPC for the 500mg and 1000mg tablets. The contact details of France and Portugal have been updated in the PL.

The variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pierre Demolis Co-Rapporteur: Concepcion Prieto Yerro

Timetable	Dates
Submission date:	21 August 2015
Start of procedure:	19 September 2015
CHMP Rapporteur Assessment Report:	23 November 2015
CHMP Co-Rapporteur Assessment Report:	23 November 2015
Updated CHMP Rapporteur(s) (Joint) Assessment Report:	10 December 2015
Request for supplementary information and extension of timetable adopted by the CHMP on:	17 December 2015
Submission of MAHs responses:	26 January 2016
Restart of the procedure:	27 January 2016
CHMP Rapporteur Assessment Report on the MAH's responses circulated on:	11 February 2016
Updated CHMP Rapporteur Assessment Report on the MAH's responses circulated on:	19 February 2016
Further updated CHMP Rapporteur Assessment Report on the MAH's responses circulated on:	23 February 2016
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	25 February 2016
Submission of MAHs responses:	24 March 2016
Restart of the procedure:	30 March 2016
CHMP Rapporteur Assessment Report on the MAH's responses to the 2nd RSI circulated on:	13 April 2016
CHMP members comments:	22 April 2016
Updated CHMP Rapporteur Assessment Report on the MAH's responses to the 2nd RSI circulated on:	20 April 2016
CHMP Opinion	28 April 2016

2. Scientific discussion

2.1. Introduction

b-Thalassemia major (b-TM) is a heritable blood disorder where the inability to form functional hemoglobin (Hb) results in life-threatening anemia, requiring life-long transfusions to maintain life. Iron overload is one of the major causes of morbidity in patients with thalassemia major. Chronic transfusions invariably lead to rapid accumulation of iron since the human body has no natural ability to actively excrete iron[1]. The excess iron is mainly stored in the liver (70.0 to 90.0%), but will also redistribute to the heart and endocrine tissues [2,3]. Main causes of mortality are due to sudden cardiac death, arrhythmia, and heart failure from cardiac iron overload. The majority of morbidity stems from liver cirrhosis from hepatic iron overload and endocrine dysfunction. The goal of iron chelation therapy is to reduce iron overload in the susceptible organs and to prevent end-organ damage (heart failure, liver cirrhosis, endocrinopathies), morbidities known to reduce survival in this population.

Three iron chelators are currently approved in the EU. Deferoxamine (DFO, Desferal®) is a parenterally-administered iron chelator that has been shown to reduce mortality and LIC compared to placebo[4]. Two oral products deferiprone (DFP, Ferriprox®) and deferasirox (DFX, Exjade®) were then approved for iron overload treatment in patients with thalassaemia major. Oral chelators, DFP and DFX, are conventionally used as monotherapy[5].

Efficacy of iron chelators combination is the subject of many research. However, based on the indications of DFX and DFP, their combination with other iron chelator therapies is considered as an off-label use.

Deferiprone (DFP) is an oral iron chelator that has demonstrated efficacy similar to DFO[6,7]. However, its side effects (neutropenia, agranulocytosis, elevation in hepatic enzymes, and arthralgia) have precluded its widespread[6,7].

In response to the PRAC recommendation, the MAH conducted a review of data in the clinical database and of the published literature to evaluate the safety profile of combination of Ferriprox with other chelators which was presented in the last type II variation (EMEA/H/C/236/II/89G). Efficacy and safety data on the use of combination therapy are finally presented in this extension of indication to include a new indication for Ferriprox in combination with another chelator.

[1] Galanello R, Campus S. Deferiprone chelation therapy for thalassemia major. Acta Haematol. 2009;122(2-3):155-64.

[2] Kuo KH, Mrkobrada M. A Systematic Review and Meta-Analysis of Deferiprone Monotherapy and in Combination with Deferoxamine for Reduction of Iron Overload in Chronically Transfused Patients with beta-Thalassemia. Hemoglobin. 2014;1-13.

[3] Totadri S, Bansal D, Bhatia P, et al. The deferiprone and deferasirox combination is efficacious in iron overloaded patients with beta-thalassemia major: A prospective, single center, open-label study. Pediatr Blood Cancer. 2015.

[4] Modell B, Letsky EA, Flynn DM, et al. Survival and desferrioxamine in thalassaemia major. Br Med J (Clin Res Ed). 1982;284(6322):1081-4.

[5] Kwiatkowski JL. Management of transfusional iron overload – differential properties and efficacy of iron chelating agents. J Blood Med 2011; 2:135-49

[6] Olivieri NF, Brittenham GM, Matsui D, et al. Iron-chelation therapy with oral deferiprone in patients with thalassemia major. N Engl J Med. 1995;332(14):918-22

[7] Calvaruso G, Vitrano A, Di Maggio R, et al. Deferiprone versus deferoxamine in thalassemia intermedia: Results from a 5-year long-term Italian multicenter randomized clinical trial. Am J Hematol. 201;90(7):634-8.

2.2. Clinical aspects

2.2.1. Introduction

The MAH provided a clinical overview with published literature data on the combination therapy of deferiprone with deferoxamine and deferiprone with deferasirox. This variation application provides an assessment of this clinical overview in light of results of clinical trials and recent consensus statement from the American Heart Association. A tabulation of the submitted publications is presented in Appendix A.

2.2.2. Clinical pharmacology

Most of the literature on chelators combination describes deferiprone/deferoxamine association.

A shuttling hypothesis[8] whereby synergistic cellular iron mobilization requires one chelator to have the physicochemical properties to enter cells, chelate intracellular iron and subsequently donate iron to a second 'sink' chelator has been proposed.

DFO's metabolism is due almost entirely to various enzymes in plasma, thus hepatic metabolism of oral iron chelators should not be affected. Specific substrate specificities between deferasirox (mostly UGT1AUGT1A1 and to a lesser extent UGT1A3) and deferiprone (UGT1A6) should not lead to drug interaction[9,10].

The provided pharmacology studies seem sufficient. At least additive effects can be expected and even some synergy, while pharmacological data (PK and PD) do not theoretically prevent the combination of DFO with DFP.

2.3. Clinical efficacy

2.3.1. Main studies

No new clinical data have been submitted in this application. The MAH provided a clinical overview with published literature data on the efficiency of deferiprone, deferoxamine, deferasirox in monotherapy and in combination (see Appendix A and B).

In these studies, iron overload was measured by multiple methods usually used in clinical practice. Combinations of these different techniques have been used to evaluate chelators efficiency.

Serum ferritin level can be measured frequently via blood testing and is particularly useful to monitor trends in iron burden over time. Elevated liver iron concentration (LIC) has been found to be correlated with total body iron stores in b-TM patients[11].

[8] Vlachodimitropoulou KE, Garbowski M, Porter J. Synergistic intracellular iron chelation combinations: mechanisms and conditions for optimizing iron mobilization. Br J Haematol. 2015.

[9] Summary of products of Ferriprox®

[10] Summary of products of Exjade®

[11] Kwiatkowski JL. Management of transfusional iron overload – differential properties and efficacy of iron chelating agents. J Blood Med 2011; 2:135-49

Liver iron concentration (mg/g dw)	Ferritin level[a] (ng/mL)	Clinical implications
<2	<500	Low iron stores; consider decreasing or holding chelation temporarily[b]
2–7	500–1499	Ideal range; continue current chelation
>7–15	1500–2500	Increased iron stores; increase chelator dose[c] and/or change chelator if ferritin and/or liver iron trend is not improving
>15	>2500	Elevated iron stores associated with increased risk of complications and death; increase chelator dose[c] and/or change chelator; consider combination chelation therapy

Table from Kwiatkowski. Management of transfusional iron overload-differential properties and efficacy of iron chelating agents. J. Blood.Med. 2011:2 135-149.

Measurement of the amount of iron eliminated in urine and feces provides an equivocal determination of the effectiveness of an iron chelator in removing iron from the body (normally urine and feces contain negligible amounts of iron (~1 mg/day)[12].

The proportion of ferritin measurements of >2500 mg/L was established as an important prognostic factor on cardiac disease-free survival in b-TM patients on iron chelation. However, a ferritin level below 2500 mg/L does not preclude the presence of severe cardiac iron overload[13].

Measurement of T2 relaxation time (T2*) by cardiac magnetic resonance imaging (MRI) via gradient recall echo provides a more accurate and highly reproducible assessment of cardiac iron overload[14].

Cardiac T2* (ms)	Clinical implication
≥20	No significant cardiac iron loading; continue current chelation
10 to <20	Mild to moderate cardiac iron loading with increased risk of cardiac complications; consider intensification of chelation such as increased dose[a] and/or continuous infusion (for deferoxamine); combination therapy with deferiprone and deferoxamine if available
<10	Severe cardiac iron loading with high risk of cardiac complications; intensify chelation such as increased dose[a] and/or continuous infusion (for deferoxamine); combination therapy with deferiprone and deferoxamine if available

[12] Galanello R, Kattamis A, Piga A, Fischer R, Leoni G, Ladis V, et al. A prospective randomized controlled trial on the safety and efficacy of alternating deferoxamine and deferiprone in the treatment of iron overload in patients with thalassemia. Haematologica. 2006;91(9):1241-3.

[13] Tanner MA, Galanello R, Dessi C, Smith GC, Westwood MA, Agus A, et al. Combined chelation therapy in thalassemia major for the treatment of severe myocardial siderosis with left ventricular dysfunction. Journal of Cardiovascular Magnetic Resonance. 2008;10(12)

Table from Kwiatkowski. Management of transfusional iron overload-differential properties and efficacy of iron chelating agents. J. Blood.Med. 2011:2 135-149.

A clinical trial conducted by Maggio et al.[14] included 144 patients with thalassemia major. Patient were randomly assigned to DFP (75 mg/kg/day) (n = 71) or DFO (50 mg/kg/day) (n = 73) for 1 year. No difference in the reduction of serum ferritin was observed (222 ± 783 ng/ml with DFP and 232 ± 619 ng/ml with DFO; p= 0.81). No difference in the reduction of liver and heart iron content was found by magnetic resonance between the two groups. These results demonstrated no difference after 12 months of treatment in serum ferritin levels or liver and heart iron content. However, the assessor observes that the very high variances reported in both groups should prevent any conclusion on similar effects or even non-inferiority and this study is poorly informative.

A randomized controlled trial was performed in 61 patients previously maintained on subcutaneous deferoxamine[15]. The primary end point was the change in myocardial siderosis (myocardial T2*) over 1 year in patients maintained on subcutaneous deferoxamine or those switched to oral deferiprone monotherapy. The dose of deferiprone was 92 mg/kg/d and deferoxamine was 43 mg/kg for 5.7 d/wk. The improvement in myocardial T2(*) was significantly greater for deferiprone than deferoxamine (27% vs 13%; P = 0.023). Left ventricular ejection fraction (LEFV) increased significantly more in the deferiprone-treated group (3.1% vs 0.3% absolute units; P = 0.003). The changes in liver iron level (-0.93 mg/g dry weight vs -1.54 mg/g dry weight; P = 0.40) and serum ferritin level (-181 microg/L vs -466 microg/L; P = 0.16), respectively, were not significantly different between groups. Deferiprone monotherapy was significantly more effective than deferoxamine over 1 year in improving asymptomatic myocardial siderosis in beta-thalassemia major.

In this last study, the assessor observes that DFP produces a lager effect on all three investigated parameters and the relative potency compared to DFO is roughly of a same extent. The fact that only LEVF change reached statistical significance may indicate that this parameter is more powerful to detect differences, not necessarily that DFP has a more pronounced effect specifically on this parameter.

A variety of factors differentiate the currently available iron chelators. First, the various pharmacological properties (including the stoichiometry of iron chelation, mode of administration, dosing schedule, plasma half-life, and route of excretion) of the different chelators are well described in the literature. Second, drug efficacy is variable, particularly with regard to organ-specific (hepatic, cardiac) iron removal. Third, adverse-effect profiles differ among chelators.

[14] Maggio A, D'Amico G, Morabito A, Capra M, Ciaccio C, Cianciulli P, et al. Deferiprone versus deferoxamine in patients with thalassemia major: a randomized clinical trial. Blood Cells Mol Dis. 2002;28(2):196-208.
[15] Pennell DJ, Berdoukas V, Karagiorga M, Ladis V, Piga A, Aessopos A, et al. Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis. Blood. 2006;107(9):3738-44.

Differential properties of the iron chelators [5] are summarized in the table below:

Property	Deferoxamine	Deferasirox	Deferiprone
Stoichiometry (chelator: iron)	Hexadentate (1:1)	Tridentate (2:1)	Bidentate (3:1)
Usual dose	25–60 mg/kg/day over 8–24 hours	20–40 mg/kg/day once daily	75–100 mg/kg/day in three divided doses
Route of administration	Subcutaneous, intravenous	Orally dispersible tablet	Oral tablet or suspension
Half-life	20–30 minutes	7–16 hours	1.5–2.5 hours
Excretion	Urinary, fecal	Fecal	Urinary
Ability to remove liver iron	+++	+++	++*
Ability to remove cardiac iron	++#	++**	+++
Typical adverse events	Local reactions Sensorineural hearing loss Ophthalmic changes Allergic reactions Bone abnormalities Increased risk of *Yersinia* and *Klebsiella* infections Pulmonary at high doses Neurological at high doses	Gastrointestinal Rash Rise in creatinine Proteinuria Elevated hepatic enzymes Gastrointestinal bleeding (rare) Fulminant hepatic failure (rare) Renal insufficiency (rare)	Gastrointestinal Neutropenia/Agranulocytosis Arthralgia Elevated hepatic enzymes
Availability	Licensed	Licensed	Licensed in Europe and Asia as second-line agent; not licensed in North America

Notes: *Reports of insufficient liver iron removal in some patients at doses of 75 mg/kg/day, but higher dosing, especially for subjects with high transfusional iron burden may be more effective; #with continuous infusion; **data are limited regarding efficacy with very low cardiac T2* and in heart failure; cardiac iron removal also may be less effective in patients with high liver iron concentration.

It is then acknowledged that chelation therapy needs to be individualized. The three chelators available allow the physicians to adapt the chelation therapy according to different parameters (compliance, efficacy, toxicity, …) in case of treatment failure, unsuitability of current treatment and urgent need for rapid chelation. Adaptation of the doses and switch to a different chelator remain the first options. However, combination therapy may be proposed in order to give the possibility to take advantage of the different pharmacological properties of the different chelators for specific cases. The combination therapy includes the possibility to give concomitantly or alternatively iron chelators. The way to manage combination therapy remains to be more precisely described (OC).

Main studies of deferiprone and deferoxamine combination chelation therapy

1. Efficacy on iron overload

A randomized controlled trial[16] compared combination therapy (n=32) to DFO alone (n=33) for 1 year. The patients were pretreated by DFO monotherapy. All patients were administered DFO 5 days a week at a dosage of 35 mg/kg/day, and those in the combination treatment group additionally received daily Ferriprox (75 mg/kg per day). Significantly greater improvement in serum ferritin in the combined group (-976 versus -233 µg/L; P=0.001) was observed.

Another controlled trial [17] randomized 60 patients undergoing chelation with DFO to either remain on DFO monotherapy (5 to 7 days per week) or switch to an alternating regimen (5 days of deferiprone (75 mg/kg per day) alternating with 2 days of DFO. Both arms resulted in equivalent decreases of serum ferritin (-248 ± 791 µg/l for the alternating therapy group vs - 349 ± 573 µg/l for the DFO group; p = 0.5802).

[16] Tanner MA, Galanello R, Dessi C, et al. A Randomized, Placebo-Controlled, Double-Blind Trial of the Effect of Combined Therapy With Deferoxamine and Deferiprone on Myocardial Iron in Thalassemia Major Using Cardiovascular Magnetic Resonance. Circulation. 2007;115(14):1876-84.

[17] Galanello R, Kattamis A, Piga A, Fischer R, Leoni G, Ladis V, et al. A prospective randomized controlled trial on the safety and efficacy of alternating deferoxamine and deferiprone in the treatment of iron overload in patients with thalassemia. Haematologica. 2006;91(9):1241-3.

Alternating therapy has also been evaluated in a long-term trial that included a 5-year follow-up [18]. 213 patients (pretreated by DFO or DFP) were randomized to DFP at 75 mg/kg, divided into three oral daily doses, for 4 d/week and DFO by subcutaneous infusion (8–12 h) at 50 mg/kg per day for the remaining 3 d/week (n=105) was compared with DFP alone at 75 mg/kg (n=108), administered 7 d/week during a 5-year follow-up. The group receiving alternating therapy showed a significant reduction in serum ferritin.

In conclusion, in the randomized trial with 65 patients, DFP-DFO combination administered concomitantly is associated with greater efficacy than DFO alone as regards serum ferritin level in patients previously treated.

In a randomized trial with 60 patients, alternating therapy (5 days of deferiprone (75 mg/kg per day) alternating with 2 days of DFO) compared to DFO alone did not show greater efficacy in decrease in serum ferritin level than DFO alone. However, a randomized trial with 213 patients showed that alternating therapy (4 days of deferiprone (75 mg/kg per day alternating with 3 days of DFO) compared to DFP alone was correlated with a greater efficacy in decrease of serum ferritin level. The fact that alternating therapy demonstrated its superiority over DFP and not over DFO may indicate that this solution may rather rescue inefficient DFP monotherapy.

2. Efficacy on cardiac iron overload

A consensus statement from the American Heart Association has been established in 2013. Use of deferiprone-DFO combination therapy is recommended in patients suffering moderate to severe cardiac iron overload or when cardiac dysfunction is detected: “The first principle of management of acute heart failure is control of cardiac toxicity related to free iron by urgent commencement of a continuous, uninterrupted infusion of high-dose intravenous deferoxamine, augmented by oral deferiprone”.

A randomized placebo-controlled clinical trial[19] compared the use of deferoxamine alone or in combination with deferiprone (75 mg/kg per day) in the treatment of 65 patients with mild to moderate cardiac iron loading (cardiac T2* 8–20 ms). The beneficial effect of combined therapy on cardiac iron removal and improvement in cardiac function was confirmed. After one year, those receiving combination therapy had significantly greater improvement in cardiac T2* (from 11.7 to 17.7 ms compared with 12.4 to 15.7 ms) and in LVEF (2.6% compared with 0.6%) than those receiving deferoxamine alone.

Efficacy of deferoxamine and deferiprone combination was confirmed in a single arm trial [20] of 15 patients with severe myocardial siderosis (T2* <8 ms) and myocardial dysfunction. At baseline, deferoxamine was prescribed at 38 +/- 10.2 mg/kg for 5.3 days/week, and deferiprone at 73.9 +/- 4.0 mg/kg/day. Treatment with deferoxamine combined with deferiprone resulted in significant improvement in cardiac T2* (5.7 to 7.9 ms) and LVEF (51.2% to 65.6%).

[18] Maggio A, Vitrano A, Capra M, Cuccia L, Gagliardotto F, Filosa A, et al. Long-term sequential deferiprone-deferoxamine versus deferiprone alone for thalassaemia major patients: a randomized clinical trial. Br J Haematol. 2009;145(2):245-54.

[19] Tanner MA, Galanello R, Dessi C, Smith GC, Westwood MA, Agus A, et al. A Randomized, Placebo-Controlled, Double-Blind Trial of the Effect of Combined Therapy With Deferoxamine and Deferiprone on Myocardial Iron in Thalassemia Major Using Cardiovascular Magnetic Resonance. Circulation. 2007;115(14):1876-84.

[20] Tanner MA, Galanello R, Dessi C, Smith GC, Westwood MA, Agus A, et al. Combined chelation therapy in thalassemia major for the treatment of severe myocardial siderosis with left ventricular dysfunction. Journal of Cardiovascular Magnetic Resonance. 2008;10(12)

In contrast to what was observed for alternating therapy, simultaneous combination therapy of DFO/DFP may improve a marker of cardiac overload when compared to DFO, making the simultaneous combination superior to DFO when heart iron overload must receive control.

3. Effect on liver iron concentration

One observational study described a more rapid decline of liver iron concentration with combination compared to monotherapy[21]. In a study of 52 patients[22] who switched from deferoxamine monotherapy to deferiprone and deferoxamine combination therapy at baseline, 98% of patients had hepatic iron overload and 64% had severe hepatic overload: after 3 years of combination therapy, these proportions declined to 60% and 10%, respectively, and by 5 years, none of the 50 patients remaining on the study had iron overload.

Thus, combination therapy could be an alternative therapeutic option in case of mild or severe hepatic iron overload uncontrolled by iron chelator monotherapy.

4. Effect on endocrine complications

Regarding endocrine complications, a small study in 11 patients showed that combined therapy (DFO at 35–50 mg/kg, 3–4 times a week associated with DFP at 75 mg/kg, per os, daily) improved glucose metabolism[23]. In a study from Greece, reversal of endocrine complications with very intensive combined chelation (DFP 75-100 mg/kg/day and DFO 20-60 mg/kg/day) has been reported. Abnormal glucose metabolism was normalized in 11 of 39 (44%)[23], several cases of hypothyroidism, and hypogonadism reversal were reported[25]. However, zinc deficiency has also been implicated in the development of hypogonadism and has been more commonly associated with DFP chelation therapy than DFO or DFX[24]. DFP cannot be associated with a better decrease endocrine complication. Further studies are awaited.

5. Effect on survival

Randomized trial evaluating the survival of the deferiprone-DFO combination treatment were provided[25]. The multivariate analysis in Cyprus showed that combined chelation was associated with improved survival. The proposed explanation by the authors of the significant trend of increasing between 1980 and 2000 ($p<0.001$) and a decline (but not significant) after 2000 cardiac deaths ($p=0.06$) was the introduction of the combination therapy. In the small long-term comparative study (16 patients on DFO monotherapy and 19 patients on deferiprone and DFO combination therapy), there was no increased mortality with the combination[26].

[21] Berdoukas V, Chouliaras G, Moraitis P, Zannikos K, Berdoussi E, Ladis V. The efficacy of iron chelator regimes in reducing cardiac and hepatic iron in patients with thalassaemia major: a clinical observational study. J Cardiovasc Magn Reson. 2009;11(1):20.

[22] Farmaki K, Tzoumari I, Pappa C, Chouliaras G, Berdoukas V. Normalisation of total body iron load with very intensive combined chelation reverses cardiac and endocrine complications of thalassaemia major. Br J Haematol. 2009

[23] Christoforidis A, Perifanis V, Athanassiou-Metaxa M. Combined chelation therapy improves glucose metabolism in patients with beta-thalassaemia major. Br J Haematol. 2006;135:271-2.

[24] Perera NJ, Lau NS, Mathews S, Waite C, Ho PJ, Caterson ID. Overview of endocrinopathies associated with beta-thalassaemia major. Intern Med J. 2010;40(10):689-96.

[25] Telfer P, Coen PG, Christou S, Hadjigavriel M, Kolnakou A, Pangalou E, et al. Survival of medically treated thalassemia patients in Cyprus. Trends and risk factors over the period 1980-2004. Haematologica. 2006;91(9):1187-92.

[26] Kolnagou A, Economides C, Eracleous E, Kontoghiorghes GJ. Long Term Comparative Studies in Thalassemia Patients Treated with Deferoxamine or a Deferoxamine/Deferiprone Combination. Identification of Effective Chelation Therapy Protocols. Hemoglobin. 2008;32(1):41-7.

A major factor affecting mortality in any disease (especially severe and life threatening) over a recent period of 20 years is the global improvement in healthcare systems efficiency. To take the example of heart failure, improved prevention/detection, availability of new drugs (beta blockers, RAS inhibitors).

Roger V et al reported in the JAMA 2004 that "*survival after heart failure diagnosis improved over time (5-year age-adjusted survival, 43% in 1979-1984 vs 52% in 1996-2000, P<.001). However, men and younger persons experienced larger survival gains, contrasting with less or no improvement for women and elderly persons*."

Applied to a younger population and most often before diagnosis of heart failure in a population goes for very intensive follow-up, this improvement may be even larger.

As a consequence, the demonstration that combination therapy explained mortality improvements in Cyprus is considered very weak by the assessor. No statement related to this improvement should take place in the AR and in the PI.

Main studies of deferiprone and deferasirox combination chelation therapy

Among the 5 publications presented in the Appendix B: 2 of them were case studies[27,28] with one patient; two others were prospective, single center studies carried by Farmaki et al.[29] in 15 patients and Totadri et al. [30]in 36 patients showed serum ferritin significant decreases. In addition, liver iron concentration and cardiac iron load decreased in Farmaki et al. study.

Data from the randomized prospective study[31]showed that both combination regimes DFP/DFX and DFP/DFO were similarly effective in reducing liver iron concentration and serum ferritin in heavily iron loaded TM patients with normal cardiac function. However, this study was carried only in two centers, 48 patients in each group. No data was provided in comparison with monotherapy.

In conclusion, further studies were needed to complete the evaluation of the effect of this combination on larger number of patients and with different grades of iron overload severity.

2.3.2. Discussion on clinical efficacy

As noted by the MAH, most studies are observational, only few are prospective and/or randomized. The high number of publications shows the interest of combination therapy by the scientific community in the treatment of severe bTM. Comparative studies and some randomized clinical trials show that DFP-DFO combination is associated with relatively more rapid or pronounced serum ferritin decreases when compared with monotherapy. In addition, a decrease in serum ferritin could be associated with a

[27] Alavi S, Sadeghi E, Ashenagar A. Efficacy and safety of combined oral iron chelation therapy with deferasirox and deferiprone in a patient with beta-thalassemia major and persistent iron overload. Blood Res. 2014;49(1):72-3.

[28] Voskaridou E, Christoulas D, Terpos E. Successful chelation therapy with the combination of deferasirox and deferiprone in a patient with thalassaemia major and persisting severe iron overload after single-agent chelation therapies. Br J Haematol. 2011.

[29] Farmaki K, Tzoumari I, Pappa C. Oral chelators in transfusion-dependent thalassemia major patients may prevent or reverse iron overload complications. Blood Cells Mol Dis. 2011

[30] Totadri S, Bansal D, Bhatia P, Attri SV, Trehan A, Marwaha RK. The deferiprone and deferasirox combination is efficacious in iron overloaded patients with beta-thalassemia major: A prospective, single center, open-label study. Pediatr Blood Cancer. 2015;

[31] Elalfy, Adly AM, Wali Y, Tony S, Samir A, Elhenawy Y. Efficacy and safety of a novel combination of two oral chelators deferasirox/deferiprone over deferoxamine/deferipronre in severely iron-overloaded young beta thalassemia major patients. Eur J Haematol. 2015

decrease in iron liver. However, effects on endocrine complications and survival remain unclear. Use of the combination on moderate and severe cardiac complications is the only clear indication. For the DFP-DFX combination, data are also too preliminary and further studies on larger number of patients and with different grades of iron overload severity are needed.

Randomized trial with alternating therapy (Maggio et al., 2009) or combination therapy (Gomber et al., 2004; Aydinok et al., 2007) compared to DFP alone concluded to a greater efficacy of combination to decrease serum ferritin level. As supported by the Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT) 3rd Edition (Cappellini et al. 2014), these studies show that SF can be controlled with a relatively low frequency of DFO given twice a week when combined with DFP standard doses (75 mg/kg/day). The fact that DFO-DFP combination therapy demonstrated its superiority over DFP and not over DFO (Galanello et al., 2006; Aydinok et al., 2007) may indicate that this solution may rather rescue inefficient DFP monotherapy or provide a more acceptable option to patients not accepting frequent infusions anymore (which may correspond to an inefficient monotherapy due to tolerability issues and is covered by the Rapporteurs' indication wording).

A similar SF decrease was observed between DFP-DFO combination compared to DFO (Aydinok et al., 2007) but a greater efficacy of the combination was found in patients which received more days of DFO (5 days vs. 2 days) (Tanner et al., 2007). Tanner et al. (2007) compared the use of DFO alone or in combination with DFP (75 mg/kg per day) in the treatment of 65 patients with mild to moderate cardiac iron loading (cardiac T2* 8–20 ms). The beneficial effect of combined therapy on cardiac iron removal and improvement in cardiac function was confirmed. Efficacy of DFO-DFP combination was confirmed in a single arm trial of 15 patients with severe myocardial siderosis (T2* <8 ms) and myocardial dysfunction (Tanner et al., 2008). In contrast to what was observed for alternating therapy, simultaneous combination therapy of DFO/DFP may improve a marker of cardiac overload when compared to DFO, making the simultaneous combination superior to DFO when heart iron overload must receive control.

In summary, data from the published literature on iron balance studies in patients with thalassaemia major show that the use of Ferriprox concurrently with deferoxamine (coadministration of both chelators during the same day, either simultaneously or sequentially, e.g., Ferriprox during the day and deferoxamine during the night), promotes greater iron excretion than either drug alone. Doses of Ferriprox in those studies ranged from 50 to 100 mg/kg/day and doses of deferoxamine from 40 to 60 mg/kg/day. However, chelation therapy may not necessarily protect against iron-induced organ damage.
A randomized, placebo-controlled, double-blind trial evaluated the effect of concurrent therapy with Ferriprox and deferoxamine in patients with thalassaemia major, who previously received the standard chelation monotherapy with subcutaneous deferoxamine and had mild to moderate cardiac iron loading (myocardial T2* from 8 to 20 ms). Following randomization, 32 patients received deferoxamine (43.4 mg/kg/day for 5 days/week) and Ferriprox (75 mg/kg/day) and 33 patients received deferoxamine monotherapy (34.9 mg/kg/day for 5 days/week). After one year of study therapy, patients on concurrent chelation therapy had experienced a significantly greater reduction in serum ferritin (1574 µg/l to 598 µg/l with concurrent therapy vs. 1379 µg/l to 1146 µg/l with deferoxamine monotherapy, p<0.001), significantly greater reduction in myocardial iron overload, as assessed by an increase in MRI T2* (11.7 ms to 17.7 ms with concurrent therapy vs. 12.4 ms to 15.7 ms with deferoxamine monotherapy, p=0.02) and significantly greater reduction in liver iron concentration, also assessed by an increase in MRI T2* (4.9 ms to 10.7 ms with concurrent therapy vs. 4.2 ms to 5.0 ms with deferoxamine monotherapy, p< 0.001).

The above information has been included in section 5.1. of the SmPC.

The wording of the indication has been agreed as:

Ferriprox **monotherapy** is indicated for the treatment of iron overload in patients with thalassaemia major when **current chelation** ~~deferoxamine~~ 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 4.2).

Dose adjustments when used with other iron chelators have been included in the SmPC section 4.2. as follows:

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.

2.3.3. Conclusions on the clinical efficacy

The CHMP acknowledge the conditions in which the combination chelation therapy is needed: a failure to control the iron burden at maximum dosage of current chelators and when current chelators cannot be adequately used, e.g. associated with dose-limiting toxicities.

Moreover, in the absence of evidence that a particular combination is a problem, its use should not be restrained, and the possibility to use Ferriprox in combination should be given to the clinician based on its own assessment of the potential benefit for the patient. Therefore the combination of Ferriprox with another chelator 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 – is supported by the above data.

Efficacy data of the DFP-DFX combination is very limited due to the small number of patients exposed and the lack of information about the safety of this combination (only 5 patients exposed in the MAH clinical trials). Thus, the use of deferiprone with deferoxamine or deferasirox has been differentiated in the SmPC. Additional precautions for use have been added on the combination of deferiprone and deferasirox as limited data are available.

2.4. Clinical safety

2.4.1. Main Studies

Safety data collected by ApoPharma during later-stage clinical trials and safety results published in the literature were provided in this application instead of new relevant data from dedicated trial.

In the pooled safety database of all patients enrolled in ApoPharma clinical trials (N=712 as of 31 August 2014), 115 patients received combination Ferriprox-DFO therapy, with a mean exposure of slightly over 2 years. Five other patients received combination Ferriprox-DFX therapy (not included in

the table below). A list of ADRs from Apopharma database that compares the proportion of ADRs between Ferriprox monotherapy and combination therapy was provided in Appendix C. The total exposure for Ferriprox in combination with DFO is lower than for Ferriprox monotherapy (244 vs 1343 PY (patient-years). The incidence rate of events (for 100 PY) is higher in the arm of Ferriprox in combination with DFO in 2 system organ class: cardiac disorders (1.64 vs 0.15), infections (1.64 vs 0.74), investigations (14.75 vs 14.60) and Ear disorders (0.82 vs 0.37). The main cardiac disorders reported are rhythm troubles (but we cannot totally exclude the fact that it could be related to iron overload in heart). The safety database was also reviewed for reports of serious ADRs from post-marketing surveillance. While this review did not allow for comparison of incidence, the nature of the reported reactions did not raise any safety concerns. A list of post-marketing serious ADRs that were associated with deferiprone-DFO combination therapy is provided in Appendix D, and for deferiprone-DFX combination therapy in Appendix E.

A search for studies that reported safety data on combination therapies between 1998 and June 2015 identified 57 publications that presented safety data on combination therapy:

49 publications on deferiprone-DFO (Appendix F) and 8 publications on deferiprone-DFX (Appendix G).

Based on the indications of deferiprone, the combination of deferiprone with other iron chelator therapies (deferoxamine or deferasirox) is considered as an off-label use. Deferiprone-DFO combination therapy was not associated with new safety concerns in the provided studies. Thus, data are reassuring but should be taken with considerable caution as dose regimen were very heterogenous according the studies. Only dedicated studies could provide an answer on the relevance of this combination as long as on the efficacy and safety aspect.

In addition, no clear conclusion could be drawn from association deferiprone- deferasirox as only isolated patients received such combination in published literature. In the SPC of Exjade, combination with other chelators are contra-indicated as the safety of such combination were not clearly established. Combination with other iron chelator therapy is an exclusion criteria in clinical trial development program of Exjade.

Whatever the iron chelators associated, we cannot totally exclude that this potential risk remains.

Furthermore, in post-marketing setting, in Eudravigilance database, there are 7 fatal (3 fatal agranulocytosis and 4 fatal cardiac complications)

a) one Swedish published case32 in a 10-years old patient with DBA (off-label use) : in this case, the girl developed agranulocytosis 9 weeks after chelation with deferiprone was initiated (45 mg/kg daily, 60% of recommended dose) in addition to her ordinary deferoxamine therapy. The blood count checked weekly dropped markedly between week 8 and 9. She rapidly developed a septicemia. Despite G-CSF and corticoid therapy, she remained neutropenic and died 6 weeks after admission. According to the authors, DBA patients may be more prone than thalassemia patients to developing deferiprone associated agranulocytosis as DBA patients may develop bone marrow hypoplasia. However, it should kept in mind that in this case the agranulocytosis developed rapidly after addition of deferiprone to her ordinary deferoxamine therapy and agranulocytosis is not predictable and as well possibly not dose dependent.

b) One Swedish case (in Swedish in EV) was reported in a 12 years-old girl with beta-thalassemia : the patient has received transfusions since early age and had a failed bone marrow transplantation. She received deferiprone (1.5g) in addition of deferoxamine (unknown dose). After six months of treatment, during ferriprox dose escalation, neutrophils count drop <0.1 G/l and platelets dropped to 70 (N : 140-400) within one week despite weekly controls. The day after the onset of fever, CRP was 250mg/L. Ferriprox was stopped and treatment with G-CSF was started. The patient developed a sepsis (E coli) and a sore throat with streptococcus B. She experienced several cardiac arrests. An increased sensitivity due

to cardiac iron overload was also suspected and died.

c) One case from Iran was reported in a 22 years-old beta-thalassemic patient. The patient began treatment with deferiprone (75mg/kg/day) due to iron overload in combination with deferoxamine (3g). Two months later, the patient had neutrophils count decreased and agranulocytosis was diagnosed with septic shock. The patient developed ARDS and died 10 days after event onset.

And 4 fatal cardiac complications (including one with DFP+DFX and 3 with DFP+DFO), probably due to disease progression (cardiac iron overload).

In addition, 23 other life-threatening cases were retrieved with combined DFP+DFO in eudravigilance database (mainly agranulocytosis occurring in young beta-thalassemic patients and occurring most frequently within the 1st months of combined therapy. In most cases, the patient recovered without sequelae after drug interruption).

Recently, a French serious case of arthropathy/arthralgia occurred within 3 months with combination DFO+DFP (doses unknown) in a 6 years-old thalassemic patient. Symptoms improved after DFP discontinuation but remains under DFO monotherapy. This case (coded as leading to disability or incapacity) suggests a possible addition of adverse effects of each iron chelator associated which is worrying.

However, as concludes the COCHRANE report (2013)[33] on the use of oral DFP for iron chelation in people with thalassaemia, a meta-analysis of a further two trials showed a significant increased risk of adverse events associated with combined DFP-DFO compared with DFO alone, RR 3.04 (95% CI 1.18 to 7.83) and there is no adequately-powered, high-quality trials comparing the overall clinical efficacy and long-term outcome of deferiprone with desferrioxamine, allowing to have a precise idea on how to manage in clinical practice the association of chelators in terms of posology and regimen to insure the safety for patients.

2.4.2. Discussion on clinical safety

The MAH provided in a first part of this procedure a review of the safety data collected by itself during later-stage clinical trials and in a second part safety results published in the literature.

DFP-DFO combination therapy was not associated with new safety concerns in the provided studies. Thus, data are reassuring but should be taken with considerable caution as dose regimen were very heterogenous according the studies. Only dedicated studies could provide an answer on the relevance of this combination as long as on the efficacy and safety aspect.

In addition, no clear conclusion could be drawn from association DFP-DFX as only isolated patients received such combination in published literature.

Whatever the iron chelators associated, we cannot totally exclude that this potential risk remains. 7 fatal cases caused by agranulocytosis or cardiac complications have been observed in Eudravigilance database. Thus, the warning “Fatalities and life-threatening situations (caused by agranulocytosis) have been reported with deferiprone in combination with deferoxamine” has been included in the section 4.4 of the SmPC.

A list of ADRs from Apopharma database that compares the proportion of ADRs between deferiprone monotherapy and combination therapy was provided. Data from pooled safety database from clinical trials (244 patients-year exposed for Ferriprox monotherapy and 1343 patients-year exposed to Ferriprox and deferoxamine) showed statistically significant ($p<0.05$) differences in the incidence of adverse reactions based on SOC for “Cardiac disorders", "Musculoskeletal and connective tissue

[44]Fisher SA, Brunskill SJ, Doree C, Gooding S, Chowdhury O, Roberts DJ. Desferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia. Cochrane Database Syst Rev. 2013;8:CD004450.

disorders" and "Renal and urinary disorders". The incidences of "Musculoskeletal and connective tissue disorders" and "Renal and urinary disorders" were lower during combination therapy than monotherapy, whereas the incidence of "Cardiac disorders" was higher during combination therapy than monotherapy. The higher rate of "Cardiac disorders" reported during combination therapy than monotherapy was possibly due to the higher incidence of pre-existing cardiac disorders in patients who received combination therapy.

In consequence, the CHMP proposes to modify the section 4.4 of the SmPC in order to include precaution for use related to cardiac disorders (see section 2.9 of this procedure: Update of Product Information).

In the safety profile of DFP-DFO combination provided by the MAH, only 18 children have been exposed to the combination. Thus, it is very difficult to draw any sound conclusion on these findings. However, the number of children treated with the combination and the incidence of adverse events have been documented in the section 4.8 of the SmPC.

Information on Combined use with other iron chelators has been included in section 4.4. of the SmPC; The use of combination therapy should be considered on a case-by-case basis. The response to therapy should be assessed periodically, and the occurrence of adverse events closely monitored. Fatalities and life-threatening situations (caused by agranulocytosis) have been reported with deferiprone in combination with deferoxamine. Combination therapy with deferoxamine is not recommended when monotherapy with either chelator is adequate or when serum ferritin falls below 500 µg/l. Limited data are available on the combined use of Ferriprox and deferasirox, and caution should be applied when considering the use of such combination.

The safety profile of combination therapy (deferiprone and deferoxamine) observed in clinical trials, post-marketing experience or published literature was consistent with that characterized for monotherapy.
Data from the pooled safety database from clinical trials (1343 patient-years exposure to Ferriprox monotherapy and 244 patient-years exposure to Ferriprox and deferoxamine) showed statistically significant ($p<0.05$) differences in the incidence of adverse reactions based on System Organ Class for "Cardiac disorders", "Musculoskeletal and connective tissue disorders" and "Renal and urinary disorders". The incidences of "Musculoskeletal and connective tissue disorders" and "Renal and urinary disorders" were lower during combination therapy than monotherapy, whereas the incidence of "Cardiac disorders" was higher during combination therapy than monotherapy. The higher rate of "Cardiac disorders" reported during combination therapy than monotherapy was possibly due to the higher incidence of pre-existing cardiac disorders in patients who received combination therapy. Careful monitoring of cardiac events in patients on combination therapy is warranted (see section 4.4).

The incidences of adverse reactions experienced by 18 children and 97 adults treated with combination therapy were not significantly different between the two age groups except in the incidence of arthropathy (11.1% in children vs. none in adults, $p=0.02$). Evaluation of rate of reactions per 100 patient-years of exposure showed that only the rate of diarrhoea was significantly higher in children (11.05) than in adults (2.01, $p=0.01$).

2.4.3. Conclusions on clinical safety

As safety data of the combination deferiprone and deferasirox are too preliminary, this combination is not recommended. Thus, the use of deferiprone with deferoxamine or deferasirox has been differentiated in the SmPC. Additional precautions for use have been added on the combination of deferiprone and deferasirox as limited data are available.

Deferiprone and deferoxamine combination therapy was not associated with new safety concerns in the provided studies. Thus, data are reassuring but should be taken with considerable caution as dose regimen were very heterogenous according the studies. In consequence, relevant warnings and precautions concerning cardiac disorders and agranulocytosis are included in the section 4.4 of the SmPC. All available information on the safety profile of the combination is included in section 4.8. of the SmPC.

Appendix A: Summary of the efficacy data from studies of combined use of deferiprone and deferoxamine

Author Year	N	T duration (months)	DFP dose (mg/kg/day)	DFP (dose regimen)	DFO dose (mg/kg/day)	DFO (days/wk)	SF (µg/L)		LIC (mg/g dw)		MRI T2* H (ms)		MRI T2* L (ms)		LVEF (%)	
							initial	final	initial	final	initial	final	initial	final	initial	final
Wonke 1998[102]	5	7-15	88-110	t.i.d.	4g/48h/wk 2g/24h 5d/wk 3g/24h 6d/wk	2-6	7500	2438 p=0.0791								
Balveer 2000[9]	7	12	75-80	not indicated	1-2 g/wk	2	7066.11 (2577-12.896)	3242.24 (955-6120)	19.6	18.2						
Mourad 2004[65]	11	12	75	t.i.d.	2g/d	2	4153 ± 517	2805 ± 327 p<0.01								
Gomber 2004[41]	10	12	75	not indicated	40	2	3347.78 ± 1526.46	3376.57 ± 1222.41								
Athanassiou Metaxa 2004[6]	25	18	75	t.i.d.	40	3	2628.00 ± 526.87	1844.28 ± 611.26								
D'Angelo 2004[22]	7	10-30 (16.28)	75	t.i.d.	40-50	7-10d following transfusion	2.864 ± 326	1.475 ± 92 p<0.01								
Alymara 2004[4]	25	13.5	60	t.i.d.	40-50	4-6	2637 ± 1291	1580 ± 1024 p=0.002								
Origa 2005[67]	64	12-57	70-80	t.i.d.	40-50	5-6	5243 ± 2345	3439 ± 2426 p<0.001							54.7± 8.6%	59.6± 5.1% p<0.0001
Kattamis 2006[50]	50	12	25	b.i.d.	30-55	3	3363.7 ± 2144.5	2323.2 ± 1740.8 p<0.0001								
Ha 2005[45]	17	18	75	t.i.d.	30-60	2		-987.0 ± 2984.0 pmol/L		0.95 ± 15.49						
Tanner 2007[89]	32	12	75	not indicated	34.9	5	1574	598 p<0.001			11.7	17.7 p<0.001	4.9	10.7 p<0.001	65.8 ± 6.2%	68.4 ± 4.7% p=0.05

Peng 2006[69]	31	4-37 (27.7±7.7)	75-80	t.i.d.	30-50	3-7	4699.4±3340.3	3301.8±2536.4 p=0.01								
Daar 2006[23]	55	60-48	75	t.i.d.	40	4-5	3088±1299	2051±935 p<0.001							ejection fraction (compliant group N=42) 69.04±5.182	ejection fraction 79.99± 5.4
Kolnagou 2006[55]	11	9-28	80-110	not indicated	40-60	3	2575.9±1598.2	1129.4 ± 933.2								
Farmaki 2006[30]	42	44.5±12.4 range 20-54	75-90	t.i.d.	20-40	2-6	2991 ± 2093	639 ± 1345 p<0.001								
Christoforidis 2006[18]	16	24	75 per os	not indicated	30-50	3-4	2303	2123 p=0.278	5.31 value converted to mg/g dw as per Tanner 2008	5.69 p= 0.17						
	28	24					2062	1633 p=0.0002	5.93	6.18 p=0.22						
Christoforidis 2007(20)	30	3	75-100	not indicated	40-50	2-3	1480 ± 1254	1208 ± 1072 p= 0.001								
Eshghi 2007(27)	32	20.1±1.4	75	t.i.d.	30-40	2-3	3179 ± 1599	2408.3 ± 1616								

Author Year	N	T duration (months)	DFP dose mg/kg/day	DFP (dose regimen)	DFO dose mg/kg/day	DFO (days/wk)	SF (µg/L)		LIC (mg/g dw)		MRI T2* H (ms)		MRI T2* L (ms)		LVEF (%)	
							initial	final	initial	final	initial	final	initial	final	initial	final
Aydinok 2007[7]	8	12	75	not indicated	40-50	2	4350 ± 3342	2954 ± 2765	26.6±15.4	18.1±11.6					71.7±8.6%	72.6±6.6%
Tsironi 2008[97]	5	18	70-80	t.i.d.	35	5	2654.8 ± 1583.7	289.4 ± 87.9 p<0.026			20.50± 12.85	23.66± 10.45 p<0.05	2.78 ±1.67	9.17±8.89	63.92±13.36	71.89±4.7
Kolnagou 2008[52]	19	12-60	75-100	not indicated	30-60	1-5	2255.78± 1400.3	1492.1±1677.4								
Tanner 2008[88]	15	11.7±1.6	73.9 ±4.0 (start) 65.7± 10.7 (end month 12)	not indicated	38±10.2 (start) 20.3±10.9 (end mo 12)	5.3 (start) 4.5 (end month 20)	2057 (CV 7.6%)	666 (CV 13.2%)	3.57	1.15 values converted to mg/g dw as per Tanner 2008	5.7±0.98	7.9±2.47 p=0.010	3.7± 2.9	10.8±7.3 p=0.0006	51.2±10.9	65.6±6.7%
Zareifar 2009[107]	35	12	75	t.i.d.	40-50	3-5	4053±1452	2686±929								
Ha 2009[47]	31	12	75	not indicated	40-60	3-5	7464±3555	5141±3241 p=0.751			18.5±12.8	20.1 ± 11.1	3.4 ± 2.6	5.1 ± 4.9	60.9 ± 7.1	62.6 ± 10.3
Farmaki 2009[32]	52	60-84	70-100	t.i.d.	20-60	not indicated	3421 ± 882.0	87 ± 25 p<0.001	15.7 ± 11.1	0.9 ± 0.2 p<0.001	13.8 ± 9.8	35.5 ± 8.1 p<0.001	1.5 ± 8.2	34.4 ± 5.4 p<0.01		
Maggio 2009[62]	105	35	75	t.i.d.	50	3	1787 ± 735	1369 ± 816 p=0.005								
Economou 2010[24]	14	not indicated	60-80	not indicated	11-48	5	1401.81 ± 1205.13	1147.4 ± 838								
Ricchi 2009[82]	13	84	75	not indicated	25-35	5	2592 ± 1707	899 ± 833 P<0.001	7.4 ± 3.2	3.3 ± 1.6 p<0.001	18.9 ± 13.4	22.2 ± 12.5			55.7 ± 8.8	58.2 ± 9.25
	6		50	not indicated	25-35	5										
	10		75	not	25-35	3										

				indicated												
	7		50	not indicated	25-35	3										
Tsiapras 2010[96]	26	24	80-100	not indicated	40	3		168 ± 149 (44-625) P<0.001			18.3 ± 4.2 (1326)	26.4 ± 3.8 (18-36) P<0.001			63±4	65±3
	10	24	75		40	2-3	1184 ± 256 (710-1805)	496 ± 222(128880) p<0.001								
	4	24	75		40	6-7										
Kolnagou 2010[53]	8	21-68	75-100	not indicated	40-60	3	1446 ± 1035 (539-3845) (G mean)	114.7 ± 139.8 (40-421) (G mean) p< 0.0052			10.32 ± 6.72 (4.5-24.2)	29.6 ± 6.6 (22-41) P<0.00076				
Tamaddoni 2010[87]	40	12	75	not indicated	40-50	2	2986 ± 612	2.082 ± 221 p<0.001								
Ha 2011[46]	29	30	75-100	not indicated	40-60	3-5	7850 ± 3619 pmol/l	4573 ± 3135 pmol/l			15.7 ± 10.0	22.8 ± 12.7	2.9 ± 2.2	5.3 ± 5.0 p=0.003	60.6±6.5	63.8±4.4
Kolnagou 2011[54]	8	21-68	80-100	not indicated	40-60	3	1692 ± 366 (539-3845)	158 ± 49 (40-421) p<0.0052			11.1 ± 2.5 (4.5-24.2)	30.2 ± 2.3 (22-41)	4.3 ± 1.8 (1.4-14)	27.6 ± 2.8 (9.1-35)		
Cassinerio 2012[17]	3	32±7	73±7	not indicated	46±7	4					5.87 ± 1.33	10.7 ± 6.58			52.00±6.56	53.3±7.5
	5										13.7 ± 3.02	27.07± 10.61 p=0.03			57.6±13.8	60.2±8.2
Mirbehbahani 2012[64]	12	6	75	t.i.d.	30-50	every other day	7539.8 ± 3434.9	4848.7 ± 2706.2								
Pepe 2013[76]	51	18	61.9 ±24.3 6.1± 1.4d/	not indicated	40.7±6.0	3.5±1.1										

			wk												
Author Year	**N**	**T duration (months)**	**DFP dose (mg/kg/day)**	**DFP (dose regimen)**	**DFO dose (mg/kg/day)**	**DFO (days/wk)**	**SF (µg/L)**		**LIC (mg/g dw)**		**MRI T2* H (ms)**		**MRI T2* L (ms)**		**LVEF (%)**	
							initial	**final**	**initial**	**final**	**initial**	**final**	**initial**	**final**	**initial**	**final**
Shahvazian 2012[(343)]	36	12	50-86	not indicated	24-52	not indicated									59.3 ± 5.7	63.7 ± 5.1
Porter 2013[(81)]	11	12	75	not indicated	50-60	7	3259.2 ± 1924.8	1937.0 ± 1528.0	12.7 ± 10.8	8.0 ± 8.7	8.4 ± 5.7	9.8 ± 7.4			51.8 ± 5.2	56.3 ± 7.2
Songdej 2015[8][(85)]	42	36	50–100	t.i.d. – q.i.d	40 ± 5	2	3,014.6	1,058.3								
Elalfy 2015[(26)]	48	12	75	b.i.d.	40	6	4379.07	3625.76	12.69	10.96	16.32	17.8				

In the trial conducted by Songdej et al., cardiac and liver MRI T2* were done in only 9 of the 42 patients at the 24-month time point, and only the individual results are ovided.

Appendix B: Summary of the efficacy data from studies of combined use of deferiprone and deferasirox

Author Year	N	T duration (months)	DFP dose (mg/kg/day)	DFP (dose regimen)	DFX dose (mg/kg/day)	DFX (days/wk)	SF (µg/L)		LIC (mg/g dw)		MRI T2* H (ms)		MRI T2* L (ms)		LVEF (%)	
							initial	final	initial	final	initial	final	initial	final	initial	final
Farmaki 2011[31]	15	12-24	75-100	t.i.d.	20-25	1	581 ± 346	103 ± 60 p=0.0001	1.6 ± 1.1	1.0 ± 0.2 p=0.0019	34.1 ± 5.8	36.9 ± 5.6 p=0.0381	18.6 ± 8.9	30.5 ± 5.9 p=0.0012		
Alavi 2014[3]	1	8	75	t.i.d.	25	7	1,596	<100			15	23.1	6.78	9.0		
Elalfy 2015[26]	48	12	75	b.i.d.	30	7	4289.19	3219.98	12.52	10.17	16.59	19.75				
Totadri 2015[95]	36	12	75 - 100	t.i.d.	30 - 40	7	6,768	3,493								
Voskaridou 2011[100]	1	12	75	not indicated	30	7	2080	397			13.7	21.1	7.8	15.3		

Appendix C: Summary of Adverse Drug Reactions in patients treated with Ferriprox monotherapy and in patients treated with Ferriprox in combination with deferoxamine (DFO) in pooled clinical studies

	DFP Monotherapy Total Exposure: 1,343 yrs** Total # of patients exposed=592 Total # of patients reporting=354 Total # of events=1,522		Combination DFP and DFO Total Exposure: 244 yrs** Total # of patients exposed=115 Total # of patients reporting=45 Total # of events=140		
System Organ Class Preferred Term	**N patients (%)***	**Events (Rate per 100 patient years)**	**N patients (%)***	**Events (Rate per 100 patient years)**	**P-value (Fisher's exact)**
Blood and lymphatic system disorders	57 (9.6)	73 (5.44)	11 (9.6)	12 (4.92)	1.0000
Neutropenia	40 (6.8)	44 (3.28)	10 (8.7)	10 (4.10)	0.4305
Agranulocytosis	14 (2.4)	15 (1.12)	1 (0.9)	1 (0.41)	0.4862
Leukopenia	5 (0.8)	7 (0.52)	0 (0.0)	0 (0.00)	1.0000
Thrombocytopenia	4 (0.7)	4 (0.30)	1 (0.9)	1 (0.41)	0.5895
Anaemia	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Blood disorder	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Hypersplenism	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Cardiac disorders	2 (0.3)	2 (0.15)	3 (2.6)	4 (1.64)	0.0327
Arrhythmia	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Torsade de pointes	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Atrial fibrillation	0 (0.0)	0 (0.00)	1 (0.9)	1 (0.41)	0.1627
Cardiogenic shock	0 (0.0)	0 (0.00)	1 (0.9)	1 (0.41)	0.1627
Sinus tachycardia	0 (0.0)	0 (0.00)	1 (0.9)	1 (0.41)	0.1627
Supraventricular tachycardia	0 (0.0)	0 (0.00)	1 (0.9)	1 (0.41)	0.1627
Ear and labyrinth disorders	5 (0.8)	5 (0.37)	2 (1.7)	2 (0.82)	0.3189
Deafness	2 (0.3)	2 (0.15)	1 (0.9)	1 (0.41)	0.4134
Ear pain	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Tinnitus	1 (0.2)	1 (0.07)	1 (0.9)	1 (0.41)	0.2991
Vertigo	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Gastrointestinal disorders	152 (25.7)	399 (29.71)	21 (18.3)	65 (26.63)	0.0977
Nausea	78 (13.2)	117 (8.71)	10 (8.7)	15 (6.15)	0.2176
Vomiting	59 (10.0)	95 (7.07)	10 (8.7)	31 (12.70)	0.8635
Abdominal pain upper	37 (6.3)	74 (5.51)	2 (1.7)	3 (1.23)	0.0704
Abdominal pain	22 (3.7)	26 (1.94)	2 (1.7)	3 (1.23)	0.4028
Diarrhoea	16 (2.7)	23 (1.71)	5 (4.3)	9 (3.69)	0.3642

System Organ Class Preferred Term	N patients (%)*	Events (Rate per 100 patient years)	N patients (%)*	Events (Rate per 100 patient years)	P-value (Fisher's exact)
Dyspepsia	12 (2.0)	23 (1.71)	0 (0.0)	0 (0.00)	0.2316
Abdominal discomfort	8 (1.4)	12 (0.89)	2 (1.7)	2 (0.82)	0.6699
Abdominal distension	5 (0.8)	7 (0.52)	1 (0.9)	1 (0.41)	1.0000
Epigastric discomfort	4 (0.7)	8 (0.60)	0 (0.0)	0 (0.00)	1.0000
Eructation	4 (0.7)	5 (0.37)	0 (0.0)	0 (0.00)	1.0000
Gastritis	3 (0.5)	3 (0.22)	1 (0.9)	1 (0.41)	0.5092
Constipation	2 (0.3)	2 (0.15)	0 (0.0)	0 (0.00)	1.0000
Abdominal pain lower	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Aphthous stomatitis	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Gastrooesophageal reflux disease	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Stomatitis	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
General disorders and administration site conditions	20 (3.4)	25 (1.86)	2 (1.7)	2 (0.82)	0.5569
Fatigue	5 (0.8)	6 (0.45)	1 (0.9)	1 (0.41)	1.0000
Asthenia	4 (0.7)	4 (0.30)	0 (0.0)	0 (0.00)	1.0000
Local swelling	4 (0.7)	4 (0.30)	0 (0.0)	0 (0.00)	1.0000
Chest pain	2 (0.3)	2 (0.15)	1 (0.9)	1 (0.41)	0.4134
Malaise	2 (0.3)	3 (0.22)	0 (0.0)	0 (0.00)	1.0000
Oedema peripheral	2 (0.3)	2 (0.15)	0 (0.0)	0 (0.00)	1.0000
Discomfort	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Influenza like illness	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Pyrexia	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Thirst	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Hepatobiliary disorders	6 (1.0)	7 (0.52)	0 (0.0)	0 (0.00)	0.5965
Hepatic pain	3 (0.5)	3 (0.22)	0 (0.0)	0 (0.00)	1.0000
Hepatitis	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Hepatomegaly	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Jaundice	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Liver tenderness	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Immune system disorders	1 (0.2)	2 (0.15)	0 (0.0)	0 (0.00)	1.0000
Hypersensitivity	1 (0.2)	2 (0.15)	0 (0.0)	0 (0.00)	1.0000

System Organ Class Preferred Term	N patients (%)*	Events (Rate per 100 patient years)	N patients (%)*	Events (Rate per 100 patient years)	P-value (Fisher's exact)
Infections and infestations	9 (1.5)	10 (0.74)	3 (2.6)	4 (1.64)	0.4245
Influenza	2 (0.3)	2 (0.15)	0 (0.0)	0 (0.00)	1.0000
Cytomegalovirus hepatitis	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Diabetic foot infection	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Gastroenteritis	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Gastroenteritis viral	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Nasopharyngitis	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Sepsis	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Upper respiratory tract infection	1 (0.2)	1 (0.07)	1 (0.9)	1 (0.41)	0.2991
Yersinia infection	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Oesophageal candidiasis	0 (0.0)	0 (0.00)	1 (0.9)	1 (0.41)	0.1627
Respiratory tract infection	0 (0.0)	0 (0.00)	1 (0.9)	1 (0.41)	0.1627
Serratia sepsis	0 (0.0)	0 (0.00)	1 (0.9)	1 (0.41)	0.1627
Injury, poisoning and procedural complications	3 (0.5)	3 (0.22)	0 (0.0)	0 (0.00)	1.0000
Epicondylitis	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Overdose	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Transfusion reaction	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Investigations	104 (17.6)	196 (14.60)	17 (14.8)	36 (14.75)	0.5882
Alanine aminotransferase increased	48 (8.1)	67 (4.99)	7 (6.1)	11 (4.51)	0.5698
Neutrophil count decreased	41 (6.9)	51 (3.80)	9 (7.8)	13 (5.33)	0.6930
Weight increased	12 (2.0)	12 (0.89)	0 (0.0)	0 (0.00)	0.2316
Aspartate aminotransferase increased	10 (1.7)	14 (1.04)	2 (1.7)	3 (1.23)	1.0000
Transaminases increased	6 (1.0)	6 (0.45)	1 (0.9)	2 (0.82)	1.0000
White blood cell count decreased	6 (1.0)	26 (1.94)	1 (0.9)	2 (0.82)	1.0000
Electrocardiogram t wave inversion	5 (0.8)	5 (0.37)	0 (0.0)	0 (0.00)	1.0000
Gamma-glutamyltransferase increased	5 (0.8)	5 (0.37)	1 (0.9)	1 (0.41)	1.0000
Blood zinc decreased	3 (0.5)	3 (0.22)	0 (0.0)	0 (0.00)	1.0000

System Organ Class Preferred Term	N patients (%)*	Events (Rate per 100 patient years)	N patients (%)*	Events (Rate per 100 patient years)	P-value (Fisher's exact)
Arthroscopy	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Blood creatinine increased	1 (0.2)	1 (0.07)	1 (0.9)	1 (0.41)	0.2991
Blood lactate dehydrogenase increased	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Platelet count decreased	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Platelet count increased	1 (0.2)	2 (0.15)	0 (0.0)	0 (0.00)	1.0000
Weight decreased	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Blood bilirubin increased	0 (0.0)	0 (0.00)	1 (0.9)	1 (0.41)	0.1627
Blood phosphorus increased	0 (0.0)	0 (0.00)	1 (0.9)	1 (0.41)	0.1627
Serum ferritin abnormal	0 (0.0)	0 (0.00)	1 (0.9)	1 (0.41)	0.1627
Metabolism and nutrition disorders	33 (5.6)	36 (2.68)	2 (1.7)	2 (0.82)	0.0996
Increased appetite	26 (4.4)	28 (2.09)	0 (0.0)	0 (0.00)	0.0137
Decreased appetite	7 (1.2)	7 (0.52)	1 (0.9)	1 (0.41)	1.0000
Fluid retention	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Hypoglycaemia	0 (0.0)	0 (0.00)	1 (0.9)	1 (0.41)	0.1627
Musculoskeletal and connective tissue disorders	92 (15.5)	217 (16.16)	8 (7.0)	9 (3.69)	0.0130
Arthralgia	69 (11.7)	120 (8.94)	5 (4.3)	6 (2.46)	0.0188
Back pain	13 (2.2)	22 (1.64)	0 (0.0)	0 (0.00)	0.1424
Pain in extremity	12 (2.0)	22 (1.64)	0 (0.0)	0 (0.00)	0.2316
Arthropathy	7 (1.2)	7 (0.52)	2 (1.7)	2 (0.82)	0.6449
Joint swelling	6 (1.0)	14 (1.04)	1 (0.9)	1 (0.41)	1.0000
Arthritis	5 (0.8)	5 (0.37)	0 (0.0)	0 (0.00)	1.0000
Musculoskeletal pain	3 (0.5)	7 (0.52)	0 (0.0)	0 (0.00)	1.0000
Myalgia	3 (0.5)	3 (0.22)	0 (0.0)	0 (0.00)	1.0000
Bone pain	2 (0.3)	3 (0.22)	0 (0.0)	0 (0.00)	1.0000
Muscle spasms	2 (0.3)	3 (0.22)	0 (0.0)	0 (0.00)	1.0000
Joint crepitation	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Joint effusion	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Joint range of motion decreased	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Joint stiffness	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Metatarsalgia	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000

System Organ Class Preferred Term	N patients (%)*	Events (Rate per 100 patient years)	N patients (%)*	Events (Rate per 100 patient years)	P-value (Fisher's exact)
Muscular weakness	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Musculoskeletal chest pain	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Osteonecrosis	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Osteopenia	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Polyarthritis	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Synovial cyst	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Nervous system disorders	23 (3.9)	45 (3.35)	1 (0.9)	2 (0.82)	0.1549
Headache	15 (2.5)	36 (2.68)	1 (0.9)	2 (0.82)	0.4909
Dizziness	5 (0.8)	6 (0.45)	0 (0.0)	0 (0.00)	1.0000
Somnolence	2 (0.3)	2 (0.15)	0 (0.0)	0 (0.00)	1.0000
Hypogeusia	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Renal and urinary disorders	95 (16.0)	476 (35.45)	1 (0.9)	1 (0.41)	<0.0001
Chromaturia	94 (15.9)	475 (35.37)	1 (0.9)	1 (0.41)	<0.0001
Pollakiuria	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Reproductive system and breast disorders	3 (0.5)	4 (0.30)	0 (0.0)	0 (0.00)	1.0000
Amenorrhoea	2 (0.3)	3 (0.22)	0 (0.0)	0 (0.00)	1.0000
Menstruation irregular	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Respiratory, thoracic and mediastinal disorders	3 (0.5)	3 (0.22)	0 (0.0)	0 (0.00)	1.0000
Asthma	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Dry throat	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Oropharyngeal pain	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Skin and subcutaneous tissue disorders	14 (2.4)	19 (1.41)	1 (0.9)	1 (0.41)	0.4862
Rash	7 (1.2)	7 (0.52)	0 (0.0)	0 (0.00)	0.6058
Pruritus	4 (0.7)	5 (0.37)	0 (0.0)	0 (0.00)	1.0000
Urticaria	2 (0.3)	2 (0.15)	0 (0.0)	0 (0.00)	1.0000
Alopecia	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Hyperhidrosis	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Rash pruritic	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Skin hypopigmentation	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000

Events System Organ Class Preferred Term	N patients (%)*	Events (Rate per 100 patient years)	N patients (%)*	P-value (Rate per 100 patient years)	(Fisher's exact)
Xeroderma	1 (0.2)	1 (0.07)	0 (0.0)	0 (0.00)	1.0000
Rash generalised	0 (0.0)	0 (0.00)	1 (0.9)	1 (0.41)	0.1627

1. Treatment Emergent Adverse Events are coded with MedDRA Dictionary Version 17.0. Lack of efficacy treatment emergent AEs are not included. Fisher's exact test comparing the difference in proportions in the two groups.
2. 3) Combined safety data from studies: LA-01, LA-02/06, LA-03, LA-04/06B, LA08-9701, LA10-9902, LA-11, LA-15, LA16-0102, LA28-CMP, LA30-0307 and LA38-0411.
3. Based on the worst case scenario of causality between the Investigator's and Company's assessment.
4. * Percentage is calculated out of the number of patients with systemic iron overload in each therapy group. Note combination with DFO at the start of the program is tabulated.
5. ** Years of Exposure is calculated as ((End Date of Exposure - First Exposure Start Date +1) - sum of interruption days) /365.25. The 15th of the month is assumed for partial dates for calculation.
6. Data cut-off: 31AUG2014

Appendix D: Post-Marketing Surveillance. Frequency of serious ADRs when DFO listed as concomitant or co-suspect medication with DFP

System Organ Class Preferred Term	No. events (N=265)
Blood and lymphatic system disorders	155
Neutropenia	82
Agranulocytosis	68
Leukopenia	2
Febrile neutropenia	1
Pancytopenia	2
Cardiac disorders	5
Cardiac failure	1
Cardiac failure congestive	1
Atrial fibrillation	1
Sinus tachycardia	1
Ventricular tachycardia	1
Congenital, familial and genetic disorders	2
Sickle cell anaemia with crisis	1
Congenital anomaly	1
Eye disorders	4
Diplopia	2
Retinal toxicity	1
Visual acuity reduced	1
Gastrointestinal disorders	13
Vomiting	2
Abdominal pain	2
Diarrhoea	3
Caecitis	1
Enterocolitis	1
Faecal incontinence	1
Parotid gland enlargement	1
Rectal haemorrhage	1
Stomatitis	1
General disorders and administration site conditions	16
Pyrexia	9
Chills	2
Asthenia	1
Face oedema	1
Hyperpyrexia	1
Fatigue	1

Pain	1
Hepatobiliary disorders	3
Jaundice	1
Cholelithiasis	1
Hepatomegaly	1
Immune system disorders	2
Hypersensitivity	1
Anaphylactic shock	1
Infections and infestations	24
Sepsis	9
Neutropenic sepsis	1
Septic shock	4
Pharyngotonsillitis	1
Pneumonia	1
Encephalitis enteroviral	1
Hepatitis infectious	1
Impetigo	1
Intervertebral discitis	1
Klebsiella sepsis	1
Pharyngeal abscess	1
Rash pustular	1
Urinary tract infection	1
Investigations	8
Alanine aminotransferase increased	1
Haemoglobin decreased	1
Neutrophil count decreased	1
Aspartate aminotransferase increased	1
Blood creatine phosphokinase increased	1
Nuclear magnetic resonance imaging abnormal	1
Transaminases abnormal	1
White blood cell count decreased	1
Musculoskeletal and connective tissue disorders	7
Arthralgia	2
Arthritis	1
Arthropathy	2
Muscular weakness	1
Myositis	1
Nervous system disorders	6
Cerebellar syndrome	1
Dizziness	1
Polyneuropathy	1

Cerebral haemorrhage	1
Myoclonus	1
Pyramidal tract syndrome	1
Psychiatric disorders	1
Disorientation	1
Renal and urinary disorders	2
Glomerulonephritis acute	1
Urinary incontinence	1
Respiratory, thoracic and mediastinal disorders	11
Dyspnoea	1
Pulmonary embolism	1
Acute respiratory distress syndrome	2
Haemoptysis	1
Laryngeal pain	1
Lung disorder	1
Oropharyngeal pain	2
Pharyngeal erythema	1
Respiratory acidosis	1
Skin and subcutaneous tissue disorders	3
Urticaria	2
Rash maculo-papular	1
Social circumstances	1
Walking disability	1
Vascular disorders	2
Hypertension	1
Hypotension	1

1) Reported MedDRA Version 17.0 Preferred Terms include: all terms where the serious flag was "Y" at the event level. Terms coded to "Pregnancy" or "Pregnancy of Partner" are not considered ADRs.
2) Cases were tabulated based on whether DFO was listed as a medication (concomitant or suspect) for that case, note this might include cases with both DFO and DFX reported.
3) Investigator led studies for patients with non systemic iron overload have been excluded.
4) Registry cases received < 26NOV2013 are treated as spontaneous in terms of assessment of causality. Data cut off: 31AUG2014

Appendix E: Post-Marketing Surveillance. Frequency of serious ADRs when DFX listed as concomitant or co-suspect medication with DFP

System Organ Class Preferred Term	No. events (N=33)
Blood and lymphatic system disorders	14
Neutropenia	7
Agranulocytosis	7
Congenital, familial and genetic disorders	1
Sickle cell anaemia with crisis	1
Gastrointestinal disorders	4
Vomiting	2
Abdominal pain	1
Nausea	1
General disorders and administration site conditions	4
Pyrexia	2
Fatigue	2
Hepatobiliary disorders	1
Cholelithiasis	1
Infections and infestations	3
Pharyngotonsillitis	1
Intervertebral discitis	1
Staphylococcal infection	1
Investigations	2
Aspartate aminotransferase increased	1
Blood creatine phosphokinase increased	1
Musculoskeletal and connective tissue disorders	2
Arthropathy	1
Myositis	1
Nervous system disorders	1
Disturbance in attention	1
Skin and subcutaneous tissue disorders	1
Urticaria	1

1) Reported MedDRA Version 17.0 Preferred Terms include: all terms where the serious flag was "Y" at the event level. Terms coded to "Pregnancy" or "Pregnancy of Partner" are not considered ADRs.
2) Cases were tabulated based on whether DFX was listed as a medication (concomitant or suspect) for that case, note this might include cases with both DFO and DFX reported.
3) Investigator led studies for patients with non systemic iron overload have been excluded.
4) Registry cases received < 26NOV2013 are treated as spontaneous in terms of assessment of causality. Data cut off: 31AUG2014

Appendix F: Summary of the safety data from published studies of combined use of deferiprone and deferoxamine

Author Year	N[35]	T duration (months)	DFP dose (mg/kg/day)	DFP (dose regimen)	DFP (days/wk)	DFO dose (mg/kg/day)	DFO (days/wk)	Neutropenia	Agranulocytosis	Elevated ALT and/or AST	Arthropathies	GI	Other AEs	Comments
								n (%)[36]						
Wonke 1998[(102)]	5	7-15	75-110	t.i.d.	7	4g/48h/wk 2g/24h 5d/wk 3g/24h 6d/wk	2-6	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		The DFP-DFO combination therapy was not associated with new and/or unanticipated safety concerns.
Balveer 2000[(9)]	7	12	75-85	not indicated	7	1-2 g/wk	2	0 (0%)	0 (0%)	2 (29%)	0 (0%)	5 (71%)	skin rash associated with mild abdominal discomfort	No new and/or unanticipated safety concerns
Mourad 2003[(65)]	11	12	75	t.i.d.	7	2g/d	2	0 (0%)	0 (0%)	0 (0%)	3 (27.3%)	7 (64%)	headache3 transient skin rash 2 fatigue 1 loss of appetite 1	The study did not show any increased incidence of toxicity on DFP-DFO combination therapy as compared to DFP monotherapy
Kattamis 2003[(49)]	60	2	50-75	b.i.d./t.i.d.	7	30-55	7	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		No information on safety

[35] It is unclear whether the same subjects participated in more than one study.

[36] The percentage was calculated based on a number of patients receiving combination therapy, unless the ratio was specified in the publication.

Gomber 2004[41]	10	12	75	7	7	40	2	0 (0%)	0 (0%)	0 (0%)	2 (9.52%) (in both DFP mono and DFP-DFO	0 (0%)		No new and/or unanticipated safety concerns
Athanassiou Metaxa 2004[6]	25	18	75	t.i.d.	not indicated	40	3	4 / 43 pts in both mono and combination groups (9.3%)	2 / 43 pts in both mono and combination groups (4.7%)	4 / 43 pts in both mono and combination groups (9.3%)	2 / 43 pts in both mono and combination groups (4.7%)	4 / 43 pts in both mono and combination groups (9.3%)	increased weight 6 (out of 43 pts on both mono and combination therapy)	No new and/or unanticipated safety concerns
D'Angelo 2004[22]	7	10-30	75	t.i.d.	7	40-50	7-10 [days following transfusion]	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		No information on safety
Alymara 2004[4]	25	13.5	60	t.i.d.	6	40-50	4-6	4 (16%)	0 (0%)	7 (28%)	2 (8%)	18 (72%)	taste disorder 2 transient dizziness and fatigue 3 anorexia and weight loss 1	Combined therapy DFO and DFP in this study was shown to be safe and no major toxicities were reported
Origa 2005[67]	79	12-57	70-80	t.i.d.	7	40-50	2-6	7 (8.8%)	3 (3.8%)	18%	2 (2.5%)	25 (32%)	zinc reduction 26 / 64 pts (40%)	No new and/or unanticipated safety concerns
Ha 2005[45]	17	18	75	t.i.d.	7	30-60	2	0 (0%)	0 (0%)	6 / 26 pts who received DFP monotherapy or DFP-DFO combinati	4 / 26 pts who received DFP monotherapy or DFP-DFO combination therapy	8 / 26 pts who received DFP monotherapy or DFP-DFO combinati	skin rash 1 (4.0%) fatigue 2 (8.0%)	safety results consistent with DFP-DFO associated adverse events reported in literature

										on therapy (23%)	(15%)	on therapy (31%)		
Kolnagou 2006[55]	11	9-28	75 - 95	not indicated	7	40-60	2-4	1 (9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	allergic reactions and pain at the site of DFO injection	The response of the iron loaded thalassaemia patients to the ICOC combination L1/DFO therapy protocol was generally successful, both with regard to efficacy in iron removal from the heart and also to the absence of adverse effects.
Peng 2006[69]	31	4-37	75-80	t.i.d.	7	30-50	3-7	1 / 88 pts receiving mono and combined therapy (1.1%)	0 (0%)	0 (0%)	1 / 88 pts receiving mono and combined therapy (1.1%)	2 / 88 pts receiving mono and combined therapy (2.2%)		No elevated incidence of toxicity on DFP-DFO combination therapy.
Daar 2006[23]	91	6-48	75	t.i.d.	7	40	4-5	0 (0%)	2 (2%)	1 (1%)	2 (2%)	6 (7%)	sepsis 2 allogenic bone marrow transplantation 2	No unanticipated safety concerns emerge from

														the data provided.
Farmaki 2006[30]	42	20-54	75-90	t.i.d.	7	20-40	2-6	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		No new safety concerns emerge from the data provided.
Christoforidis 2006[18]	44	24	75	not indicated	7	30-50	3-4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		No information on safety
Kattamis 2006[50]	50	6-12	50-75	b.i.d./t.i.d.	7	30-55	3	1 (2%)	2 (4%)	9 (18%)	1 (2%)	10 (20%)	Yersinia enterocolitica infection 1	The study did not show any increased incidence of toxicity on DFP-DFO combination therapy.
Kolnagou 2008[52]	19	20-76	60-100	not indicated	7	30-60	1-5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		No information on safety

Author Year	N***	T duration (months)	DFP dose (mg/kg/day)	DFP (dose regimen)	DFP (days/wk)	DFO dose (mg/kg/day)	DFO (days/wk)	Neutropenia	Agranulocytosis	Elevated ALT and/or AST	Arthropathies	GI	Other AEs	Comments
								n (%)†††						
Tanner 2007[89]	32	12	75	not indicated	7	34.9	5	2 (6%)	1 (3%)	0 (0%)	3 (9%)	12 (38%)	reactions at DFO infusion site (3%)	All reported adverse events were documented in previous studies of DFP monotherapy and combination therapy.

Christoforidis 2007[20]	30	3	75-100	not indicated	7	40-50	2-3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		No information on safety
Eshghi 2007[27]	32	20.1±1.4	75	t.i.d.	7	30-40	2-3	4 (12%)	0 (0%)	0 (0%)	2 (6.25%)	nausea 8 (25%) nausea w/vomiting or abdominal pain 4 (12%)	thrombocytopenia 2 (6%)	No new safety concerns emerge from the data provided.
Aydinok 2007[7]	12	12	75	not indicated	7	40-50	2	1 (8%)	1 (8%)	ALT levels > than the upper normal limit (data not shown)	1 (8%)	5 (42%)		No new safety concerns emerge from the data provided.
El-Beshlawy 2008[25]	22	13.5	60-83	not indicated	7	23-50	2	1 (5%)	0 (0%)	2 (9%)	6 (27%)	4 (18%)	anorexia 5 weakness/fever 2 insomnia 1 skin reactions/allergy, swelling 3 musculoskeletal pain (hips, back) 3	No new safety concerns emerge from the data provided.
Tsironi 2008[97]	5	18	70-80	t.i.d.	7	35	5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	not reported	No information on safety
Tanner 2008[88]	15	11.7±1.6	73.9±4.0 - 65.7±10.7	not indicated	7	38±10.2 - 20.3±10.9	5.3 - 4.5	0 (0%)	0 (0%)	1 (7%)	1 (7%)	4 (27%)		The incidence of adverse effects was low and consistent with prior studies of these chelators.
Zareifar 2009[107]	35	12	75	t.i.d.	7	40-50	3-5	8 (22.9%)	0 (0%)	3 (8.6%) elevate	2 (5.7%)	4 (11.4%)		Assessment cannot be provided as it is not clear which group of AEs

									d liver enzymes				belonged to which chelation regimen.
Ha 2009[47]	31	12	75	not indicated		40-60	3-5	2.6% (in 38 pts on DFP mono and DFP-DFO combination therapy)	5.3% (in 38 pts on DFP mono and DFP-DFO combination therapy)	0 (0%)	4 / 38 pts on DFP mono and DFP-DFO combination therapy (10.5%)	4 / 38 pts on DFP mono and DFP-DFO combination therapy (10.4%)	fatigue 2 (5.3%) (this includes AEs in patient on combination therapy of DFP and DFX; not clear which event belongs to which regimen)	It is difficult to assess the incidence of reported adverse events, as it was reported for both DFP groups (i.e. DFP monotherapy and DFP-DFO combination therapy).
Farmaki 2009[32]	52	60-84	70-100	t.i.d.		20-60	not indicated	2 (4%)	0 (0%)	11%	5%	8%	tinnitus 1 (2%) (associated with DFO) ocular problems 1 (2%) (associated with DFO)	No new safety concerns emerge from the data provided.
Maggio 2009[63]	105	35	75	t.i.d.	4	50	3	15 (23.1%)	0 (0%)	22 (33.8%)	5 (7.7%)	7 (10.8%)		Adverse events in thalassaemia major patients during alternating DFP-DFO intervention
Maggio 2009[63]	86	60 - 96	not indicated	not indicated	not indicated	not indicated	not indicated	0%	0%	0%	0%	0%		No information on safety, only the prevalence of complications in the two considered groups was provided
Ricchi 2009[82]	13	2.7-96	75	not indicated	7	25-35	5	0 (0.0%)	1／13 (7.69%)	1／13 (7.69%)	0 (0.0%)	2／13 (15.38%)	increased weight (overall) 8／36 pts (22.22%) (including by groups: 3／13 pts (23.08%), 1／6 pts (16.67%), 3／10 pts (30.0%), 1／7 pts (14.28%)). neutropenia (overall) 3 / 36 pts (8.33%) agranulocytosis (overall) 2 / 36 pts (5.55%) increased ALT 5 / 36 pts (13.88%) GI symptoms (overall) 6／36 pts (16.67%) arthropathy and/or joint symptoms (overall) 0 / 36 pts (0.0%)	The DFP-DFO combination therapy was not associated with different incidence of adverse effects.
	6		50	not indicated	7	25-35	5	2／6 pts (33.33%)	0 (0.0%)	1／6 pts (16.67%)	0 (0.0%)	1／6 pts (16.67%)		
	10		75	not indicated	7	25-35	3	1／10 pts (10%)	0 (0.0%)	1／10 pts (10.0%)	0 (0.0%)	2／10 pts (20.0%)		
	7		50	not indicated	7	25-35	3	0 (0.0%)	1／7 (14.28%)	2／7 (28.57%)	0 (0.0%)	1／7 (14.28%)		
Lai 2010[58]	15	42±6	75	t.i.d.	7	40-50	5-7	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		No information on safety

Economou 2010[24]	14	not indicated	60-80	not indicated	7	11-48	5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	proteinuria 10 / 42 pts (24%)(not clear in which treatment group) hypercalciuria 15/42 pts (35.5%) (not clear in which treatment group)	No information on safety
Tsiapras 2010[96]	26	24	80-100	not indicated	7	40	3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		No information on safety
	10	24	75	not indicated	7	40	2-3							
Author Year	**N*** **	**T duration (months)**	**DFP dose (mg/kg/day)**	**DFP (dose regimen)**	**DFP (days/wk)**	**DFO dose (mg/kg/day)**	**DFO (days/wk)**	**Neutropenia**	**Agranulocytosis**	**Elevated ALT and/or AST**	**Arthropathies**	**GI**	**Other AEs**	**Comments**
								n (%)†††						
	4	24	75	not indicated	7	40	6-7							
Kolnagou 2010[53]	8	21-68	75-100	not indicated	7	40-60	3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		No new safety concerns emerge from the data provided.
Tamaddoni 2010[87]	40	12	75	not indicated	7	40-50	2	0 (0%)	0 (0%)	8 (20%)	2 (5%)	nausea 12 (30%) nausea and abdominal pain 3 (7.5%) diarrhea 2 (7.5%)	skin reactions on DFO alone	The DFP-DFO combination therapy was not associated with new and/or unanticipated safety concerns.
Keikhaei 2010[63]	228	6	50-80		7	30-50	2-4	5 (2.19%)	2 (0.87%)	0 (0%)	24 (10.5%)	nausea/vomiting 37 (16.2%) anorexia 7 (3.1.%) abdominal pain 5 (2.2%)	skin rash 4 (1.8%)	The DFP-DFO combination therapy was not associated with serious toxicity.
Galanello 2010[63]	158	502 patient-years	not indicated	not indicated	not indicated	not indicated	not indicated	14 (9%)	5 (3%)	45 (28%)	10 (6%)	40 (25%)		The frequency and severity of the adverse events observed in this long-term clinical experience were no

														different from those observed in patients on DFP monotherapy.
Al Hawsawi 2011[2]	28	12	75	t.i.d.	7	40-50	2 (plus additional dose during blood transfusion)	0 (0%)	0 (0%)	0 (0%)	1 (3.57%)	nausea 15 (53.57%) vomiting 10 (33.71%) abdominal pain 15 (53.57%)	skin rash 2 (7.14%)	No new safety concerns emerge from the data provided.
Ha 2011[46]	29	30	75-100	not indicated	7	40-60	3-5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	not reported	No information on safety
Kolnagou 2011[54]	8	21-68	80-100	not indicated	7	40-60	3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		No new safety concerns emerge from the data provided.
Cassinerio 2012[17]	3 5	32±7	73±7	not indicated	7	46±7	4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		No serious adverse events were experienced by patients treated with any of the chelation regimen.
Mirbehbahani 2012[64]	12	6	75	t.i.d.	7	30-50	3-4	1 (8%)	0 (0%)	4 (33.3%)	1 (8.3%)	1 (8.3%)		No new safety concerns emerge from the data provided.
Shahvazian 2012[83]	36	12	50-86	t.i.d.	7	24-52	3-7	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		No information on safety
Pepe 2013[76]	51	18	61.9±24.3	not indicated	6.1±1.4	40.7±6.0	3.5±1.1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		No information on safety
Porter 2013[81]	11	12	75	t.i.d.	7	50-60	7	1 (9%)	0 (0%)	1 (9%)	0 (0%)	1 (9%)	hypotension 1 (leading to DFP interruption) Total: 17 SAEs with combination therapy (7 'at least remotely related' to treatment) septic shock 1 retinal toxicity 1 line infection 1 meningitis 1 hyperkalemia with hyperglycemia 1 Atrial fibrillation 1 urinary infection 1	This study did not find significant new issues with tolerability with combination therapy.
Tanphaichitr 2014[91]	45	13.56±10.32	75-100	not indicated	7	20-40	3–5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	no SNHL (sensorineural hearing loss) reported with	No information on safety except for absence of

													combination therapy	sensorineural hearing loss.
Dee 2014[63]	4	not indicated	not indicated		not indicated	not indicated	not indicated	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		No information on safety
Elalfy 2014[63]	48	12	75	b.i.d.	7	40	6	3 (6.25%)	0 (0%)	3 (6.25%)	9 (18.7%)	10 (20.8%)	serum creatinine above baseline 1 (2.08%)	No new safety concerns emerge from the data provided.
Songdej 2015[63]	42	36	50-100	t.i.d./q.i.d.	7	40± 5	2	2 episodes in 2 pts (4.8%)	0 (0%)	5 episodes in 5 pts (11.9%)	0 (0%)	4 episodes in 2 pts (4.8%)	thrombocytopenia 2 episodes in 1 pt (2.4%) elevated serum creatinine 1 episode in 1 pt (2.4%) significant proteinuria 1 episode in 1 pt (2.4%) cholecystitis with IAHS 1 episode in 1 pt (2.4%)	No new safety concerns emerge from the data provided.
TOTAL	**1852**	**2 - 84**	**50 - 110**	**b.i.d/t.i.d.**	**4-7**	**11 mg - 4g/48h/ wk**	**1 - 10**							**Deferiprone-DFO combination therapy was not associated with a greater incidence of ADRs and/or with the occurrence of unanticipated ADRs.**

Appendix G: Summary of the safety data[###] from published studies of combined use of deferiprone and deferasirox

Author Year	N**	T duration (months)	DFP dose (mg/kg/day)	DFP (dose regimen)	DFP (days/wk)	DFX dose (mg/kg/day)	DFX (days/wk)	Neutropenia	Agranulocytosis	Elevated ALT and/or AST	Arthropathies	GI	Other AEs	Comments
								n (%)[§§§]						
Berdoukas 2010[10]	3	7 - 28	75 - 100	not indicated	7	20-40	7	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (33%)		No new unexpected adverse events reported.
Balocco 2010[8]	1	12	85	t.i.d.	3-4	30	3-4	0 (0%)	0 (0%)	0 (0%)	(0%)	0 (0%)		No new unexpected adverse events reported.
	1	12	75	t.i.d.	3-4	30	3-4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
Voskaridou 2011[100]	1	12	75	t.i.d.	7	30	7	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		No safety concerns were reported.
Farmaki 2011[31]	15	12-24	75-100	t.i.d.	not indicated	20-25	1	0 (0%)	0 (0%)	2 (13%)	0 (0%)	3 (20%)		The incidence of adverse reactions was comparable to monotherapy with each chelator.
Elalfy 2015[26]	48	12	75	b.i.d.	7	30	7	5 (10.4%)	0 (0%)	4 (8.33%)	8 (16.6%)	6 (12.5%)	serum creatinine above baseline 3 (6.2%) skin rash 2 (4.16%)	No new unexpected adverse events reported.
Totadri 2014[95]	36	12	75-100	t.i.d.	not indicated	30-40	not indicated	0 (0%)	0 (0%)	4 (11%)	8 (22.2%)	8 (22.2%)	elevated creatinine 9 (25%) reddish brown colored urine 3 (8.3%) skin rash 1(2.8%) proteinuria 1 (2.8%)	No new unexpected adverse events reported.
Song 2014[84]	6		40	b.i.d.	not indicated	30	not indicated	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		No adverse events were reported in this study.

	2		80	not indicated	not indicated	30	7	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
Alavi 2014[(3)]	1	8	50-75	t.i.d.	4	15-25	3-7	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		No adverse events or toxicity were reported during combination treatment with an alternative schedule.
TOTAL	**114***	**7 - 28**	**40 - 100**	**2-3 times per day**	**3-7**	**15 - 40**	**1 - 7**	**5**	**0**	**10**	**16**	**18**		The results of presented studies demonstrated that DFPDFX combination therapy was not associated with a greater incidence of adverse events or any unanticipated adverse events. In all reported cases combination therapy was well tolerated.

‡‡‡ Safety results are based on published data in reviewed studies and not intended to represent the actual incidence of adverse events in a target population.

§§§ The percentage was calculated based on a number of patients receiving combination therapy, unless the ratio was specified in the publication. **** It is unclear whether the same subjects participated in more than one study.

2.5. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The RMP remains unchanged.

2.7. Update of the Product information

Following the review and assessment of the available data (see Clinical efficacy and Clinical Safety discussions above), the CHMP agrees to extend the Ferriprox indication as follows:

Ferriprox **monotherapy** is indicated for the treatment of iron overload in patients with thalassaemia major when **current chelation** ~~deferoxamine~~ 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 4.2).

Sections 4.2, 4.4, 4.8 and 5.1 of the SmPC were also updated to reflect the relevant information.

The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity of this procedure to update the Product Information in compliance with the QRD template version 9.1 and combine the SmPC for the 500mg and 1000mg tablets. The contact details of France and Portugal have been updated in the PL.
Please refer to Attachment 1 which includes all agreed changes to the Product Information.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Iron overload is one of the major causes of morbidity in patients with thalassemia major. Main causes of mortality are sudden cardiac death, arrhythmia, and heart failure from cardiac iron overload. The majority of morbidity stems from liver cirrhosis from hepatic iron overload and endocrine dysfunction. The goal of iron chelation therapy is to reduce iron overload in the susceptible organs and to prevent end-organ damage (heart failure, liver cirrhosis, endocrinopathy), morbidities known to reduce survival in this population. Three chelators are available in the EU and their respective indications, while not specifying monotherapy, do not recommend combination use and do not describe when a combined treatment should be used, nor the practical modalities of such treatments. Efficacy and safety data of combinations are not mentioned in the available information for these products.

The conditions in which the combination chelation therapy is needed are acknowledged: a failure to control the iron burden at maximum dosage of current chelators and when current chelators cannot be adequately used, e.g. associated with dose-limiting toxicities.

Comparative studies and some randomized clinical trials show that DFP-DFO combination is associated with relatively more rapid or pronounced serum ferritin decreases when compared with monotherapy. In addition, a decrease in serum ferritin could be associated with a decrease in iron liver. No pharmacological problems prevent this use and even a theoretical synergy may suggest that DFO/DFP is a right choice.

Randomized trials with alternating therapy or combination therapy compared to DFP alone concluded to a greater efficacy of combination to decrease serum ferritin level (e.g. Maggio et al., 2009). As supported by the Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT) 3rd Edition (Cappellini et al. 2014), these studies show that SF can be controlled with a relatively low frequency of DFO given twice a week when combined with DFP standard doses (75 mg/kg/day). The fact that DFO-DFP combination therapy demonstrated its superiority over DFP and not over DFO may indicate that this solution may rather rescue inefficient DFP monotherapy or provide a more acceptable option to patients not accepting frequent infusions anymore.

Randomized trial (Tanner et al., 2007) showed greater efficacy of the combination DFP-DFO compared to DFO alone in patients which received 5 days of DFO. Simultaneous combination therapy of DFO/DFP may improve a marker of cardiac overload when compared to DFO, making the simultaneous combination superior to DFO when heart iron overload must receive control.

As a request of the CHMP on the last round, the MAH proposed a new wording with a starting and a limited dose of deferiprone in association with deferoxamine in section 4.2 of the SmPC.

Efficacy data of the DFP-DFX combination is very limited due to the small number of patients exposed and the lack of information about the safety of this combination (only 5 patients exposed in the MAH clinical trials). Thus, the use of deferiprone with deferoxamine or deferasirox has been differentiated in the SmPC. Additional precautions for use have been added on the combination of deferiprone and deferasirox as limited data are available.

Uncertainty in the knowledge about the beneficial effects

The expected superior effect of combination over mono-components is established on iron overload markers only, but not on hard clinical endpoints such as frequency/severity of complications or prolonged survival. One report based on a 20-year survey in Cyprus concludes that the introduction of the combination resulted in an improvement of survival in patients with beta-thalassemia major, was discussed.

Risks

Unfavourable effects

Deferiprone-DFO combination therapy was not associated with new safety concerns in the provided studies. Thus, data are reassuring but should be taken with considerable caution as dose regimen were very heterogeneous according the studies.

In Eudravigilance database, 7 fatal cases have been observed when deferiprone was used in association. 3 caused by agranulocytosis with DFP+DFO and 4 caused by cardiac complications including one with DFP+DFX and 3 with DFP+DFO. Thus, whatever the iron chelators associated, we cannot totally exclude that this potential risk remains. There is a need for much attention to this risk when deferiprone is used in combination which must appear in The SmPC.

Combination is necessarily associated with the addition of side effects.

A list of ADRs from Apopharma database that compares the proportion of ADRs between deferiprone monotherapy and combination therapy was provided. Data from pooled safety database from clinical trials (244 patients-year exposed for Ferriprox monotherapy and 1343 patients-year exposed to Ferriprox and deferoxamine) showed statistically significant ($p<0.05$) differences in the incidence of adverse reactions based on SOC for “Cardiac disorders", "Musculoskeletal and connective tissue disorders” and "Renal and urinary disorders". The incidences of “Musculoskeletal and connective tissue disorders” and "Renal and urinary disorders" were lower during combination therapy than monotherapy, whereas the incidence of “Cardiac disorders" was higher during combination therapy than monotherapy. The higher rate of “Cardiac disorders" reported during combination therapy than monotherapy was possibly due to the higher incidence of pre-existing cardiac disorders in patients who received combination therapy.

In consequence, the Rapporteurs propose to modify the SmPC in order to include precaution for use related to cardiac disorders (see section 4.4).

Uncertainty in the knowledge about the unfavourable effects

In the safety profile of DFP-DFO combination provided by the MAH, only 18 children have been exposed to the combination. Thus, it is very difficult to draw any sound conclusion on these findings. However, the number of children treated with the combination and the incidence of adverse events have been documented in the SmPc (section 4.8).

Benefit-Risk Balance

The Benefit /Risk Balance of the deferiprone-deferoxamine combination 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 - is considered positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include a new indication for Ferriprox in combination with another chelator. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.
In addition, the MAH took the opportunity of this procedure to update the Product Information in compliance with the QRD template version 9.1 and combine the SmPC for the 500mg and 1000mg tablets. The contact details of France and Portugal have been updated in the PL.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH should provide a patient/carer reminder card in each pack, the text of which is included in the Package Leaflet.