Australian Public Assessment Report for Deferiprone

Proprietary Product Name: Ferriprox

Sponsor: Orphan Australia Pty Ltd

October 2011

About the Therapeutic Goods Administration (TGA)

· The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.

· TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.

· The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.

· The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.

· To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

· An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.

· AusPARs are prepared and published by the TGA.

· An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.

· An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.

· A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission:	Extension of indications, Increase in Dosage, Other Changes to the Product Information
Decision:	Extension of indications – Rejected Increase in Dosage – Approved Other Changes to the Product Information – Rejected
Date of Initial Decision:	17 March 2011
Date of Final Decision:	15 August 2011
Active ingredient(s):	Deferiprone
Product Name(s):	Ferriprox
Sponsor's Name and Address:	Orphan Australia Pty Ltd 300 Frankston-Dandenong Road Dandenong Vic 3175
Dose form(s):	Tablets, oral solution
Strength(s):	Tablets: 500 mg Oral solution: 25 g/250 mL, 50 g/500 mL
Container(s):	Tablets: High density polyethylene containers with child resistant closures. Oral solution: Round amber polyethylene terephthalate bottles with white polypropylene child resistant pictorial caps.
Pack size(s):	Tablets: 100 Oral solution: Each pack contains one re-closable bottle and one graduated 30 mL plastic dosing cup. Only the 250 mL presentation is currently marketed.
Approved Therapeutic use:	Treatment of iron overload in patients with thalassaemia major who are unable to take desferrioxamine therapy or in whom desferrioxamine therapy has proven ineffective.
Route(s) of administration:	Oral
Dosage:	75-100 mg/kg/day in 3 divided doses
ARTG Number (s):	93946, 125665, 125666

Product Background

Deferiprone is an orally active iron chelating agent registered for second line use (after desferrioxamine injection) in transfusional iron overload associated with thalassaemia major. The current indication is as follows:

For the treatment of iron overload in patients with thalassaemia major who are unable to take desferrioxamine therapy or in whom desferrioxamine therapy has proven ineffective.

This AusPAR describes the evaluation of a submission by Orphan Australia Pty Ltd (the sponsor) to seek approval for the use of Ferriprox, as first line treatment, for treatment of iron overload in patients with transfusional iron overload due to chronic blood transfusions (transfusional haemosiderosis). The sponsor also requested the broadening of the indications for treatment of transfusional iron overload, from patients with thalassaemia, to include any disease, such as sickle cell disease and myelodysplastic syndrome, which require chronic blood transfusions. In addition, the sponsor requested approval to increase the dose to 100 mg/kg body weight after initiating treatment at 75 mg/kg body weight, if the response was insufficient.

The proposed indication was as follows:

Ferriprox is indicated for the treatment of patients with transfusional iron overload due to chronic blood transfusions (transfusional haemosiderosis).

Another registered oral iron chelator is deferasirox dispersible tablets (Exjade). Exjade (for patients 6 years and older) and desferrioxamine (DFO) injection are registered for first line use in iron overload and are not restricted to thalassaemia major.

Regulatory Status

The TGA granted Orphan Drug Designation to Ferriprox (deferiprone) in May 2001 for the treatment of iron overload in patients with thalassaemia major, unwilling or unable to take desferrioxamine (DFO) therapy. In April 2003 and March 2008, the TGA granted registration approval, with the same restrictions, for Ferriprox 500 mg tablets and 100 mg/mL oral solution, respectively.

Ferriprox is registered in the EU for a similar indication to that currently approved in Australia (as second line treatment of thalassaemia major) although it has labelling that reads "usually given as 75" and that "above 100 mg/kg/day is not recommended because of the potentially increased risk of adverse reactions".

A similar application has been submitted to the US FDA as a new drug application.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Quality Summary and Conclusions

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical Findings

Introduction

Orphan Australia Pty Ltd applied to extend the indications, change the dosage regimen and amend the PI for Ferriprox (deferiprone). The proposed indication extension is to include the treatment of patients with transfusional iron overload due to chronic blood transfusions (transfusional haemosiderosis), while the dosage regimen is proposed to change from 75 mg/kg/day orally (PO) to a starting dose of 75 mg/kg/day, which can be increased to 100 mg/kg/day if the response is insufficient (that is, 25-33 mg/kg PO three times daily [tds]).

In addition to a number of study reports and papers that had previously been submitted with the original application for Ferriprox, the sponsor submitted 9 new study reports and 275 supporting references.

A number of safety related concerns were raised previously in the original submission for deferiprone, including the absence of adequate safety pharmacology, pharmacokinetic, toxicity, carcinogenicity and reproductive toxicity data. Some of these deficiencies have been partly addressed by the newly submitted data; however, due to the low doses and exposures used in these studies, the toxicity profile of deferiprone has not been fully revealed.

Pharmacology

Primary pharmacology

Deferiprone is a bidentate chelating agent that chelates trivalent iron cations (Fe^{3+}) in a 3:1 (deferiprone:iron) complex (pFe^{3+}) (Liu *et al.*, 2001).[1] Deferiprone was also reported to bind other metals including copper, aluminium and zinc. Both the free ligand and the deferiprone iron complex are uncharged at physiological pH and deferiprone is rapidly absorbed from the gut. Previously submitted papers indicated deferiprone could promote the removal of iron from ferritin in the liver and from reticuloendothelial cells in the liver, spleen and blood. Deferiprone was also able to mobilise iron from iron loaded cardiac cells in culture.

The efficacy of deferiprone in iron loaded animals was supported by published papers submitted previously. Mice, rats, gerbils, rabbits, marmosets and Cebus monkeys had been iron loaded with iron dextran, ^{59}Fe-lactoferrin, ^{59}Fe-ferritin, ferric saccharate or iron hydroxide polyisomaltose and the extent of iron excretion and/or mobilisation from tissues monitored. The efficacy of deferiprone in increasing iron excretion was demonstrated in a number of species, mainly at doses giving a lower exposure than that expected clinically. In the newly submitted pharmacology study, only 7% iron mobilisation (assessed from liver, intestinal and faecal material), was detected in the 24 hour period following deferiprone treatment (63 mg/kg; 0.15 times the clinical daily dose on a body surface area basis[2]) to ferritin loaded rats, compared with 3% in controls and about 30% with other iron chelators. Although mobilisation in this particular model was only marginal, the efficacy of deferiprone in other iron loaded models and previous clinical experience should be adequate to support the extension of indications.

Safety pharmacology

No significant inhibition of hERG K^+ channels was observed with deferiprone at concentrations up to 417.5 µg/mL (3000 µM). *In vivo*, no electrocardiogram (ECG) findings were observed in monkeys given deferiprone at 125 mg/kg/day PO for 52 weeks (yielding plasma concentrations of deferiprone 1.3 times the clinical maximum plasma concentration [C_{max}]).[3] While no indications of QT prolongation were evident in these studies, the tested concentrations are not adequate to alleviate concerns. In general, for *in vitro* studies a ≥30 fold difference between the inhibitory concentration and the clinical

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[1] Liu ZD, Piyamongkol S, Liu DY, Khodr HH, Lu SL, Hider RC. Synthesis of 2-amido-3-hydroxypyrin-4(1H)-ones: novel iron chelators with enhanced pFe^{3+} values. Bioorg Medicin Chem 2001; 9: 563-573.

[2] Assuming a clinical daily dose of 75 mg/kg/day and using mg/kg to mg/m^2 conversion factors of 33 and 6 for humans and rats, respectively.

[3] The clinical C_{max} for the higher dose of 33 mg/kg PO was not provided but it was estimated to be 23.1 µg/mL based on a C_{max} of 17.5 µg/mL for a 25 mg/kg PO dose and assuming linear pharmacokinetics. As the unbound fraction of deferiprone is at least 80% (Yokel *et al.*, 1995), for conservative reasons, 100% free fraction was assumed.

plasma free fraction has been suggested to be an adequate safety margin (Redfern *et al.*, 2003); the tested concentrations were ~18 times the clinical C_{max}, while C_{max} values in the monkey study were only marginally above that expected clinically.[4] As there was no significant toxicity in the monkey study (see below) higher doses should have been considered to give C_{max} values several fold that expected clinically. The tested doses/concentrations were low, limiting the predictive value of negative findings.

Pharmacokinetics

The analytical method to determine serum levels of deferiprone did not differentiate between free or iron complexed deferiprone and therefore any difference in the pharmacokinetic profile (or relative amounts) of these two forms of the drug would not have been detectable. Deferiprone was rapidly absorbed by the oral route in all species (mouse, rat, cynomolgus monkey and human) with the time to maximum plasma concentration (T_{max}) values ranging from 0.5–0.75 hours (h). Exposure was generally dose proportional in all species and there were no gender differences or any significant accumulation with repeat dosing. Elimination half-lives of deferiprone in rodents were similar to that observed in humans (1.9-2.7 h), while those in monkeys were slightly shorter (<1 h). Exposure (both the area under the plasma concentration time curve [AUC] and C_{max}) was generally higher in naive compared with iron loaded animals; in rodents after a single dose and monkeys with repeat dosing. In rats, this difference was less prominent with repeat dosing. These exposure differences may be attributable to differing tissue distribution kinetics between the free and iron chelated form of deferiprone (Hamilton *et al.*, 1994) though no formal studies have been conducted to confirm this.[5] Serum elimination half-lives were independent of iron loading status.

Previously submitted studies indicated that deferiprone is glucuronidated in all animal species. Glucuronide metabolites (assumed to be primarily deferiprone 3-*O*-glucuronide) were detectable in *in vitro* studies with rat, cynomolgus monkey and human liver microsomes. The rate of glucuronide formation was higher in human and monkey microsomes than in rat microsomes, consistent with *in vivo* findings. Human liver and kidney microsomes had similar activities and were significantly higher than those for jejunum and ileum (Benoit-Biancamano *et al.*, 2009).[6] *In vitro* studies with HEK293 expressed human uridine 5′-diphosphate-glucuronosyltransferases (UGTs) revealed a significant role for UGT1A6 in glucuronidation, with minor contributions from UGT1A8, 1A9 and 1A10 (Benoit-Biancamano *et al.*, 2009). No cytochrome P450 (CYP) mediated metabolism was detected in liver microsomes from rats, monkeys or humans.

Pharmacokinetic drug interactions

Glucuronidation of deferiprone to the inactive metabolite deferiprone 3-*O*-glucuronide is the major route of metabolism of deferiprone. Exposures to deferiprone 3-*O*-glucuronide (based on AUC) have been reported to be 2–2.4 fold those to deferiprone, on a molar basis, in clinical studies and peak concentrations occurring 2 to 3 h after administration (Ferriprox PI document). Therefore coadministration of drugs that inhibit UGT1A6 may

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[4] Redfern WS, Carlsson L, Davis AS et al. Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. Cardiovascular Res 2003; 58:32-45.

[5] Hamilton KO, Stallibrass L, Hassan I, Jin Y, Halleux C, Mackay M. The transport of two iron chelators, desferrioxamine B and L1, across Caco-2 monolayers. Br J Haematol 1994; 86: 851-857.

[6] Benoit-Biancamano M-O, Connelly J, Villeneuve L, Caron P, Guillemette C. Deferiprone glucuronidation by human tissues and recombinant UDP glucuronosyltransferase 1A6: an *in vitro* investigation of genetic and splice variants. Drug Metab Dispos 2009; 37: 322-329.

increase deferiprone exposure. Likewise patients with impaired liver function may have an altered deferiprone pharmacokinetic profile.

No significant inhibition of human CYP isozymes (CYP1A1, 1A2, 2C9, 2D6, 2E1 and 3A4) was seen with deferiprone up to 400 μM (55.7 μg/mL). Generally concentrations up to 50 times the (unbound) C_{max} should be tested in *in vitro* studies. The highest tested concentration represents only ~2 times the clinical C_{max} at the proposed higher dose. Therefore the data are inconclusive to eliminate CYP450 drug interactions.

Toxicology

General toxicity

Newly submitted repeat dose toxicity studies were of 52 weeks duration in rats and monkeys, using the clinical route (PO). The duration of the studies, the species used, group sizes and the use of both sexes were consistent with International Council on Harmonisation (ICH) guidelines. Both naive and iron loaded animals were examined. Dose selection in the rat study was appropriate, although limited by treatment related mortalities and reduced body weight gain. However, the absence of any significant findings in the monkey study, suggests higher doses should have been considered.

Animals were dosed twice daily compared with the clinical regimen of three times daily. Given that the serum half-life of deferiprone was <1 h in monkeys, with undetectable levels of deferiprone in the serum 4 h after dosing, monkeys were exposed for ≤8 h per day. This is considerably less than the daily length of clinical exposure expected with three times daily dosing and a serum half-life of 2.7 h. Furthermore, maximum exposures were low; equivalent to that anticipated from a maximum clinical dose of 75 mg/kg/day but were subclinical for a 100 mg/kg/day dose (Table 1).

Table 1: Relative exposure of deferiprone in repeat dose toxicity studies

Species (Strain)	Study	Treatment duration	Dose (mg/kg PO bd)	AUC_{0-t} (μg·h/mL)	AUC_{0-24h} (μg·h/mL)	Exposure ratio[a] based on	
						75 mg/kg/day	100 mg/kg/day
Rat (SD)	97/006D	52 weeks	37.5 (Fe)	17.2	34.4	0.42	0.32
			75 (Fe)	42.5	84.9	1.0	0.79
			100 (Fe)	46.7	93.4	1.1	0.86
			75	45.8	91.6	1.1	0.85
Monkey (Cynomolgus)	97/007D	52 weeks	37.5 (Fe)	7.2	14.5	0.18	0.13
			75 (Fe)	15.8	31.7	0.39	0.29
			125 (Fe)	41.6	83.2	1.0	0.77
			75	26.5	53.0	0.65	0.49
Human[b]	Module 2.4	single	25 (33) (tid)	27.3 (36.1)	81.9 (108)	–	–

[a]calculated as animal:human AUC_{0-24h}; [b]patients with transfusional iron overload; data are for the sexes combined, and averages across sampling days (excluding Day 1); data for a 33 mg/kg PO dose were extrapolated from that of a 25 mg/kg PO dose, assuming linear pharmacokinetics

The bone marrow, thyroid, adrenal and mammary glands were target organs for toxicity in rats. Bone marrow hypocellularity was evident at all doses in both naive and iron loaded rats. A reduced polychromatic erythrocytes (PCE): normochromatic erythrocytes (NCE) ratio was seen in the mouse micronucleus test at clinically relevant exposures, suggesting

bone marrow cytotoxicity. These bone marrow changes were accompanied by leukopenia, consistent with reports that deferiprone inhibits the proliferation of white blood cell progenitors (Hoyes *et al.*, 1993).[7] The effects on bone marrow in laboratory animals accounts for the neutropenia/agranulocytosis in humans (Al-Refaie *et al.*, 1994).[8] Bone marrow cytotoxicity was not seen with other iron chelators including desferrioxamine, suggesting it was related to deferiprone toxicity rather that its pharmacology. While anaemia was observed in treated animals and was associated with increased mortality in non-iron loaded rats, it is unlikely to be due to bone marrow toxicity, as an increase in reticulocyte number accompanied the reduction in red blood cell parameters. Macrocytosis was also seen, suggesting it is also not likely to be due to iron deficiency. The exact mechanism underlying the observed anaemia is unclear but it should be noted that this haematological change was not seen in nonclinical studies with other iron chelators, including desferrioxamine (Porter *et al.*, 1991).[9]

Increased thyroid weights with microscopic findings of diffuse colloidal basophilia (males and females) and diffuse hypertrophy of the follicular epithelium (females only) were seen at all doses in both naive and iron loaded rats. In a tissue distribution study in rats, drug related material appeared to accumulate in the thyroid with concentrations ~10 times those in blood following repeated oral administration of ^{14}C-deferiprone[10] (Schnebli, 1993).[11] While increased adrenal weights were seen at ≥37.5 mg/kg twice daily (bd) in iron loaded rats, there were no corresponding histopathological findings. However, hypertrophy of the zona fasciculata has been reported in deferiprone treated rats.

An increased incidence and severity of mammary gland hyperplasia was observed in treated female rats (both naive and iron loaded) at ≥37.5 mg/kg PO bd. A relationship with dose was evident in iron loaded females. An increased incidence of mammary fibroadenoma was only seen in naive females. Although fibroadenomas are relatively common in rats, the increase in incidence and severity of mammary gland hyperplasia in both naive and iron loaded females and the increase in fibroadenoma incidence in naive females, suggest a probable association with treatment. Mammary adenocarcinoma was evident in two treated female rats, while none were seen in concurrent control groups. Although there was no apparent dose response, the increased incidence of proliferative changes in the mammary gland of treated females and given the fact that deferiprone was also shown to be genotoxic, a relationship of this malignant tumour with treatment cannot be overlooked. No information was available as to the effect of deferiprone on prolactin levels; however, alterations in oestrous cycling noted in the fertility study at ≥15 mg/kg PO bd suggest there may be some hormonal effects with deferiprone treatment. Without a clear mechanistic explanation, the clinical relevance of these mammary gland changes is uncertain. No mammary gland changes were evident in treated monkeys but exposures were subclinical and, relative to rats, the dosing period significantly shorter compared with their life expectancy and thus no great weight can be placed on the negative finding.

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[7] Hoyes KP, Jones HM, Abeysinghe RD, Hider RC, Porter JB. *In vivo* and *in vitro* effects of 3-hydroxypyridin-4-one chelators on murine haemopoiesis. Exp Haematol 1993; 21: 86.

[8] Al-Refaie FN, Wonke B, Hoffbrand AV. Deferiprone-associated myelotoxicity. Eur J Haematol 1994; 53: 298-301.

[9] Porter JN, Hoyes KP, Abeysinghe RD, Brooks PN, Huehns ER, Hider RC. Comparison of the subacute toxicity and efficacy of 3-hydroxypyridin-4-one iron chelators in overloaded and nonoverloaded mice. Blood 1991; 78: 2727-2734.

[10] Only graphical data were presented. The estimated thyroid gland and blood concentration of ^{14}C-labelled material was 50 nmol/g and 3 nmol/g, respectively, following 15 daily oral doses of 25 mg/kg ^{14}C-deferiprone.

[11] Schnebli HP. Final Report: Preclinical evaluation of CGP 37 391 1993 (L1).

Genotoxicity

Previously submitted studies indicated deferiprone was genotoxic; both mutagenic (mammalian cells but not bacterial cells) and clastogenic (*in vitro* in Chinese hamster ovary cells and *in vivo* mouse micronucleus test). This genotoxicity was postulated to be due to the chelation of iron, an essential element for enzymes involved in DNA replication; however, insufficient data were provided to eliminate the possibility of a direct genotoxic effect of the drug. A newly submitted mouse micronucleus study attempted to address some of the limitations identified in previously submitted studies. Both naive and iron loaded animals were used in the study, adequate toxicokinetic data were obtained and desferrioxamine, another iron chelator, was used as a comparator. Deferiprone (≥ 250 mg/kg PO; area under the curve for the exposure ration [ER_{AUC}], ~1.5) induced an increase in micronucleated cells, regardless of the iron status of the animals. No induction of micronucleated cells was evident in desferrioxamine treated animals. These data suggest a possible direct genotoxic effect of deferiprone. However, increased iron levels can also have a genotoxic effect; iron can produce reactive oxygen species which may lead to an increased frequency of DNA oxidation and damage (Flessel, 1977).[12] A clinical clastogenicity study indicated therapy with deferiprone was not associated with a greater frequency of chromosome aberrations than is observed with desferrioxamine.

Carcinogenicity

No life time studies have been conducted in rodents with deferiprone. In the one year rat study, an increase in incidence and severity of mammary gland hyperplasia was evident in female rats at ≥ 37.5 mg/kg bd (ER_{AUC}, 0.42) with an increased incidence of mammary fibroadenoma in naive females treated with 75 mg/kg bd (ER_{AUC}, 1.1). Mammary adenocarcinomas were seen only in treated females. The correlation of incidence and severity of pre-neoplastic and neoplastic findings with deferiprone treatment supports a relationship with treatment. As fibroadenomas are quite common in rats it is likely that deferiprone promotes the progression of this tumour, rather than initiated its formation and further progression to malignant adenocarcinomas occurred. Effects on oestrous cycling in rats suggest the increased incidence may be related to hormonal changes. The clinical relevance of these mammary gland changes is uncertain in the absence of a clear causative effect. Caution may be warranted in patients with a history or whose family has a history of breast cancer. Nonetheless, given the genotoxic findings described above, a carcinogenic potential of deferiprone must be assumed.

Reproductive toxicity

One Good Laboratory Practice (GLP) compliant fertility study in non-iron loaded rats was submitted. Adequate animal numbers were used and treatment periods were appropriate. Both male and female fertility was assessed. Doses used, however, were low, resulting in ≤ 0.3 times the clinical dose on a mg/m² basis.[13] Impaired body weight gain was evident in treated males and treated females during gestation, suggesting toxic doses were tested. No testicular or epididymal changes were evident during histological analyses and there was no apparent effect on sperm count or motility in treated males. When mated with untreated females, there was no apparent effect on fertility and no adverse effects on litter values. Previously submitted studies revealed testicular atrophy in dogs treated with ≥ 400 mg/kg/day PO deferiprone (~1.2 times the clinical dose on a body surface area basis

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[12] Flessel CP. Metals as mutagens. Adv Exp Med Biol 1977; 91: 117-128.

[13] The maximum dose tested in both males and females was 75 mg/kg PO bd. Assuming a clinical dose of 33 mg/kg PO tds and using mg/kg to mg/m² conversion factors of 6 and 33 for rats and humans, respectively, the clinical dose, on a body surface area basis, is 3300 mg/m²/day, while the maximum tested dose was 900 mg/m²/day. A mg/kg to mg/m² conversion factor of 10 was used for dogs.

[BSA]) and in rats following intraperitoneal (IP) administration, suggesting the low doses used in the new study limit the value of negative findings.

Reduced oestrus events and prolonged di-oestrus were seen in treated females (≥15 mg/kg PO bd; 0.05 times the clinical dose on a BSA basis), leading to a delay in mating. During this pre-mating phase, treated females gained more weight than control females, possibly as a result of hormonal perturbations. Once mated, there was no apparent effect on fertility, pre-implantation loss or any other litter values. Thus, the No Observable Adverse Effect Level (NOAEL) for female fertility was considered to be the highest tested dose (75 mg/kg PO bd; 0.3 times the clinical dose on a BSA basis). Given the absence of overt toxicity and the low relative doses, higher doses should have been considered. As a result, limited value can be placed on the negative findings. Chronic haemosiderosis can be associated with reduced fertility clinically. The findings in the rat study do not appear to raise additional safety concerns in patients.

Immunotoxicity

No dedicated immunotoxicity studies were submitted. Bone marrow cytotoxicity with accompanying haematological changes (for example leukopenia) was seen in toxicity studies and studies to assess immunocompetence (for example T cell dependent antibody responses) would have been desirable. However, given the history of clinical use, adequate clinical data are likely available to address this.

Impurities

The proposed specification for the process impurity, maltol, in the drug substance of deferiprone is 0.1%. According to the TGA-adopted EU guideline for drugs in which the proposed daily dose is >2 g/day, specifications greater than 0.05% require toxicological qualification.[14,15] The level of maltol in the deferiprone batch used in the 52 week rat study, the 52 week monkey study and the mouse micronucleus test is too low for toxicological qualification (0.01%). Maltol was mutagenic in one Ames test but this was not reproduced in a second Ames test, suggesting the initial finding may have been an isolated incident or associated with a mutagenic photoproduct (Watanabe-Akanuma *et al.*, 2007).[16] Based on a weight of evidence analysis there appears to be a low genotoxic concern with maltol. No increase in tumour incidence was evident in mice treated for 18 months and rats treated for 2 years with 400 mg/kg/day maltol in the diet. An acceptable daily intake (ADI) of ≤1 mg/kg was established for maltol based on a NOEL of 100 mg/kg/day in the 2-year dietary study in rats (WHO Technical Report Series, 2006).[17] Maltol is a naturally occurring compound found in coffee, chicory and soybeans and under conditions of baking (for example bread and cakes), simple sugars can be converted to maltol. Maltol is also permitted as an excipient in listed medicines in Australia, with no specified restrictions. As the maximum level of maltol expected from Ferriprox is below the ADI (that is 0.1 mg/kg/day[18]), there were no objections to the proposed specification for maltol.

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[14] EMEA, ICH Topic Q 3 A (R), 21 February 2002. Note for Guidance on Impurities Testing: Impurities in New Drug Substances (Revision of CPMP/ICH/142/95), CPMP/ICH/2737/99.

[15] Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

[16] Watanabe-Akanuma M, Inaba Y, Ohta T. Mutagenicity of UV-irradiated maltol in *Salmonella typhimurium*. Mutagenesis 2007; 22: 43-47.

[17] WHO Technical Report Series. (2006) Evaluation of certain food additives. 65th report of the joint FAO/WHO Expert Committee on food additives.

[18] The proposed maximum daily dose of Ferriprox is 100 mg/kg/day. Assuming maltol at a level of 0.1% of the active ingredient, the maximum anticipated daily exposure to maltol is 0.1 mg/kg/day.

Excipients

The oral solution of Ferriprox contains 50% w/v glycerol. As the proposed daily dose is increased from 75 mg/kg/day to 100 mg/kg/day, this corresponds with an increase in glycerol from 375 mg/kg/day to 500 mg/kg/day. According to Lin (1977) a "safe oral dose in humans is 1 g/kg every 6 hours" (quoted in IUCLID). As the daily dose of Ferriprox is intended to be divided into 3 separate doses in a day, the expected exposure of glycerol in a 6 hour period at the proposed higher dose (that is 167 mg/kg tds) is well below the dose considered to be safe. There are no objections to the level of glycerol at the proposed higher dose of Ferriprox.

Nonclinical Summary and Conclusions

A number of safety related concerns were raised in the original submission for deferiprone, including the absence of adequate safety pharmacology, pharmacokinetic, toxicity, carcinogenicity and reproductive toxicity data. Some of these deficiencies have been partly addressed by the newly submitted data; however, due to the low doses and exposures used in these studies, the toxicity profile of deferiprone has still not been fully revealed.

In a ferritin loaded rat model, deferiprone was inferior to other tested iron chelators, with only 7% iron mobilisation evident in a 24 hour period following a dose estimated to be well below the clinical dose on a body surface area (BSA) basis.

Submitted safety pharmacology studies examined the cardiovascular system. No significant inhibition of hERG K+ channels was seen at concentrations up to 18 times the clinical C_{max}, and no abnormalities in ECG parameters were seen in monkeys treated with up to 125 mg/kg/day PO, yielding plasma concentrations 1.3 times the clinical C_{max}. The tested doses/concentrations were low, limiting the predictive value of negative findings.

Pharmacokinetic studies indicated rapid absorption in rats and monkeys. Elimination half-lives of deferiprone in rodents were similar to that observed in humans, while those in monkeys were slightly shorter. Serum elimination half-lives were independent of iron loading status. *In vitro* studies indicated glucuronidation by UGT1A6 as the major route of metabolism. Pharmacokinetic drug interactions involving cytochrome P450s appear less likely but only low concentrations were tested.

Repeat dose toxicity studies of 52 weeks duration were performed in both iron loaded and naive rats and monkeys. Maximum exposures were low; equivalent to that anticipated from a clinical dose of 75 mg/kg/day but estimated to be subclinical for a 100 mg/kg/day dose. No adverse findings were evident in the monkey study. In rats, the bone marrow, thyroid, adrenal and mammary glands were target organs for toxicity. Findings included bone marrow hypocellularity (with accompanying haematological changes), diffuse colloidal basophilia and hypertrophy of the thyroid follicular epithelium, hypertrophy of the adrenal zona fasciculata, and increased incidence and severity of mammary gland hyperplasia/fibroadenoma.

Regardless of iron status, deferiprone, at clinically relevant exposures, was genotoxic in a mouse micronucleus assay. No carcinogenicity studies were conducted with deferiprone.

Aside from reduced oestrous cycling, no adverse effects on fertility were evident in either male or female rats at doses <0.5 times the clinical dose on a BSA basis.

Based on long term rodent studies, the proposed specification for the process impurity, maltol, in the drug substance was considered acceptable.

Data submitted attempted to address some of the deficiencies identified in the previous nonclinical evaluation report and included safety pharmacology, pharmacokinetic, toxicity,

genotoxicity and fertility studies. However, these studies were either largely inadequate or confirmed safety concerns identified in the previous evaluation report.

- · The low tested doses and concentrations, which were in general estimated to be subclinical for the proposed higher dose of 100 mg/kg/day, limit the predictive value of negative findings and do not help to mitigate safety concerns;
- · The genotoxicity of deferiprone was confirmed in the newly submitted micronucleus test. No genotoxicity was seen with another iron chelator, suggesting this is not due to pharmacological activity. This positive finding raises concerns given the extended wider patient population (patients with transfusional haemosiderosis) compared with patients with thalassaemia major.

Overall, there were considerable safety concerns over the proposed higher dose and the extension of indication for this product.

IV. Clinical Findings

Introduction

The application was supported by data claiming superior clinical effectiveness of deferiprone (DFP) over DFO in removing iron from the heart, a positive effect of DFP on cardiac function and reduction in iron related cardiac disease and prolongation of life in natural history studies. The sponsor also claimed that DFP is comparable to DFO in reducing total body iron as measured by serum ferritin and Liver Iron Content (LIC).

The pivotal efficacy data submitted in support of the application is based on study LA 16-0102 which compared the relative efficacy of DFP with DFO in removing excess cardiac iron in subjects with thalassaemia major. The second pivotal study, LA 12, was a historic control study. The supportive studies used to evaluate the efficacy of DFP for the proposed indication were studies that were excluded from 'pivotal' category because of the study design. These were an epidemiological population-based study (Borgna-Pignatti), single arm studies (LA11 and LA15), studies where no cardiac endpoints were measured (LA04 and LA08) and a study in children (LA30).

Pharmacology

There were no new pharmacokinetic or pharmacodynamic data presented in the submission.

Efficacy

Pivotal Study LA 16-0102

This was a multicentre, randomized, active controlled, open label clinical trial comparing the use of Ferriprox (deferiprone, DFP) versus the use of Desferal (deferoxamine, DFO) in removing excess cardiac iron in subjects with thalassaemia major. The study was conducted over 1 year (14 Jan 2003 to 13 Oct 2004) in four centres in Italy and Greece.

The primary objective was to determine whether orally administered Ferriprox exhibits superior efficacy in removing excess iron from the heart compared to that of standard subcutaneous infusions of Desferal, as reflected by magnetic resonance imaging T2-star (MRI T2*) assessments of the heart in subjects treated with either chelator.

A secondary objective was to evaluate the relative efficacy of Ferriprox with respect to that of Desferal as assessed by serum ferritin concentrations and LIC.

Patient population

Subjects who were 18 to 36 years in age with a confirmed diagnosis of thalassaemia major, and had received ongoing chelation therapy with DFO for at least the past 5 years were selected. Exclusion criteria included subjects who had compromised cardiac function as determined by reduced left ventricular ejection fraction of < 56% (In a healthy 70 kg man, the stroke volume is approximately 70 mL and the left ventricular end diastolic volume is 120 mL, giving an ejection fraction of 70/120, or 58%) and subjects who have disorders associated with neutropenia or thrombocytopenia in the preceding 12 months.

Eligible subjects were to be stratified into two groups according to their cardiac iron status as measured by MRI T2*. MRI T2* is an applied magnetic field relaxation parameter reflecting, principally, local magnetic field inhomogeneities that are increased in the presence of iron deposition. Increase myocardial iron reduces myocardial MRI T2* values and conversely, increased myocardial MRI T2* values indicate myocardial iron reduction. Values < 20 milliseconds (ms) represents iron overload in the heart. The two groups were: ≥8 ms to <14 ms and ≥14 ms to <20 ms. Subjects from each group were then randomized equally, in blocks of four, between the treatment arms A and B. Arm A received DFP oral therapy and Arm B received DFO subcutaneous therapy (Figure 1).

Figure 1: Subject screening and disposition process
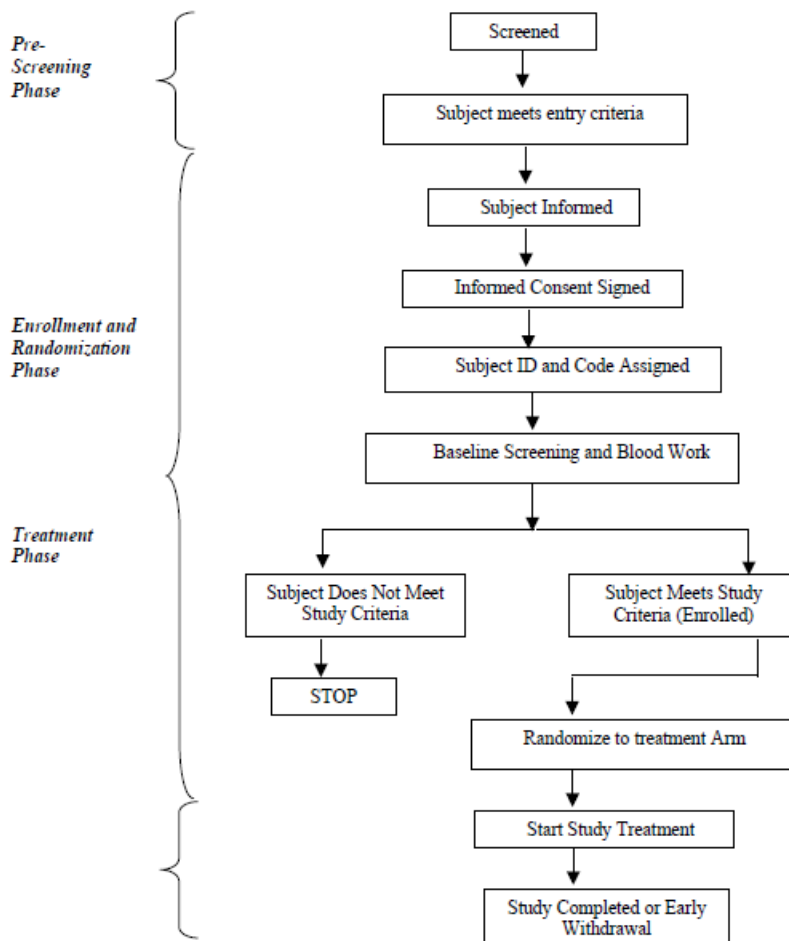
Treatment

The dose of DFP was 75 mg/kg per day in 3 divided doses for 4 weeks, followed by 85 mg/kg per day, in 3 divided doses for 4 weeks, and then finally to 100 mg/kg per day in 3

divided doses, for a total treatment period of 12 months. A lower dose could be prescribed if adverse drug reactions occurred. Subjects randomized to Arm B received DFO 50 mg/kg per day subcutaneously (SC) 5 to 7 days per week, for a total treatment period of 12 months. Again, a lower dose could be prescribed if adverse reactions occurred. Prior and concomitant therapy in both arms was at the discretion of the investigators. Subjects in the DFP arm were not allowed the use of drugs known to cause neutropenia.

Primary efficacy parameter

The primary efficacy measurement was the subjects' cardiac iron status as determined by MRI T2* assessment. The cardiac iron concentration was measured at baseline and repeated at 6 months and 12 months or at the time of early withdrawal. Cardiac function (left ventricular ejection fraction [LVEF] and left ventricular shortening fraction [LVSF]) were evaluated by cardiovascular magnetic resonance (CMR). CMR is accurate, reproducible and well validated for measuring right and left ventricular volumes and mass. CMR assessment of cardiac function was conducted in the regional centres in Athens and Cagliari and validated, in a blinded fashion, by independent reviewers at the Royal Brompton Hospital, London, UK. LVEF and LVSF were also measured by echocardiography (ECHO).

Secondary efficacy parameter

The secondary efficacy measurements were the measurement of serum ferritin as assessed by microparticle enzyme immunoassay (MEIA) and LIC as assessed by superconducting quantum interference device (SQUID) biosusceptometer.

Statistical plan

The "intent to treat" (ITT) population included all those subjects who had received at least one dose of the drug and who had at least two measurements of which one was post-baseline. The "per protocol" (PP) population included all the randomized subjects who had completed the study. Both the ITT and PP approaches were applied in statistical evaluation of efficacy data. Data from all randomized patients were to be used for analysis of safety.

A total subject population of 60 was chosen, allowing for a dropout rate of 20%, to achieve 80% power with $\alpha=0.025$, to show that DFP offered a greater increase in cardiac MRI T2* from baseline after 1 year of drug therapy than DFO, based on an expected difference of at least 2.3 ± 2.5 ms between the two treatment groups, as determined in previous MRI T2* assessment data in patients with MRI T2* between 8 and 20 ms.

Since cardiac tissue iron values have an inverse relationship with MRI T2* values, this measure was log transformed so as to linearize the relationship. A two sample t-test was used to compare the mean changes in log (MRI T2*) from baseline to 6 and 12 months between the two treatment groups. Since this study was designed as a superiority study, one sided p-value of 0.025 and in addition, for the sake of clarity, a two-sided p-value of 0.05, were used in determining statistical significance on the MRI T2* analyses.

Quality of Life

The impact on the quality of life (QOL) of oral treatment versus parenteral treatment was measured using the QOL questionnaire, the RAND 36-Item Health Survey (RAND-36). The questionnaire is divided into 8 domains whose scores range from 0 to 100. In addition, a list of 10 supplemental thalassaemia questions was also used.

Efficacy results

Study population

Of 160 subjects screened 61 subjects were enrolled in the study. Of the 61 subjects, 29 were randomized to the DFP arm and 32 to the DFO arm. In all, 56 completed the study. Five subjects (DFP: 2, DFO: 3) discontinued prematurely because of adverse events (cytomegalovirus [CMV] hepatitis, elevated liver enzymes, deteriorating cardiac function) or for personal reasons (2) (Figure 2). Of the 61 who were selected, 3 had minor protocol violations. Another 4 had study therapy deviations. All these subjects completed the study.

The subjects, who were all Caucasian, were aged between 18 and 35 years. There were no significant differences between the two groups. In all, 4 subjects in the DFP group and 11 in the DFO group had had a splenectomy at baseline. The difference was not statistically significant (p=0.0791). Hepatitis C was reported at baseline by 18 subjects in the DFP group (62%) and by 16 subjects in the DFO group (50%). The difference was not statistically significant (p=0.4408). There were no other reports of splenectomy or hepatitis C infection during the study, except that one subject in the DFP group who had a positive hepatitis C result at baseline was hepatitis C negative at the end of the study.

All the subjects took concurrent medications. The use of concurrent medications was balanced between the two groups.

Figure 2: Subjects' Disposition in Study LA16-0102
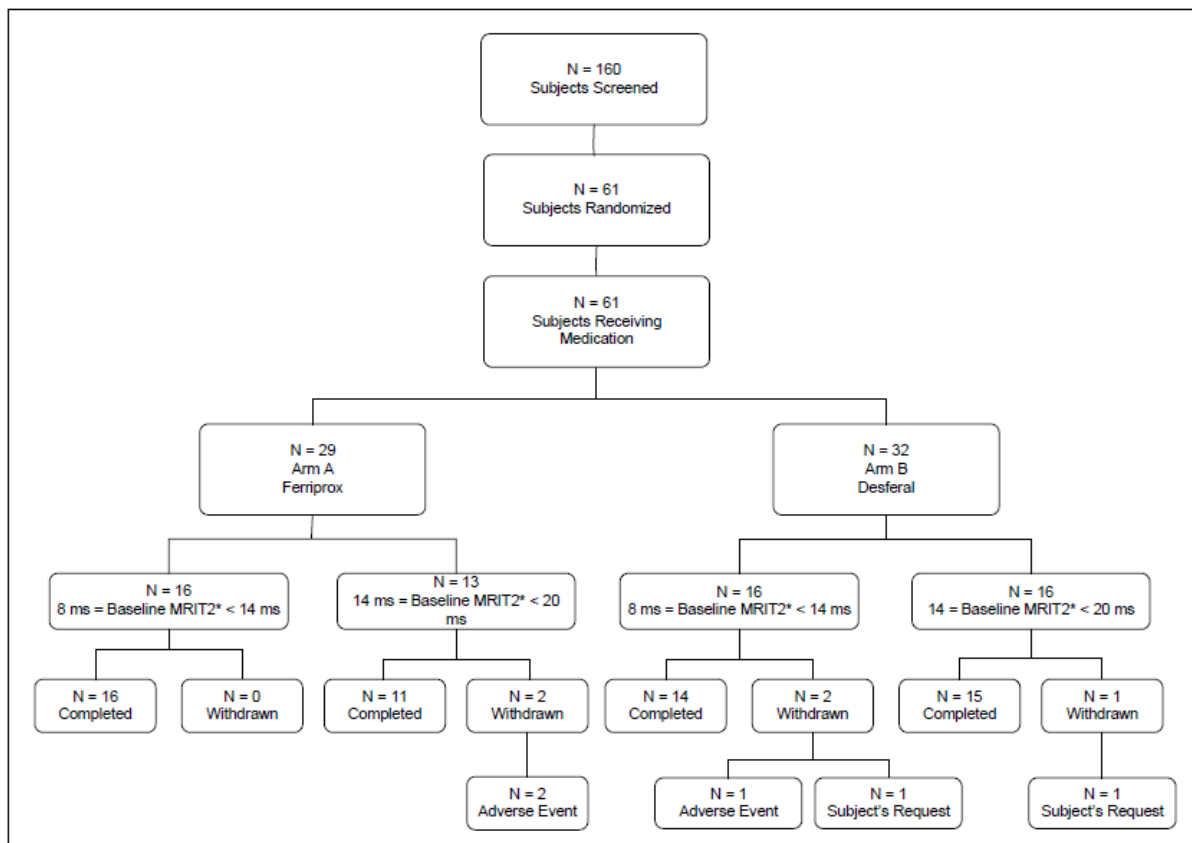
The efficacy analyses were performed on both the ITT and PP populations. One subject in the DFO group had had only the baseline assessment and was therefore excluded from the ITT population.

Primary efficacy analysis

Magnetic Resonance Imaging T2*

At baseline, the geometric mean (defined as the antilog of the mean of the log MRI T2* data) was similar between the two groups. The geometric mean increase from baseline to 6 months (18% vs 9%, p=0.0404) and baseline to 12 months (27% vs 13%, p=0.0228) was statistically significantly greater in the DFP arm than in the DFO arm (Table 2). The results for the PP population were similar (Table 3).

Table 2: Log (MRI T2*) between Ferriprox and Desferal treatment groups (ITT population)

MRI T2* (milliseconds)	Randomized Treatment Groups					
	Baseline		6 Months		12 Months	
	Ferriprox [n=29]	Desferal [n=32]	Ferriprox [n=29]	Desferal [n=31[†]]	Ferriprox [n=29]	Desferal [n=31[†]]
Geometric Mean (milliseconds)[*]	13.03	13.32	15.37	14.43	16.51	15.01
Coefficient of Variation (%)[‡]	32	30	38	37	38	39
Percentage of Baseline			118	109	127	113
Ratio of Means (%)[§]	98		109		112	
p-value[‖]	0.7731		0.0404		0.0228	

[*] Geometric mean is defined as antilog of the mean of the log data

[†] Subject C1-40 had baseline MRI T2* level value only and was not eligible to be included in the ITT population.

[‡] Coefficient of variation is defined as $\sqrt{[e^{variance}-1]}$, where variance is the variance of the mean in log scale.

[§] The ratio is defined as Ferriprox mean/Desferal mean. At 6 and 12 months, the ratio is corrected for the difference in baseline mean between the two treatment groups by dividing it by 0.98.

[‖] The Log (MRI T2*) between the Ferriprox and Desferal treatment groups was compared by the two-sample t-test.

Table 3: Log (MRI T2*) between Ferriprox and Desferal treatment groups (PP population)

MRI T2* (milliseconds)	Randomized Treatment Groups					
	Baseline		6 Months		12 Months	
	Ferriprox [n=27[†]]	Desferal [n=29[†]]	Ferriprox [n=27[†]]	Desferal [n=29[†]]	Ferriprox [n=27[†]]	Desferal [n=29[†]]
Geometric Mean (milliseconds)[*]	12.74	13.41	15.06	14.66	16.26	15.10
Coefficient of Variation (%)[§]	31	31	38	37	38	40
Percentage of Baseline			118	109	128	113
Ratio of Means (%)[‡]	95		108		113	
p-value[‖]	0.5294		0.0541		0.0147	

[*]   Geometric mean is defined as antilog of the mean of the log data
[†]   Subjects A1-20, A1-47, A1-48, C1-40 and C1-52 were not eligible to be included in the PP population.
[‡]   Coefficient of variation is defined as $\sqrt{[e^{variance}-1]}$, where variance is the variance of the mean in log scale.
[§]   The ratio is defined as Ferriprox mean/Desferal mean. At 6 and 12 months, the ratio is corrected for the difference in baseline mean between the two treatment groups by dividing it by 0.98.
[‖]   The Log (MRI T2*) between the Ferriprox and Desferal treatment groups was compared by the two-sample t-test.

Secondary efficacy analysis

Cardiovascular Magnetic Resonance (CMR) - Left Ventricular Ejection Fraction (LVEF)

Iron deposition is greatest in the ventricular walls of the heart. The degree of cardiac dysfunction is said to depend on the quantity of iron deposited in the individual myocardial fibres and the number of fibres affected. CMR was used for the assessment of LVEF. In both arms of the study, there was improvement in CMR LVEF, with greater improvement in the DFP arm. The difference between the treatment groups in change from baseline to 6 months was not statistically significant but the difference at 12 months was significant (Table 4). The results in the PP population were similar.

Table 4: CMR LVEF between Ferriprox and Desferal treatment groups – ITT population

CMR LVEF (%)	Randomized Treatment Groups					
	Baseline		Change from Baseline to 6 Months		Change from Baseline to 12 Months	
	Ferriprox [n=29]	Desferal [n=32]	Ferriprox [n=29]	Desferal [n=31[†]]	Ferriprox [n=29]	Desferal [n=31[†]]
Mean ± SD	69.66 ± 5.44	68.38 ± 4.92	2.00 ± 2.73	0.52 ± 3.52	3.07 ± 3.58	0.32 ± 3.38
Min, Max	58, 80	60, 79	-3, 9	-9, 9	-3, 11	-8, 5
p-value[*]	0.3382		0.0744		0.0034	

CMF = cardiovascular magnetic resonance; ITT = intent-to-treat; LVEF = left ventricular ejectio fraction; max = maximum; min = minimum.
[*]   Changes in CMR LVEF from baseline to 6 months and 12 months were compared between the two treatment groups by using the two-sample t-test.
[†]   Subject C1-40 had baseline CMR LVEF level value only and was not eligible to be included in the ITT population.

Echocardiogram – Left Ventricular Ejection Fraction (LVEF)

The two mean echocardiogram (ECHO)-LVEFs were similar at baseline. At 12 months, the mean ECHO-LVEF in the DFP arm had improved by 2.5%. There was decrease in the mean ECHO-LVEF in the DFO arm. The difference in the two groups in change from baseline to 12 months was statistically significant (Table 5).

Table 5: ECHO LVEF between Ferriprox and Desferal treatment groups – ITT population

| ECHO LVEF (%) | Randomized Treatment Groups | | | |
| | Baseline | | Change from Baseline to 12 Months | |
	Ferriprox [n=29]	Desferal [n=32]	Ferriprox [n=28†]	Desferal [n=31†]
Mean ± SD	64.69 ± 6.72	64.27 ± 6.88	2.50 ± 6.04	-0.56 ± 4.90
Min, Max	54, 79	50, 77	-9, 16	-8, 10
p-value*	0.8088		0.0358	

ECHO = echocardiogram; ITT = intent-to-treat; LVEF = left ventricular ejection fraction; SD = Standard Deviation.

* Mean changes from baseline to 12 months were compared between the two treatment groups by using the two-sample t-test.

† Subjects A1-47 and C1-40 did not have ECHO LVEF value at 12 months and were not eligible to be included in the ITT population.

Echocardiogram – Left Ventricular shortening fraction (LVSF)

The reduced contractility of the heart can be manifested as a decrease in LVSF. At baseline the mean ECHO-LVSF were similar in the two arms of the study. After 12 months of treatment, the mean ECHO-LVSF in the DFP arm had increased by 2.62% as opposed to a decrease of 1.1% in the DFO arm. The difference in change between the groups in ECHO LVSF from baseline to 12 months was statistically significant (Table 6).

Table 6: ECHO LVSF between Ferriprox and Desferal treatment groups – ITT population

| ECHO LVSF (%) | Randomized Treatment Groups | | | |
| | Baseline | | Change from Baseline to 12 Months | |
	Ferriprox [n=29]	Desferal [n=32]	Ferriprox [n=28†]	Desferal [n=31†]
Mean ± SD	36.32 ± 4.39	36.38 ± 4.25	2.62 ± 7.41	-1.08 ± 3.82
Min, Max	31.2, 47.0	30.0, 44.0	-8.0, 12.0	-8.8, 8.0
p-value*	0.9540		0.0175	

ECHO = echocardiogram; ITT = intent-to-treat; LVSF= left ventricular shortening fraction; SD = Standard Deviation.

* Mean changes from baseline to 12 months were compared between the two treatment groups by using the two-sample t-test.

† Subjects A1-47 and C1-40 did not have ECHO LVSF value at 12 months and were not eligible to be included in the ITT population.

Liver Iron Concentration (LIC)

LIC was measured by SQUID, which provides a direct measure of hepatic iron storage. LIC was measured at baseline and at 12 months. At baseline, the mean LICs of both groups

were similar. At 12 months, the LIC in the DFP arm showed a mean decrease of 0.93 mg iron (Fe)/g dry weight liver and in the DFO arm the decrease was 1.54 mg Fe/g dry weight liver. The changes from baseline to 12 months were compared between the treatment groups and found to be not significant.

Serum Ferritin

Assessment of serum ferritin levels was performed at baseline and then 3 monthly up to 12 months. The mean serum ferritin level at baseline was significantly lower in the DFP arm than in the DFO arm. In both treatment arms, the mean serum ferritin levels were lower at 12 months than at baseline, with the decrease more pronounced in the DFO arm. The differences between the two groups in the change from baseline to 3, 6 and 9 months were statistically significant but not the difference in change from baseline to 12 months.

Quality of life

One subject in the DFP arm withdrew from the study before the 6 month visit and did not provide any QOL data, except for baseline data. Two subjects in each treatment group withdrew before the 12 month visit and did not provide QOL data from the 6-12 month window.

The scores for the following domains were similar between the treatment arms at all time points: physical functioning, role physical, pain index, general health perception, energy/fatigue, social functioning, and emotional well being. There was no statistically significant difference between the treatment groups in the mean change of any of the above domain scores from baseline to 6 months, baseline to 12 months, and 6 months to 12 months.

The only statistically significant difference between the treatment groups was for the role emotional domain between 6 and 12 months. Subjects in the DFP arm had a stable score, but subjects in the DFO arm had a decrease in score. A decreased score indicated that the subjects experienced more problems with work or other daily activities because of emotional problems. This result has to be interpreted with caution since there was no concurrent statistical difference between treatment groups in the emotional well being or the social functioning domains.

The supplemental thalassaemia questions were developed to explore anticipated differences in QOL resulting from the two treatment alternatives. In the DFP arm, 20.7% at baseline and none at 6 months reported that treatment interfered with their normal activities. In the DFO arm, the corresponding results were 9.1% at baseline and 15.7% at 6 months. At 12 months the figures were 3.7% in the DFP arm and 16.7% in the DFO arm.

Evaluator Comment

Ferriprox was shown to be significantly superior to Desferal in decreasing cardiac iron overload in subjects with thalassaemia major. Cardiac function, as measured by LVEF and LVSF, was also significantly better in the Ferriprox group. The difference in reduction of LIC and serum ferritin levels from baseline to 12 months between the two groups was not statistically significant.

Pivotal Study LA 12-9907

This Phase III study was an open label, controlled, single centre, parallel, longitudinal, retrospective assessment of medical records of patients with transfusion dependent β-thalassaemia, treated for at least four years with DFP or DFO, to compare survival and incidence of cardiac disease. Cardiac disease was defined according to the New York Heart Association (NYHA) criteria.

Substantial numbers of patients were treated with Ferriprox since 1995. Therefore, the study evaluated the clinical data of all subjects whose medical histories, starting from 1995, were available. The clinical data of all the patients, five years of age or older, with transfusion dependent β-thalassaemia that were treated at the centre after December 1995 with DFP or DFO were reviewed for this study. No safety information was collected.

The primary objective was to investigate the incidence of cardiac disease and survival in patients treated with Ferriprox and to compare the results with those patients treated with conventional therapy, daily subcutaneous infusions of deferoxamine, over the same period.

The secondary objective was to evaluate the progression of cardiac disease in patients participating in this study treated with either Ferriprox or deferoxamine.

The outcome measures that were considered are shown in Figure 3.

Study population

All the patients were from the Centro Microcitemie of the University of Turin, where they had had the same transfusion regimen that was aimed at maintaining the pre-transfusion haemoglobin (Hb) level at 9.5 – 10 g/dL and the mean Hb at 12 g/dL. Since 1995, a portion of the patients were treated with DFP 25 mg/kg three times a day. The others continued on DFO 20 – 60 mg/kg/day SC over 8 to 12 hours, on 4 to 7 days/week.

Patients who had anaemia other than β-thalassaemia, history of malignancy or had a disorder requiring radiotherapy or chemotherapy were excluded.

The data of patients who satisfied the selection criteria were assigned to either DFP or DFO treatment arms based on total drug exposure for more than four years to one of these chelators. Compliance with DFP therapy was evaluated by retrospective analysis of the monthly discussions between doctor and patient, measurement of the medication monitoring system device (an electronic cap that records the date and time of each opening, which was presumed to represent a taken dose) and by counting the number of

Figure 3: Study LA 12-9907: Outcome measures

- Endpoints for censoring have been considered respectively:
    1. Survival: death
    2. Clinical heart disease
- Presence or occurrence of one of the following conditions:
    - Congestive heart failure (acute or chronic)
    - Symptomatic cardiopathy affecting quality of life (NYHA class > 2)
    - Arrhythmia (documented by ECG Holter abnormalities), requiring medication
    - Echocardiographic alterations (Shortening Fraction (SF) < 30%, Ejection Fraction (EF) < 55%), requiring medication
    - Pericarditis (non-infective), in the presence of severe iron overload (serum ferritin > 2,500 µg/L)

- The use of ACE inhibitors therapy for preventing heart disease has not been considered.

- ◆ Acute myocarditis not preceded nor followed by one of the above conditions is not considered.
    3. Deterioration:
        - Shifting of congestive heart disease from acute to chronic
        - Impairment of NYHA class
        - Impairment of arrhythmia, requiring additional medication or a significant change of it, or indication to ablation or pacemaker
        - Worsening of the echocardiogram findings (SF, EF) despite the use of medication
    4. Improvement:
        - Shifting from congestive heart failure to asymptomatic cardiopathy (> 6 months)
        - Improvement of NYHA class
        - Improvement of arrhythmia: regression of medication dependence
        - Improvement of echocardiogram: regression of medication dependence

DFP tablets dispensed and returned. Compliance with DFO was monitored by individual interview, physical examination of infusion sites, comparison of the number of infusions reported by the patient with the number ordered and pharmacy records of dispensed DFO.

The protocol specified the inclusion of patients with at least 3 serum ferritin concentration determinations in the last 2 years preceding initiation of treatment. However, because of the limited number of patients that satisfied this ruling, all patients with serum ferritin concentration determinations in the last 2 years preceding initiation of treatment, were included. To ensure compliance with the protocol, a subgroup analysis of patients who had at least 3 serum ferritin concentrations as specified in the protocol was also performed.

At baseline, subjects in the DFP arm were 2.3 years younger than those in the DFO arm. A second subgroup analysis was performed on 94 patients (47 in each arm), matched for age at the start of chelation therapy, so as to reduce any potential effect of age on the prevalence and/or progression of iron induced cardiac disease.

A single cardiologist performed the review of patients' cardiac data, blinded to the chelation therapy used.

Efficacy measurements

Data was collected from the first year after commencement of the study and continued for five years or more. The baseline parameters that were analysed for comparison between the two groups included transfusional iron input, the extent of cardiac disease and compliance with treatment. Efficacy was measured by the incidence of cardiac disease and survival at the end of the study (Year ≥ 5). The parameters analysed included Kaplan-Meier analysis of survival and Kaplan-Meier analysis of heart disease free survival. Changes in cardiac disease status were also determined using NYHA classification, SF and EF parameters by echocardiography and ECG. Factors that might have affected cardiac disease during the study included compliance with chelation, transfusional iron input, serum ferritin and LIC.

Any data received for serum ferritin, urinary iron concentration and LIC, measured by SQUID with a time on study greater than 72 months, were not used in any analysis.

In patients who had not had a heart assessment at baseline, the time of development of heart disease was calculated as the time difference between the first available NYHA Class of NAP (= no cardiac disease) and the first occurrence of NYHA Class 1 or greater.

Statistics

Two sample t-tests or Chi-square tests were used to compare the baseline characteristics between the treatment groups. To evaluate the difference related to chelation therapy between the two groups during the study period, a two sample t-test or Chi-square test was performed to compare the overall compliance with chelation therapy, drug exposure time, overall transfusion iron input, overall urinary iron excretion and percentage of patients with > 50% of their serum ferritin results > 2500 µg/L. All the statistical tests were two sided with a type I error of 0.05. In all two sample t-tests, when the test for equality of variances was significant (p<0.05), the test result based on unequal variances was used to determine the statistical significance of the comparison. For frequency tables, the Fisher's exact test was used to compare proportions between therapy groups when at least 50% of the cells in the 2x2 contingency table had expected counts of < 5 in the Chi-square test. No formal determination of sample size was performed.

Results

Patient population

In all, the clinical records of 168 patients with β-thalassaemia were screened and 129 patients satisfied the selection criteria. Of these, 54 were in the DFP arm and 75 in the DFO arm. Of the 39 patients excluded from the study, 16 did not have chelation therapy with either of the study chelators for four years during the review period, ten had no information about chelation therapy or cardiac assessment, six had only one cardiac assessment for analysis, six patients were under the age of 5 at the start of treatment and one was positive for human immunodeficiency virus (HIV) antibodies. None of the excluded patients had a change in their cardiac status or died during the review period.

A subgroup analysis of 107 patients (Subgroup 1), who had had at least 3 serum ferritin concentration assays as per the initial protocol, was performed to ensure compliance with the protocol. This subgroup consisted of 50 DFP patients and 57 DFO patients. The patients participating in the study had a mean age 18.25 years, with patients in the DFP arm significantly younger than those in the DFO arm (17 ± 4 vs 19.4 ± 7; p=0.018). Subgroup 2, consisting of 94 patients who were matched for age at which they first initiated chelation therapy, was formed to determine whether age was an influencing factor on the cardioprotective effect of DFP. This subgroup had 47 patients in each arm of the study.

While the cardiac status of all 129 patients was obtained in the search, not all the data for non-cardiac iron load were available. The non-cardiac iron load (mean serum ferritin concentration, percentage of patients with more than 50% of their serum ferritin results >2500 µg/L and mean hepatic iron concentration) at baseline was greater in patients in the DFP arm than in patients in the DFO arm. The differences between the two groups for each of the parameters were not significant except for the difference between the two mean hepatic iron concentrations.

Efficacy results

The cardiac status was measured in all 129 patients. At baseline, 7 (13%) in the DFP arm and 12 (16%) in the DFO arm had cardiac disease. The difference between the two groups was not significant. At the last assessment, the incidence of patients with cardiac disease in the DFP arm remained the same as at baseline (13%), but the incidence in the DFO arm (29.3%) was higher. The difference between the two groups was statistically significant.

Two patients (4.3%) in the DFP arm and 13 patients (20.6%) in the DFO arm who were previously cardiac disease free developed cardiac disease during the study. The difference between the groups was statistically significant (p=0.0133).

During the course of the study, 2 patients (3.7%) in the DFP arm and 15 (20%) in the DFO arm experienced deterioration in their NYHA classification from the first to last assessment. The difference between the two groups was statistically significant (p=0.0069). None of the patients in the DFP arm who had cardiac disease at baseline had worsening of their cardiac status during the study.

There was no difference between the two arms in the number of patients with cardiac disease who showed improvement in their NYHA classification between the first and last assessments. The difference was not statistically significant (p=0.6169).

A cardiac disease free survival analysis using the Kaplan-Meier method was conducted to compare the "time to event" data for the occurrence of cardiac disease between the two therapy groups. The log rank test showed a statistically significant difference between the two groups in favour of the DFP arm (Figure 4).

Figure 4: The Kaplan-Meier heart disease- free survival over the study period in the patients treated with Ferriprox and deferoxamine
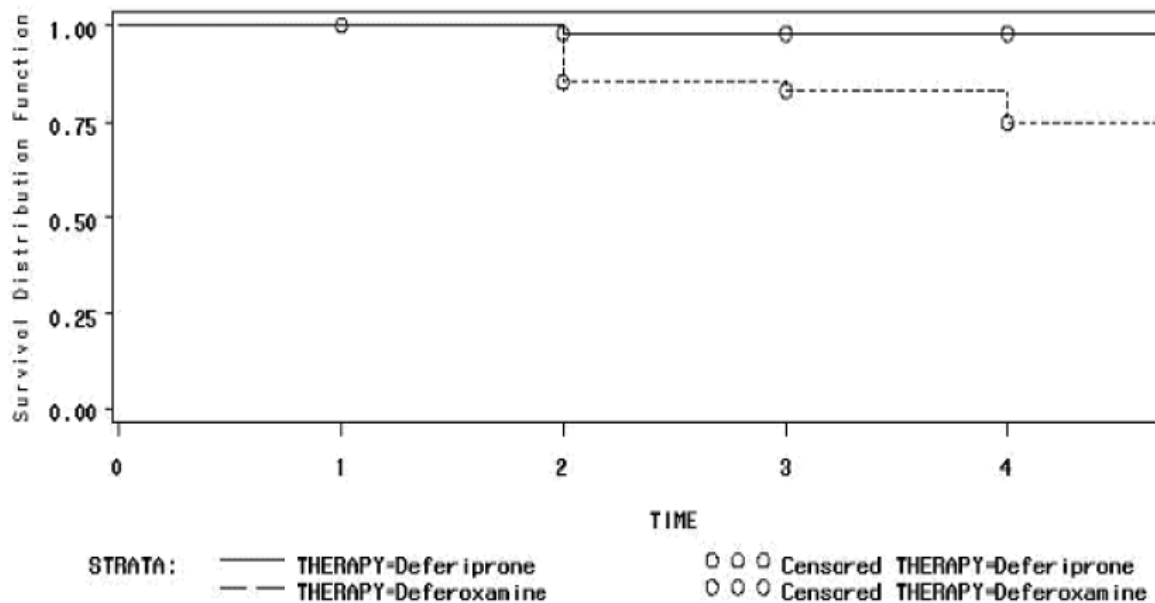
There were four patients, all from the DFO arm, who died during the study period. Of these, 3 had cardiac disease at baseline and the fourth had a history of drug addiction. This patient died within a short time of admission to hospital with acute abdominal pain. The cause of death was not known. This death was not included among the deaths used for survival analysis.

The shortening fraction (SF) and ejection fraction (EF) were measures used to assess cardiac status. Of the 129 patients, one patient had only one echocardiographic assessment and was not included in the analyses. Among the remaining 128 patients, there was no significant difference between the groups in the mean SF during the course of the study. Similarly, there was no significant difference in mean EF between the two therapy arms of the study. Also, there was no significant difference in improvement or worsening of SF between the two therapy arms over the course of the study. Similar results were obtained in the analysis of EF.

An analysis of factors that may affect cardiac disease in thalassaemia patients was examined. These included patient compliance with chelation therapy, average drug exposure time, transfusion iron input, urinary iron excretion, serum ferritin and LIC.

The mean compliance with chelation therapy was higher in the DFP arm. It was 89 ± 7% (N=53) in the DFP arm and 85 ± 11% (N=73) in the DFO arm. The difference in compliance between the two groups was statistically significant (p=0.0108).

The mean transfusional iron input at baseline was 0.464 ± 0.085 mg Fe/kg body weight/day (N=49) in the DFP arm and 0.432 ± 0.110 mg Fe/kg body weight/day (N=61) in the DFO arm. The difference was not significant. During the course of study, the DFP arm had a higher transfusional iron input. The overall mean transfusional iron input (calculated by averaging the mean of each patient for the 6-year period) was 0.432 ± 0.076 mg Fe/kg body weight/day (N=53) in the DFP arm and 0.408 ± 0.085 mg Fe/kg body weight/day (N=71) in the DFO arm. The difference was not significant.

The mean urinary iron excretion at baseline was 14.7 ± 10.7 mg Fe/day (N=49) in the DFP arm and 15.5 ± 12.2 mg Fe/day (N=48) in the DFO arm. The difference was not significant (p=0.7292). During the study, the mean urinary iron excretion was 18.8 ± 8.1 mg Fe/day (N=53) in the DFP arm and 19.3 ± 13.4 mg Fe/day (N=71) in the DFO arm. There was no significant difference between the two groups.

The mean serum ferritin values at baseline were 2033 ± 919 μg/L (N=51) in the DFP arm and 1809 ± 1464 μg/L (N=60) in the DFO arm. The difference was not significant. During the course of the study, the serum ferritin levels remained higher in the DFP arm than in the DFO arm but at the end of the study, the levels were similar. The result was not significant. Trend analysis over time of the serum ferritin concentrations, where the effect of time on serum ferritin concentration from baseline to end of study was analysed by analysis of variance (ANOVA) and simple linear regression, showed that Treatment *Time interactions were not significant (p =0.41) indicating that the slopes of serum ferritin concentrations were similar over time between the two therapy arms. Regression analysis shows that the proportion of subjects with a negative trend in serum ferritin is comparable between the two treatment groups (p > 0.05).

Limited data were available for liver iron concentration. The mean LIC levels measured by SQUID at baseline were 1.6 ± 0.7 mg/Fe/g liver wet Wt (N=46) in the DFP arm and 0.9 ± 0.6 mg/Fe/g liver wet Wt (N=16)) in the DFO arm. The difference was statistically significant (p=0.0023). During the course of the study, the LIC levels were higher in the DFP arm.

Subgroup analysis

The first subgroup of 107 patients were those who had at least 3 serum ferritin assays during the two years immediately prior to start of the study, as per protocol. The mean age of patients in the DFP arm at baseline was lower than in the DFO arm. As with the main group, the incidence of cardiac disease at the last assessment, the incidence of cardiac disease in patients who were previously cardiac disease-free and the incidence of worsening NYHA classification during the study, were all lower in the DFP arm of the study. The differences between the two treatment groups were statistically significant. The survival analysis using the Kaplan-Meier method was used to compare the time to event data for the occurrence of cardiac disease between the two therapy groups (Figure 5). The change in cardiac status was also measured by SF and EF. As in the main group, there were no changes in mean SF from the start of the study to the end in both arms. Similarly, there was no significant difference in mean EF between the groups from baseline to the end of the study.

Figure 5: The Kaplan-Meier analysis of heart disease free survival over the study period (based on patients with at least 3 serum ferritin values pre-baseline)
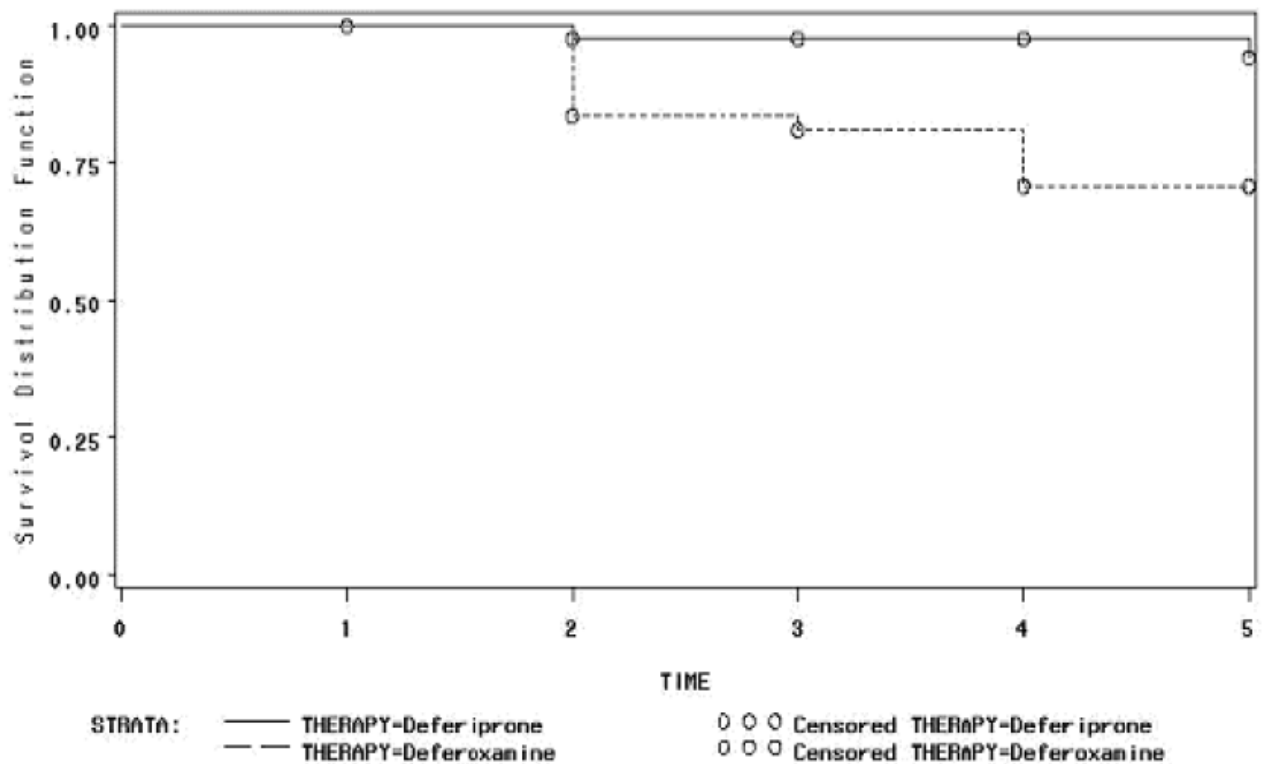
An analysis of factors that may affect cardiac disease in thalassaemia patients was examined. The findings were very similar to those in the main groups.

The second subgroup analysis was performed on 94 patients from both arms, matched for age at the start of chelation therapy. The baseline results were very similar to that in the main group. The results at the end of the study were similar to those in the main group. The proportion of patients with cardiac disease increased in the DFO arm. The difference in proportion was not statistically significant. The incidence of cardiac disease in patients who were previously cardiac disease free and the incidence of worsening NYHA classification during the study were all lower in the DFP arm of the study and the differences between the two arms were significant. The Kaplan-Meier survival curves showed a statistically significant difference between the groups (p=0.0171) (Figure 6).

Echocardiographic assessment of SF and EF showed that there was no significant change from baseline to the end of the study for patients in either group.

Figure 6: The Kaplan-Meier analysis of heart disease free survival over the study period (based on patients with similar age at the start of chelation therapy)
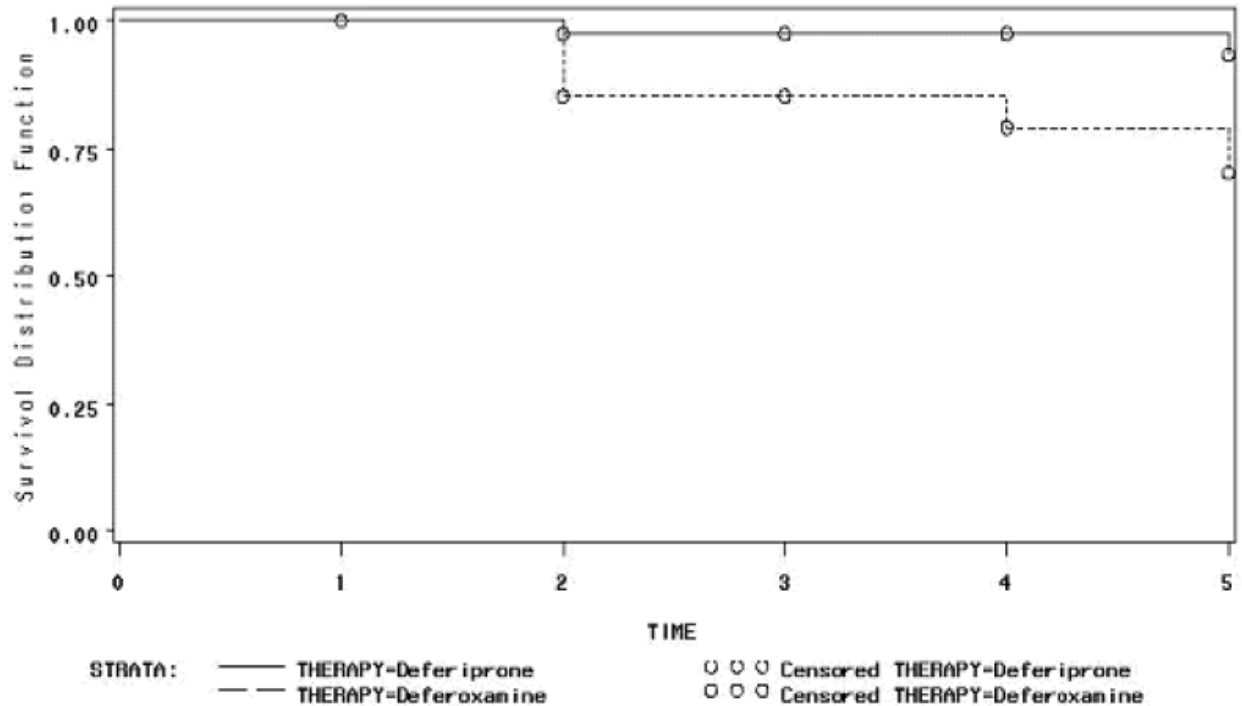
Evaluator Comment

In study LA 12, the primary objective was to compare the incidence of cardiac disease and survival in patients treated with Ferriprox for at least four years with patients treated with deferoxamine over the same period. The study showed that DFP has a greater cardioprotective effect than DFO. Echocardiographic analyses of cardiac function failed to demonstrate a significant difference between the two arms of the study. Compliance was significantly better in the DFP arm (89% vs 85%) but whether this difference had any influence on the results is uncertain. DFO showed greater efficacy in reducing non-cardiac iron load, though the difference between the two groups was not statistically significant at the end of the study.

The results therefore show that DFP has a somewhat greater cardioprotective effect than DFO but is not as effective in reducing non-cardiac iron load.

Supportive studies

Borgna-Pignatti et al.- Cardiac morbidity and mortality in deferoxamine or deferiprone treated patients with thalassaemia major.

This retrospective epidemiological study of patients with thalassaemia major, who were treated with DFO alone or switched to treatment with DFP, was conducted at 7 centres in Italy.[19] All the patients were born between 1 January 1970 and 31 December 1993. Entry to the study was on 31 January 1995 and the study continued until 31 December 2003. The primary objective was the cardiac disease-free survival time from 31 January 1995. The secondary objective was overall survival from 31 January 1995.

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[19] Borgna-Pignatti C, Cappellini MD, De Stefano P et al. Cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia major. Blood 2006; 107: 3733-7.

All the patients were treated with DFO until 31 January 1995. The switch to DFP occurred at any time between 31 January 1995 and 31 December 2003. In all, 516 patients met the selection criteria for a median duration of drug use of nearly nine years. Of the 516 patients, 359 were treated with only DFO (30-50 mg/kg/day) and 157 were switched to DFP (75 mg/kg/day). The median duration on DFP treatment was 4.3 (range: 0.02 – 8.9) years. The switch from DFO occurred at any time and varied from less than a month after study onset to about a month before study end. Approximately 38% (n=60) switched back to DFO after mean exposure to DFP of 4.78 years and were continued on DFO for a mean duration of 3 years. Some patients were enrolled in another study of another oral iron chelator (ICL670) starting in July 2001.

The baseline characteristics of the DFO and DFP group were similar, except that the mean serum ferritin level and the percentage of subjects with serum ferritin levels > 2500 µg/L were higher in the DFP group.

Following treatment, serum ferritin levels were consistently lower in the DFO arm throughout the study. During the course of the study, there were 52 cardiac events including 15 cardiac deaths. All of these occurred in the DFO group. There were no cardiac events reported in the DFP group. In the group of subjects who switched back to DFO from DFP, six subjects, exposed to DFP for periods ranging from 3 months to 5 years had cardiac events in periods ranging from 20 months to more than 3 years after the switch. In all 26 patients died during the study period. Of these 24 were in the DFO arm and 2 were in the DFP arm. Both deaths in the DFP arm were non-cardiac related (one died in a car accident and the other from bacterial endocarditis from infection in an indwelling catheter inserted for previous administration of DFO).

Evaluator Comments

There are concerns regarding the internal validity of this study. DFP was approved in Italy only in 2000. The switch to DFP could be exposed to bias with physicians either reluctant to try a new therapy or embracing it with enthusiasm. It is also possible that the switch to DFP was done as a last resort in patients at risk of early death. Of the 157 patients switched to DFP, 60 switched back to DFO. It is possible that the six patients who had cardiac events in their post DFP phase were too far removed in time for these events to be ascribed to DFP.

Study LA 08: Safety and efficacy of alternating DFO and DFP compared to DFO alone in the treatment of iron overload in thalassaemia subjects.

This was a multicentre, open label, randomized, parallel, active controlled trial which compared treatment with DFO alone (20-60 mg/kg/d, 5 to 7 days/wk) with an combined treatment regimen of DFP (75 mg/kg/d, 5 days/wk) and DFO (40 mg/kg/d, 2 days/wk) in 60 patients with transfusion dependent thalassaemia major. The trial had a one month baseline assessment followed by a 12 month treatment period. Following the baseline assessment, the patients were randomized to two equal groups. Of the 30 patients randomized to the DFP + DFO arm, one patient did not start treatment and was considered a screening failure.

The trial examined the relative efficacy of the treatment arms in reducing the body iron burden as determined by serum ferritin and LIC. Over the 12 months, the reduction in mean serum ferritin concentration in the DFO monotherapy arm was not significantly greater than in the DFP + DFO alternating regime arm (-349 ± 573 µg/L vs -248 ± 791 µg/L; p=0.5802). Reduction in LIC was also not significantly different between the DFO arm and the DFP + DFO arm (-239 ± 474 µg/L vs -65± 615 µg/L; p=0.2263).

Potential confounding by splenectomy, study site and baseline serum ferritin concentration was explored. There was no significant effect on the similarity of efficacy between the treatment arms.

Evaluator Comments

The design of this study precludes assessing efficacy of DFP by itself in the treatment of iron overload in transfusion dependent thalassaemia patients.

Study LA 04: The compassionate use of deferiprone in patients with iron overload and for whom deferoxamine is contraindicated or inadequate

The international compassionate use program was commenced by the overseas sponsor, ApoPharma in 1996. This is an ongoing program involving physicians from the US, Canada and previously Italy. This interim clinical report includes analyses of patient data from 23 May 1996 to 28 February 2006. The primary objective of this program was to provide treatment of chronic iron overload in patients with transfusion dependent anaemia for whom deferoxamine was contraindicated or inadequate. The secondary objective was to assess the long term safety and efficacy of Ferriprox (DFP) alone or in combination with deferoxamine (DFO) for the treatment of chronic iron overload in these patients. The patients were volunteered by their treating physicians after approval was given by the respective regulatory authority in the US, Canada and Italy. Admission to the program by ApoPharma was based on the provision by the treating physician of a satisfactory management plan of neutropenia and agranulocytosis and a completed baseline and screening case report form. Patients with a confirmed diagnosis of transfusion dependent anaemia with chronic iron overloading requiring chelation therapy were included. Patients with severe neutropenia/agranulocytosis or thrombocytopenia, abnormal liver function, evidence of renal failure, or patients who have received other investigational product within 30 days of DFP treatment were excluded. The primary efficacy endpoint was the change in serum ferritin concentration and/or other iron overload assessments from baseline to last observation. The safety endpoints were adverse events (AEs), serious adverse events (SAEs), haematology assessments and alanine aminotransferase (ALT) assessments.

Of the 92 patients enrolled, 86 patients between the ages 8 and 77 years were treated. Of the 86 patients, 58 had thalassaemia major, and 28 had other transfusion dependent iron overload conditions (10: myelodysplastic syndrome, 4: myelofibrosis, 3: sickle cell disease, 11: other iron overload conditions). The mean duration of treatment was 1.3 (range 0-9.8) years for all patients and 1.2 years for the 58 patients with thalassaemia major (range 0-8.4 years).

The mean reduction in serum ferritin from baseline to last observation was -402 μg/L (p=0.16) for all the patients and -584 μg/L (p=0.16) for patients with thalassaemia major. The serum ferritin levels changed by -0.32 μg/L (p=0.10) for other chronic transfusion-dependent conditions.

Evaluator Comments

In this observational study, efficacy of DFP as an iron chelator in patients with non-cardiac iron overload was demonstrated in patients with thalassaemia major. The mean reduction in serum ferritin level in patients with other chronic transfusion-dependent conditions, however, was very small, suggesting that DFP is not effective as an iron chelator in patients with iron overload from other transfusion dependent conditions.

Study LA - 11: Efficacy and safety of deferiprone in β Thalassaemia/Haemoglobin E diseases patients in Thailand.

This was an open label, uncontrolled study conducted in 24 non-transfusion dependent, Thai patients with thalassaemia major. The patients were treated with DFP at a mean daily dose of 48 (range 15–78) mg/kg. Efficacy was determined by assessing serum ferritin concentration in patients treated for more than 3 months. LIC was assessed in patients who were treated for more than 12 months.

Mean exposure to DFP was 334 ± 179 days. The mean serum ferritin value decreased by 62% from the baseline value in twenty patients e treated with DFP for > 3 months and 16 for > 12 months. . LIC was determined in 16 patients. The mean decrease from the baseline value was 63%.

Evaluator Comments

The 24 Thai patients who had non-transfusion dependent thalassaemia major, were treated with a smaller mean daily dose of DFP (48 mg/kg). The efficacy data was of limited value because this was a single arm study in non-transfusion dependent thalassaemia patients treated with a smaller dose of DFP than that proposed in this application.

Study LA - 15: Safety and efficacy of Ferriprox for the treatment of iron overload in subjects with transfusion dependent thalassaemia in Iran

The primary objective of this study was to monitor the efficacy and safety of Ferriprox for the treatment of iron overload in subjects, with transfusion dependent thalassaemia, who were 10 years or older and with serum ferritin levels > 2500 µg/L. Of 36 patients screened, 29 were enrolled in the study. All the patients had been treated with DFO prior to enrolment. Following enrolment, Ferriprox 75 mg/kg/day in three divided doses was administered orally. Treatment was continued for 3 months.

The baseline mean serum ferritin levels declined from 3364 ± 900 µg/L to 1271 ± 302 µg/L during the 3 months. The mean difference was significant (p=0.0001).

Evaluator Comments

This single arm study examined the efficacy and safety of DFP in transfusion dependent thalassaemia patients over a period of only 3 months. The efficacy data from this study were therefore of limited vale.

Study LA – 30-0307: A 24 week, open label, uncontrolled study of the safety and efficacy of Ferriprox (deferiprone) oral solution in iron overloaded paediatric subjects with transfusion dependent anaemia.

The primary objective of this study was to assess the safety of Ferriprox oral solution for the treatment of iron overload in paediatric subjects with transfusion dependent anaemia. The efficacy of Ferriprox in reducing iron overload in these subjects was the secondary objective. One hundred children (91: thalassaemia major, 8: haemoglobin E-β thalassaemia, 1: sickle cell disease) who were ≤ 10 years of age, with a confirmed diagnosis of transfusion dependent anaemia and had chronic iron overload requiring chelation were included in the study. At baseline, 51 children were being treated with DFO (mean duration 1.82 ± 1.95 years), 20 with DFP (mean duration 0.5 ± 0.6 years), 8 with deferasirox (mean duration 0.4 ± 0.5 years), and 21 were naïve to chelation therapy.

The dose of Ferriprox was initiated at 50 mg/kg body weight per day and increased to 75 mg/kg body weight per day, if required and tolerated. In subjects with serum ferritin concentrations > 2500 µg/L at baseline, the dose was increased to 100 mg/kg body weight after 4 weeks of Ferriprox therapy. All the subjects had at least one dose of study

treatment and 99 had at least one post-baseline observation and were therefore eligible for efficacy analyses.

The reduction in serum ferritin from baseline to Week 24 was significant (2532 ± 1463 µg/L to 2176 ± 1144 µg/L; p<0.0005). There was a greater decline in serum ferritin values in patients with baseline serum ferritin values > 2500 µg/L than in those with values < 2500 µg/L, at Week 24. There was no significant difference in the reduction of serum ferritin values by age (< 6 years vs >6 years).

Evaluator Comments

This was a study of the safety and efficacy of DFP in children over a 24 week period. The results showed that DFP caused a greater decline in serum ferritin when the baseline serum ferritin levels were > 2500 µg/L. The efficacy of DFP as an iron chelator in those patients with other transfusion-dependent conditions was not described in this study. The efficacy results were only of limited value because it was a single arm study.

Efficacy conclusion

In study LA 16, a statistically significant difference in cardiac iron chelation (as measured by MRI T2*) was shown between subjects treated with DFP, and those treated with DFO. The geometric mean increase in MRI T2* values at 6 months from baseline was 18% in the DFP arm versus 9% in the DFO arm (p=0.0404) and at 12 months from baseline, 27% in the DFP arm versus 13% in the DFO arm (p=0.0228).

LVEF as assessed by CMR showed greater improvement in the DFP arm than in the DFO arm. Interestingly, after 12 months treatment with either DFP or DFO, there was no subject with CMR LVEF levels less than 56% in either arm of the study, which indicated that the LVEF was normal for all the subjects in both treatment groups after 12 months treatment. On echocardiography, LVEF and LVSF showed significant improvement in the DFP arm compared with decline in the DFO arm.

The efficacy of DFP in relation to reducing non-cardiac iron load was compared to that of DFO. There was no significant difference between the two groups in the reduction of LIC from baseline to 12 months. The decrease in serum ferritin in the DFP arm was less than that in the DFO arm. The differences between the two arms in reduction of serum ferritin from baseline to 3, 6 and 9 months were significant. The difference from baseline to 12 months was not significant, suggesting that DFP and DFO reduce serum ferritin concentration similarly after 12 months of treatment.

Assessment of QOL showed that there was no difference between the treatment arms except for the role emotional domain. In the absence of concurrent statistical difference between treatment groups in the emotional well being or the social functioning domains, interpretation of the result was difficult.

 In study LA 12, the primary objective was to compare the incidence of cardiac disease and survival in patients treated with Ferriprox for at least four years with patients treated with deferoxamine over the same period. The study showed that DFP has a greater cardioprotective effect than DFO, in that the incidence of cardiac disease was lower in the DFP arm of the study. Echocardiographic analyses of cardiac function, however, failed to demonstrate a significant difference between the two arms of the study. Compliance was significantly better in the DFP arm (89% vs 85%), but whether this difference had any influence on the results is uncertain. DFO showed greater efficacy in reducing non-cardiac iron load, though the difference between the two groups was not statistically significant at the end of the study.

The results therefore show that DFP has a somewhat greater cardioprotective effect than DFO but is not as effective in reducing non-cardiac iron load.

Borgna-Pignatti et al showed that following treatment, the serum ferritin levels were consistently lower in the DFO arm throughout the study.[19] During the course of the study, there were 52 cardiac events including 15 cardiac deaths. All of these occurred in the DFO group. There were no cardiac events reported in the DFP group.

In Study LA 04, efficacy of DFP as an iron chelator in patients with non-cardiac iron overload was demonstrated in patients with thalassaemia major. The change in serum ferritin values from baseline in patients with other transfusion-dependent iron overload conditions was small.

The efficacy data provided in the other single arm studies were only of limited value.

Safety

Study LA 16-0102

The frequency and severity of adverse events (AEs), adverse drug reactions (ADRs), as well as serious adverse events (SAEs) and serious adverse drug reactions (SADRs) were recorded. An adverse event was defined as any untoward medical occurrence in a subject administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. An ADR and a SADR were reported when causality of an AE or SAE was attributable to the drug. The management of neutropenia, a known ADR of DFP was specified.

All the safety analyses were performed on the OC (observed cases) population, defined as all randomized subjects (n=61). The total exposure (last date of study medication - first date of study medication - total interruption days + 1[subject year]) was calculated for both treatment groups. The total exposure in the DFP arm was 27 years and in the DFO arm, it was 30 years. The mean dose of DFP was 92 mg/kg/d. The mean dose of DFO was 43 mg/kg for 5.7 days per week which is equivalent to a dose of 49 mg/kg/d for 5 days per week.

Adverse Events

The incidence of each ADR was compared between groups using the Fisher's exact test (Table 7).

Table 7: Summary of most frequently reported (higher than 10%) Adverse Drug Reactions

	Ferriprox Group		Desferal Group		
	Total Reports: 279		Total Reports: 131		
	Total Subjects Reporting: 29		Total Subjects Reporting: 32		
	Total Subjects: 29		Total Subjects: 32		
	Total Exposure (subject-years): 27.34		Total Exposure (subject-years): 30.2		
Body System	#	%	#	%	p value*
Preferred Term	Subjects		Subjects		
Gastrointestinal Disorders	19	65.52	6	18.75	0.0003
General Disorders And Administration Site	3	10.34	11	34.38	0.0343
Investigations	19	65.52	13	40.63	0.0732
Metabolism And Nutrition Disorders	9	31.03	0	0.00	0.0006
Musculoskeletal And Connective Tissue Disorders	12	41.38	7	21.88	0.1656
Nervous System Disorders	8	27.59	6	18.75	0.5447
Skin And Subcutaneous Tissue Disorders	3	10.34	6	18.75	0.4779

* Based on Fisher's exact test in comparing the incidences of each ADR between the two treatment groups

There was a significantly higher incidence of the System Organ Class (SOC) *Gastrointestinal Disorders* (specifically, nausea, vomiting and eructation) and *Metabolism and Nutrition Disorders* (increased appetite) in the DFP arm while *General Disorders (and Administration Site Problems)* were of significance in the DFO arm. The incidences of raised levels of liver enzymes; namely: aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltransferase (γGT), were greater in the DFP arm. The majority of these ADRs were mild to moderate in severity, except for a case of headache in the DFP group that was considered to be severe. Treatment was temporarily discontinued and the headache resolved. There was one case of mild neutropenia (confirmed absolute neutrophil count [ANC] ≥ 1.0 x 109/L and <1.5 x 109/L) in the DFP arm which resolved without discontinuation of DFP. There were no cases of agranulocytosis in either arm.

Serious Adverse Events

There were 2 SAEs reported in the DFP arm. Cytomegalovirus (CMV) hepatitis was considered possibly related to DFP treatment and the subject was withdrawn. Corneal abscess was considered to be unrelated. There were no SAEs in the DFO arm.

Laboratory evaluations

Liver enzymes

Fluctuating ALT levels were reported in the DFP arm, especially in anti-hepatitis C positive subjects. The mean levels of ALT at the 3, 6, 9 and 12 month assays after baseline, were increased in the DFP arm compared with the DFO arm. In the DFO arm, the mean levels dropped at the 3, 6 and 9 month assays before rising slightly at the 12 month assay. There was no significant difference between the two treatment arms in the percentage of subjects with ALT concentrations greater that 2 or 3 times the upper limit of the normal (ULN) reference range. There was no statistically significant difference between the DFP arm and the DFO arm (when hepatitis C status was factored in) on ALT > 2 and ALT > 3 times ULN.

Haematology

Weekly monitoring of haemoglobin, total white blood cells (WBC), neutrophils, normoblasts and platelets were performed. Comparison of the mean values of these

laboratory data between the two treatment groups was done at each visit using the two sample t test. The difference between the two groups was not statistically significant for mean haemoglobin levels, and neutrophil means. The WBC means were significantly different between DFP (7.7×10^9/L) and DFO (9.8×10^9/L) treatment groups (p=0.0330) but were not significantly different after 12 months (7.4×10^9/L and 8.9×10^9/L, p=0.0655) for DFP and DFO respectively.

Both treatment arms recorded a decrease in the mean ANC from baseline to 12 months, but the difference in change between the treatment groups, over this time, was not statistically significant.

Zinc

Since zinc deficiency was reported in studies with DFP, zinc assays were performed at baseline, 6 and 12 months. The difference in change from baseline between the two treatment groups at 12 months was not statistically significant.

Creatinine

There was a slight increase in mean creatinine levels in the DFP arm at 12 months compared to the DFO arm. However, the difference in change from baseline between the two treatment groups at 12 months was not statistically significant.

Vital signs

Vital signs were evaluated at baseline, 6 and 12 months. They included temperature, pulse, systolic and diastolic blood pressure, height and weight. The two sample t test was used to compare the mean changes between the treatment groups. There were no significant differences between the two groups except for weight. At baseline, the weight means were not significantly different between the two groups, but there was a significant difference in weight change at 6 months and at 12 months. The gain was more in females than in males.

Study LA 12-9907

No safety data was provided because the study was not designed to evaluate the safety of Ferriprox in comparison with deferoxamine.

Supportive studies

Borgna-Pignatti et al[19]

Of the 157 patients who were switched to DFP, 46 patients (29%) discontinued DFP as a consequence of adverse events. The reasons for discontinuing DFP included increase in serum ferritin or LIC (21), arthropathy or arthralgia (10), neutropenia (8), agranulocytosis (1), raised levels of ALT (2), gastric discomfort (2), worsening renal failure (1), and hepatic insufficiency in a hepatitis C patient (1). Sixteen patients discontinued DFP for reasons other than adverse events. In all 26 patients died during the study period. Of these 24 were in the DFO arm and 2 were in the DFP arm. Both deaths in the DFP arm were non-cardiac related as previously described.

LA 08

In all 30 patients were randomized to each group. The total exposure was 27.98 patient years for the DFP+DFO group and 29.53 patient years for the DFO monotherapy group. The incidence of adverse events was not significantly different between the DFP+DFO group and the DFO group (p=0.1455). Vomiting, diarrhoea, abdominal pain and nausea were more common in the DFP+DFO arm and headache, back pain and dysmenorrhoea were more common in the DFO arm. There were no cases of agranulocytosis. There was one case of mild neutropenia in the DFO arm. There were no significant changes in laboratory values. There were no deaths in either arm of the study. The safety data in this

study was not a true representation of DFP safety, because it was used in combination with DFO.

Study LA 04

For the 86 patients treated with DFP, the total exposure to DFP was 108.6 patient years. DFP was administered at 25-33 mg/kg body weight three times per day (mean dose 83 mg/kg body weight/day).

There were 5 deaths (cardiac failure, cardiomyopathy, acute pneumonitis, hepatic and renal failure). None of these were considered by the treating physician to be related to DFP treatment. There were two other deaths more than one month after discontinuation of DFP. These too were considered to be unrelated to treatment with DFP. Of the 41 SAEs, the most commonly reported were neutropenia in 8 patients (9.3%), agranulocytosis in 4 patients (4.65%), cardiac failure (2.3%), pyrexia (2.3%) and pneumonia (2.3%). Four cases of agranulocytosis, 5 cases of neutropenia and one case of torsades de pointes were considered to be related to treatment with DFP. All the cases of agranulocytosis were reported as serious. DFP was discontinued in only one case of agranulocytosis. The most common adverse events were nausea (18.6%), pyrexia (16.3%), headache (12.8%) and abdominal pain (10.5%).

Study LA - 11

In this open label, uncontrolled study conducted in 24 Thai patients with thalassaemia major, the total exposure to DFP was 21.99 patient years (mean 344±179 days; range 5 to 536 days). The mean dose of DFP during the study was 48.1 ± 5.74 (range 15.2 to 78.4) mg/kg/day. Nausea and vomiting were the most common adverse events. There was one case of neutropenia and no cases of agranulocytosis. A 27 year old splenectomised male patient developed septicaemia and severe diarrhoea after food poisoning and died. The investigator considered the death to be "doubtfully" related to treatment with DFP.

Study LA - 15

Of the 32 patients enrolled in this study, 29 were treated with DFP 50 mg/kg/day, on average 5 days per week. The total number of patient years of exposure was 7.02 years. Exposure ranged from 26 to 108 days, with a mean of 88 days. The most common adverse events were nausea, vomiting or abdominal pain. One patient experienced mild neutropenia two months after enrolment. In all 3 patients discontinued therapy during the study. One, because of arthropathy, which resolved two months later, another because of neutropenia, which resolved 4 days later and a the third patient discontinued for personal reasons. There were no deaths.

Study LA – 30-0307

The overall exposure to DFP for the 100 children was 44.79 subject years (mean 0.45 ± 0.07; minimum, maximum: 0.02, 0.47). Over the 24 weeks, the most common adverse drug reactions were neutropenia, increased ALT and vomiting. Of the 6 subjects who experienced neutropenia, the neutropenia resolved despite continuation of Ferriprox in 5. The sixth case progressed to agranulocytosis. There was also another case of agranulocytosis reported. Both cases of agranulocytosis resolved with discontinuation of Ferriprox and G-CSF support.

Of the 98 subjects with normal creatinine values at baseline, 58 experienced an increase in creatinine values by Week 12 and 34 exhibited an increase in creatinine values between Weeks 12 and 24. The two subjects with abnormal creatinine values at baseline had a return to normal creatinine values during the study. There was a significant increase in

serum ALT levels from baseline (45 ± 30 IU/L) to Week 12 (59 ± 52 IU/L; p=0.01) but not to Week 24 (56 ± 54 IU/L; p=0.05).

Of the 5 subjects who withdrew, two subjects withdrew because of adverse reactions (agranulocytosis). There were no deaths.

Safety conclusions

The adverse events that were reported in the DFP arm of the pivotal study (LA 16) were mainly mild to moderate in severity except for severe headache in one patient. There was one case of mild neutropenia which resolved spontaneously without DFP treatment being discontinued. Agranulocytosis was not reported in either arm of the study.

Of the two serious adverse events reported, CMV hepatitis was considered to be possibly related to treatment with DFP. The other SAE was not. There were no deaths. There was no statistically significant difference in ALT levels between the two arms of the study even when ALT levels were raised to 2 or 3 times ULN. There were no significant differences between the treatment groups from baseline to 12 months in the changes in zinc and creatinine levels. There was significant increase in the mean weight of subjects in the DFP arm compared with those in the DFO arm. This was more so in female subjects.

Safety was not evaluated in the second pivotal study (LA 12) which was not designed to compare safety of DFP versus DFO.

In the epidemiological study of Borgna-Pignatti et al, 46 patients discontinued DFP because of adverse events. Of these 8 did so because of neutropenia and one because of agranulocytosis.

The incidence of agranulocytosis in the compassionate use program (LA 04) was 4.65%. The incidence of neutropenia was 5.8%.

In the study conducted among non-transfusion dependent Thai patients, a smaller dose of DFP (48 mg/kg body weight/day) was used. There were no cases of agranulocytosis.

In the Iranian study (study LA 15), where a smaller dose of DFP was also used, there was one case of mild neutropenia and the patient was withdrawn from the study. The episode was considered resolved after 4 days. There were no cases of agranulocytosis reported.

In the paediatric study (LA 30), there were 6 (6%) reports of neutropenia and 2 (2%) reports of agranulocytosis. In 5 cases, the neutropenia resolved despite continuation of Ferriprox. The sixth case progressed to agranulocytosis. There was also another case of agranulocytosis reported. Both cases of agranulocytosis resolved with discontinuation of Ferriprox and G-CSF support.

The other reported adverse events in all the supportive studies were in keeping with the known adverse event profile of DFP.

Clinical Summary and Conclusions

This application was for the use of Ferriprox as first line treatment in the treatment of iron overload in patients with transfusional iron overload due to chronic blood transfusions (transfusional haemosiderosis). The sponsor requested a broadening of indications for treatment of transfusional iron overload to include any disease which results in transfusional iron overload. The sponsor also sought approval to increase the dose to 100 mg/kg body weight after initiating treatment at 75 mg/kg body weight, if the response was insufficient.

Most of the data, including the pivotal studies, related to patients with transfusion dependent iron overload in thalassaemia patients. Only two of the supportive studies (LA 04, LA 30) had any data that referred to patients with other chronic transfusion dependent

conditions. These two studies provided no justification to support broadening of the treatment group to include patients with other transfusion dependent conditions. Again, only two studies had a DFP dose escalation to 100 mg/kg/day from the recommended daily dose of 75 mg/kg. Clear justification for the use of the 100 mg/kg/day dose in the form of dose response data was not provided. The effects of DFP on cardiac function were examined only in the two pivotal studies. In these studies, the cardioprotective effects of DFP were shown to be superior to DFO. DFP was also shown to be superior to DFO in relation to cardiac function as measured by LVEF (by echocardiography) in Study LA 16, but not in the other pivotal study (LA 12). It was also interesting that in study LA 16, normal LVEF (CMR LVEF >56%) was achieved in both DFP and DFO treatment groups by the end of the study.

All the studies showed that DFP was not as effective as DFO in reducing the non-cardiac iron overload.

The considerable risk of agranulocytosis (2% to 4.5%) that is associated with deferiprone treatment is of significance. In the pivotal study LA 16 and the supportive study LA 08, there were no reports of agranulocytosis. It is possible that this was because the exposure to DFP in these two studies was for one year only. In all the studies where the standard dose of DFP (75 mg/kg/day) was used, agranulocytosis and neutropenia were reported.

On balance therefore, it would appear that the cardioprotective benefit of DFP therapy is better than DFO therapy. Cardiac function in the two studies was similar, at least at the end in Study LA 16. However, any cardioprotective benefit that DFP therapy has over DFO therapy is outweighed by the considerable safety risk of agranulocytosis and neutropenia that is associated with DFP treatment of patients with transfusional iron overload due to chronic blood transfusions.

This evaluator did not recommend approval of the application to change the patient group for whom Ferriprox is indicated by removing the restrictions in the currently approved indication.

V. Pharmacovigilance Findings

Risk Management Plan

Safety Specification

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR). The RMP was dated May 2010. The sponsor identified the safety concerns indicated in Table 8.

Table 8: Safety concerns

	Safety Concerns / Risks
Important Identified	Neutropenia, agranulocytosis
	Use in pregnancy: teratogenicity, clastogenicity
	Arthralgia
	Pancreatitis
Important Potential	Hepatitis
	Effects on breast, thyroid and adrenal

The OPR evaluator noted that there was no information on safety in patients of use in the proposed sickle cell disease, myelodysplastic syndromes and thalassaemia intermedia. This is of particular importance in myelodysplastic syndromes as these patients may have neutropenia.

Pharmacovigilance Plan

The sponsor indicated that routine pharmacovigilance (PhV) will be undertaken for the identified risks.[20] However, it was stated that ApoPharma has appointed an expert panel to consider further ways of minimising risk of neutropenia and agranulocytosis. There was no information on the time frame for recommendations for further action regarding PhV and risk minimisation for these AEs from the panel or consideration of the possible implications for the RMP.

Proposed PhV for hepatitis consisted of review of cumulative postmarketing reports and for effects on breast, thyroid or adrenal tissue consisted of enhanced follow up of any relevant reported cases.

Risk Minimisation Activities

The sponsor concluded that the two conditions where risk minimisation is considered most relevant are the avoidance of use in pregnant women and the prevention or early detection of severe neutropenia and agranulocytosis. It was indicated that these are covered in the product information (PI) and consumer medicine information (CMI).

OPR Review

The OPR evaluator indicated that the RMP was not acceptable. Key concerns were:

· Lack of clarity in the information provided on the human data base;
· A number of sections required for a RMP have not been addressed; and
· Implications for usage, safety PhV and risk minimisation for the proposed extension of indications and increased dosage are not considered.

It was recommended to the Delegate that, if this application is approved, the sponsor should provide an updated RMP that:

· Provides information on the human data base as per the RMP template;
· Ensures that referencing in the body of the document corresponds with the reference list;
· Indicates the predicted usage in Australia with the proposed extension of indications and the basis on which this has been derived;
· Distinguishes between AE data from clinical trials and post marketing reports and for clinical trials indicate the numbers of, and information on, serious AEs, subjects who withdrew and fatalities;
· Provides further analysis on the patient population who experienced neutropenia and agranulocytosis AEs;
· Presents information on the reports of pancreatitis and hepatitis;

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[20] Routine pharmacovigilance practices involve the following activities:
  · All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
  · Reporting to regulatory authorities;
  · Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
  · Submission of PSURs;
  · Meeting other local regulatory agency requirements.

· Considers the implications of the proposed increased dosage on safety;
· Addresses the following sections:
   o Identified and potential interactions.
   o Pharmacological class effects.
   o Additional requirements.
· Includes safety of DFP use in patients with sickle cell disease, myelodysplastic syndromes, thalassaemia intermedia and other iron overload conditions as missing information;
· Indicates the time frame for recommendations for further action regarding PhV and risk minimisation for the neutropenia and agranulocytosis AEs from the expert panel and considers the possible implications for the RMP; and
· Provides the template for recording events of hepatitis;
· Considers the need for risk minimisation activities to mitigate the potential for medication errors; and
· Presents a revised RMP summary that includes changes to PhV and risk minimisation activities subsequent to consideration of the above.

The sponsor provided a revised RMP which addressed the recommendations of the RMP evaluation report.

However, the OPR evaluator noted that there were issues remaining. The key issue was the lack of information on safety in the non thalassaemia population. This was highlighted in the RMP as "Safety data in transfusional iron overload patients other than thalassaemia major" and was considered to be missing information.

In addition, the OPR evaluator noted the following points:

· There was a paucity of safety information with the proposed increased dosage.
· There was no consideration of the defining the population in whom the AEs of neutropenia and agranulocytosis are more likely to occur.
· The expert panel considering neutropenia and agranulocytosis has yet to present its recommendations; and
· Although it was indicated that enhanced follow up with an agreed template will occur with some safety concerns, no templates were provided and no information was provided on how they will be implemented.

It was recommended to the Delegate that if this application is approved, the sponsor should:

· Undertake additional PhV for the missing information "Safety data in transfusional iron overload patients other than thalassaemia major" through implementing a cohort study and /or compulsory patient registry to document use and safety in this population;
· Provide the TGA with the protocol(s) to be used for the additional PhV activities;
· Specify and provide information on the methodology for monitoring safety with use of the proposed increased dosage;
· Specify when expert panel recommendations on neutropenia and agranulocytosis and any consequent changes to PhV and risk minimisation will be forwarded to the TGA; and
· Provide the templates for enhanced PhV and indicate how these will be implemented.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

The new nonclinical data were limited. Maximum deferiprone exposures were low in toxicity studies of 52 weeks duration in rats and monkeys. Exposure equivalent to the proposed clinical dose of 100 mg/kg/day was not adequately tested. In rats, the target organs for toxicity were the bone marrow, thyroid, adrenal and mammary glands.

The genotoxicity of deferiprone was confirmed in a mouse micronucleus assay. There were no carcinogenicity studies.

The evaluator had reservations about approval of the new indication or higher dose because of considerable gaps in the safety data.

Clinical

Efficacy

In a randomised, open label, parallel group trial (LA-16) in patients with thalassaemia major who had received chelation therapy with DFO for at least 5 years, 29 patients were switched to Ferriprox and 31 remained on DFO. Subjects were aged 18 to 35 years. The study was conducted in Italy and Greece. The mean dose of Ferriprox was 92 mg/kg/day and DFO 43 mg/kg/day (mean 5.7 days per week in the case of DFO). After 12 months, there were no significant differences between Ferriprox and DFO in reduction in serum ferritin or liver iron concentration.

However, Ferriprox was significantly better at reducing cardiac iron measured by magnetic resonance imaging (MRI) T2*. At 12 months, geometric mean MRI T2* increased 27% in the Ferriprox group and 13% in the DFO group (p=0.02). Left ventricular ejection fraction (LVEF) also increased by a significantly greater amount with Ferriprox than DFO at 12 months – 3.1% versus 0.3% for LVEF measured by MRI. The clinical significance of this difference was uncertain since LVEF was normal (> 56%) in all subjects throughout the study. There were no deaths.

A retrospective study (LA-12) of patients with transfusion dependent thalassaemia being treated with either Ferriprox (n=54) or DFO (n=75) for at least 4 years supported the greater efficacy of Ferriprox in improving cardiac function. Patients were aged 5 years and older. The dose of Ferriprox was 25 mg/kg three times a day and the dose of DFO 20-60 mg/kg/day SC on 4-7 days per week. The incidence of cardiac disease remained unchanged in patients on Ferriprox (13%); however, it increased in patients on DFO (from 13% to 29%). The difference between groups was statistically significant (p=0.028). There were 4 deaths (3 due to cardiac disease) in DFO patients and none in Ferriprox patients. The age of Ferriprox patients was significantly lower by a mean of 2.3 years than DFO patients which may have favoured the Ferriprox group; however, an age matched subgroup analysis supported the results of the main analysis.

A larger Italian retrospective study by Borgna-Pignatti (n=516 from 7 centres) also supported the cardiac efficacy of Ferriprox.[19] Of the patients entered, 359 received DFO and 157 Ferriprox. The DFO dose was 30-50 mg/kg/d and the Ferriprox dose 75 mg/kg/d. There were 26 deaths over the 9 years of the study; 15 cardiac and 11 non-cardiac. All the

cardiac deaths and 9 non-cardiac deaths occurred with DFO. Two non-cardiac deaths occurred with Ferriprox. Six patients with cardiac events on DFO had previously received Ferriprox. There was a significant difference in exposure between the two treatments – 3,610 subject years on DFO versus only 750 subject years on Ferriprox.

Five other observational studies did not provide any new information.

Safety

The randomised trial LA-16 enrolled 61 subjects, of whom 29 received Ferriprox and 32 DFO over 12 months. Ferriprox exposure was 27 subject years and DFO exposure 30 subject years. The following adverse events occurred at a significantly greater incidence with Ferriprox than DFO: nausea (38% vs 0%), vomiting (28% vs 6%), upper abdominal pain (24% vs 3%), eructation (14% vs 0%), weight increase (41% vs 9%), appetite increase (31% vs 0%), ALT increased (38% vs 13%), AST increased (21% vs 3%), γGT increased (14% vs 0%) and electrocardiogram T wave inversion (17% vs 0%). There were two serious adverse events in the Ferriprox group (7%) compared with none in the DFO group. One, cytomegalovirus hepatitis, was considered possibly related to Ferriprox. There was one case of mild neutropenia which resolved without discontinuing Ferriprox and no cases of agranulocytosis.

There was a pooled analysis of 590 subjects who received Ferriprox and 118 who received DFO in clinical trials both from this submission (6 trials) and the previous submission (5 trials). This analysis included trial LA-16 but not the retrospective studies LA-12 and Borgna-Pignatti which had minimal or no safety data. The median age of subjects was 18 (range 1-77) years. Most (63%) were aged ≥ 16 years; 10% were aged 1-5 years and 27% 6-15 years. Most (87%) were treated for transfusion-dependent thalassaemia. The Ferriprox dose was 75 mg/kg/day in the majority (70%). Only 85 subjects (14%) received a dose of 100 mg/kg/day. Other subjects received less than 75 mg/kg/day. Ferriprox exposure was 1,189 subject years and DFO exposure 129 subject-years.

Common adverse reactions due to Ferriprox are shown in Table 9 (15.9%). There were 11 cases (1.9%) of agranulocytosis but only 9 (1.5%) were assessed by investigators as reactions. Of the 11 cases, 9 occurred with the 75 mg/kg/day dose and 2 with 100 mg/kg/day, so the incidence of agranulocytosis with the 75 mg/kg/day dose was 9/411 (2.2%) and with 100 mg/kg/day 2/85 (2.4%). Eight of the 11 subjects with agranulocytosis were patients with transfusion-dependent thalassaemia, two had myelodysplastic syndrome and one sickle cell disease, so the incidence of agranulocytosis with Ferriprox in transfusion dependent thalassaemia was 8/513 (1.6%) and in the other conditions 3/77 (3.9%).

Less common but serious reactions were thrombocytopenia (0.3%), torsades de pointes (0.2%), hepatitis (0.2%) and cytomegalovirus hepatitis (0.2%).

The Ferriprox withdrawal rate was high at 224 (38%) of whom 92 (16%) were withdrawn due to adverse effects and 33 (6%) at patient request in the pooled analysis. The DFO withdrawal rate was 9 (8%), 2 (2%) due to adverse effects and 2 (2%) at patient request. The Borgna-Pignatti study also had a high rate of discontinuation of Ferriprox due to adverse effects - 46/157 (29%).

Postmarketing experience with Ferriprox from 1999-2009 was estimated at 26,000 subject years. Several serious adverse drug reactions have been reported. There were 17 deaths, 13 due to agranulocytosis, 3 due to cardiac failure and one due to sepsis.

In response to the clinical evaluation, the sponsor submitted a Periodic Safety Update Report (PSUR) for the period 1 September 2009 to 31 August 2010. Estimated exposure during the report period was 5,000 subject years. There were 43 case reports, 29 serious.

Ten reports were of agranulocytosis. The reports of agranulocytosis were consistent with previous experience. Unlisted reactions included elevated AST, creatine kinase and suspected myositis, decreased red blood cell count, pyramidal tract syndrome and Grade 3 skin reaction.

Table 9: Pooled analysis Common reactions

Body System Preferred term	Deferiprone N = 590 (%)
Blood and lymphatic system disorders	
Neutropenia	34 (5.8%)
Agranulocytosis	9 (1.5)
Gastrointestinal disorders	
Nausea	79 (13.4)
Vomiting	63 (10.7)
Abdominal pain upper	39 (6.6)
Abdominal pain	22 (3.7)
Diarrhoea	17 (2.9)
Dyspepsia	12 (2.0)
Abdominal discomfort	7 (1.2)
General disorders and administrative site conditions	
Oedema peripheral	6 (1.0)
Investigations	
ALT increased	47 (8.0)
Neutrophil count decreased	43 (7.3)
Weight increased	12 (2.0)
AST increased	8 (1.4)
WBC count decreased	6 (1.0)
Metabolism and nutrition disorders	
Increased appetite	26 (4.4)
Anorexia	6 (1.0)
Musculoskeletal and connective tissue disorders	
Arthralgia	59 (10.0)
Back pain	13 (2.2)
Pain in extremity	12 (2.0)
Arthropathy	9 (1.5)
Joint swelling	6 (1.0)
Nervous system disorders	
Headache	15 (2.5)
Renal and urinary disorders	
Chromaturia	94 (15.9)

The evaluator did not recommend approval of either the new indication or increased dose.

Risk Management Plan

The RMP was unsatisfactory. The evaluator recommended that the RMP address the issues raised. Registration will be conditional on implementation of the final RMP agreed with the TGA Office of Product Review.

Risk-Benefit Analysis

Delegate Considerations

Ferriprox was comparable with DFO in reducing total body iron and liver iron over 12 months in a small randomised trial but appeared better at reducing cardiac iron measured by MRI T2* (trial LA-16). There was a correlation between MRI T2* and LVEF. However, the clinical significance of the differences in MRI T2* and LVEF between treatments was uncertain. Longer follow-up is needed to determine the relationships between MRI T2* and cardiac disease and mortality.

There was support from longer retrospective Italian studies, LA-12 and Borgna-Pignatti, of improved cardiac outcomes and lower mortality with Ferriprox compared with DFO. The LA-12 study was 4 years and the Borgna-Pignatti study 9 years. The dose of Ferriprox was 75 mg/kg/day in LA-12 and not stated in the Borgna-Pignatti study. There were several possible biases. For example, the treatment groups could not be guaranteed to be equivalent in the subjects' degree of iron overload or dose of chelator. Carryover effects when treatment was changed from DFO to Ferriprox and vice versa were not taken into account. Exposure to the two treatments was significantly different – in the Borgna-Pignatti study, DFO exposure was five times Ferriprox exposure. Lastly, physicians may have been reluctant to prescribe Ferriprox for their sicker patients since it was a new drug at the time of the studies.

The retrospective data taken with the small randomised trial are not sufficient to conclude that Ferriprox is better at reducing cardiac iron and preventing cardiac disease and mortality than DFO. This claim should not be permitted in the product information for the present.

In the randomised trial LA-16, the average dose of Ferriprox was near the recommended maximum of 100 mg/kg/day whilst the average dose of DFO was only about half the recommended maximum of 80 mg/kg/day. If the dose of DFO had been higher, then the cardiac benefits achieved with the two treatments may have been similar. In the retrospective LA-12 trial, the cardiac benefit was achieved with the currently recommended Ferriprox dose of 75 mg/kg/day. However, the degree of iron overload may have been lower in this trial than LA-16. *The sponsor should clarify this in their Pre-ACPM Response.*

Trial LA-16 enrolled too few subjects to adequately assess the safety of Ferriprox. The retrospective analyses contained minimal safety data. A pooled analysis of safety in 590 subjects from previously submitted and new clinical trials was consistent with a previous pooled analysis in 360 subjects. The high withdrawal rate in subjects treated with Ferriprox most due to adverse effects or patient request was a concern.

The incidence of agranulocytosis was slightly higher with Ferriprox 100 mg/kg/day (2.4%) than 75 mg/kg/day (2.2%); however, there were limited data at 100 mg/kg/day. More data are needed to clarify whether agranulocytosis and other adverse reactions are significantly increased with a dose increase to 100 mg/kg/day.

Also, based on limited data, the incidence of agranulocytosis with Ferriprox was 1.6% in thalassaemia patients and 3.9% in patients with other anaemias (specifically myelodysplastic syndrome and sickle cell disease). More data were needed to clarify whether the risk of agranulocytosis is increased in other anaemias. Weekly monitoring of neutrophil counts is recommended.

The new nonclinical data were limited. Exposure equivalent to the proposed clinical dose of 100 mg/kg/day was not adequately tested. There were no studies in young animals. The genotoxicity of deferiprone was confirmed which raised concerns with respect to

carcinogenicity. There were no carcinogenicity studies.

The extension of Ferriprox to first line and to a wider population than thalassaemia patients is based on equivalence with or superiority to DFO. From previous data and the new trials, the Delegate concluded that Ferriprox has similar efficacy (as an iron chelator) to DFO but possibly lower safety. The previous safety concerns with Ferriprox remain, in particular, the high incidence of agranulocytosis, the high withdrawal rate due to adverse reactions and the lack of data on carcinogenicity, reproductive toxicity and impact on growth (iron chelation typically begins in early childhood and continues for life). There were minimal data for patients with anaemias other than thalassaemia and possibly an increased risk of agranulocytosis in these patients. The Delegate did not recommend extending the population to be treated with Ferriprox until the drug's safety is better characterised.

In regard to the application for an increased maximum dose of 100 mg/kg/day, the Delegate accepted that the higher dose is likely to result in greater efficacy in terms of iron chelation in patients with high iron overload. However, the level of iron overload to justify the 100 mg/kg/day dose has not been defined nor has the safety of the 100 mg/kg/day dose.

The Delegate recommended rejection of the application to extend the indication of Ferriprox from second line to first line and to broaden the patient population beyond those with thalassaemia major on the grounds that the safety of Ferriprox for such use has not been established.

The Delegate also recommended that the application to increase the maximum Ferriprox dose from 75 mg/kg/day to 100 mg/kg/day be rejected on the grounds that the treatment population in terms of degree of iron overload has not been defined and that there was insufficient exposure to establish the safety of the 100 mg/kg dose.

Response from Sponsor

The sponsor addressed the points made by the Delegate.

Nonclinical concerns

Rats were given doses limited by haematological toxicity and death. Monkeys received up to 125 mg/kg twice daily, that is, close to doses (150-250 mg/kg once daily) associated with gross blood changes and death. Therefore, while exposures were similar to those encountered clinically, significantly higher exposures could not be practically achieved. The handling and conservation of iron in animals differs from that in humans, which may be related to the absence of evidence of drug dependent thyroid, adrenal or mammary toxicity in the latter either in clinical trials or during a decade of postmarketing adverse event reporting. Effects on blood cell elements in iron overloaded patients have been limited to idiosyncratic neutropenia or agranulocytosis.

Conversely, in nonclinical species all peripheral blood cell populations are affected at high doses, and generalized bone marrow hypocellularity is evident.

Positive results with deferiprone in *in vitro* and *in vivo* clastogenicity assays are attributable to iron chelation mediated inhibition of ribonucleotide reductase and subsequent nucleotide pool imbalance.[21,22] Deferiprone was unequivocally non-mutagenic

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[21] Hoyes KP, Hider RC, Porter JB. Cell cycle synchronization and growth inhibition by 3-hydroxypyridin-4-one iron chelators in leukemia cell lines. Cancer Res. 1992; 52: 4591-9.

[22] Cooper CE, Lynagh GR, Hoyes KP, Hider RC, Cammack R, Porter JB. The relationship of intracellular iron chelation to the inhibition and regeneration of human ribonucleotide reductase. J Biol Chem. 1996; 271:20291-9.

in a bacterial gene mutation assay and does not belong to a class of chemicals recognized as giving false negative results in this test.

Deferasirox (Exjade) was positive in an *in vivo* rat bone marrow micronucleus test for clastogenicity, an effect that was also attributed to its pharmacological action. Seven of 11 iron chelators were genotoxic in a mouse lymphoma TK+/- assay.[23] DFO was the most potent of the agents tested and was genotoxic with or without metabolic activation.

There is now a quite substantial amount of information from paediatric patients indicating that neither efficacy nor safety in this population differs from efficacy and safety in adults with transfusional iron overload and that data derived from human patients is more telling than data from juvenile animal studies. Juvenile animal studies are at least arguably of some value before a drug is taken into children, but the biochemical and physiological development of lab species differs considerably from that of humans, so looking for subtle effects after the event is of debatable use.

Clinical concerns

Clinical significance

As identified by the Delegate, Ferriprox was superior to DFO in reducing cardiac iron and in improving LVEF. The effect of Ferriprox in the LVEF is of particular importance as patients with thalassaemia major (TM) have higher "normal" values for LVEF (71.0 ± 6.1 %) than age and gender matched healthy volunteers.[24] Therefore LA-16 had included patients with subclinical LV dysfunction.[25] The increase in LVEF suggests that Ferriprox was effective in relieving this dysfunction. Reduced LVEF is linked to adverse survival in TM as well as coronary artery disease and heart failure and improved prognosis occurs with treatments that improve LVEF. Results of independent studies are consistent that Ferriprox improves the LVEF of patients with thalassaemia.[26,27]

A study recently published reported on the ability of MRI T2* to predict cardiac dysfunction in transfusional siderosis.[28] In summary, the study demonstrated that cardiac MRI T2* identifies TM patients at high risk of cardiac disease from myocardial siderosis and that the predicting value of MRI T2* is superior to that of serum ferritin and liver iron concentration. The editorial that accompanied the article concludes that cardiac MRI T2* should become the standard of care for all patients receiving long term transfusions.[29]

The sponsor emphasised that sufficient evidence now exists, both from ApoPharma sponsored studies and from independent investigations, to conclude that Ferriprox is superior to DFO in reducing cardiac iron overload, improving cardiac function, decreasing iron-induced cardiac morbidity and in increasing survival of patients with thalassaemia

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[23] Whittaker P, Seifried HE, San RH, Clarke JJ, Dunkel VC. Genotoxicity of iron chelators in L5178Y mouse lymphoma cells. Environ Mol Mutagen. 2001; 38: 47-56.

[24] Westwood MA, et al. Normalized left ventricular volumes and function in thalassemia major patients with normal myocardial iron. J Magn Reson Imaging 2007; 25: 1147-51.

[25] Pennell DJ, et al. Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis. Blood 2006; 107: 3738-44.

[26] Ladis V., et al. Relation of chelation regimens to cardiac mortality and morbidity in patients with thalassaemia major: an observational study from a large Greek unit. Eur J Haematol 2010

[27] Peng CT, et al. Safety monitoring of cardiac and hepatic systems in ß-thalassemia patients with chelating treatment in Taiwan. Eur J Haematol 2003; 70: 392-7.

[28] Kirk P, Roughton M, Porter JB et al. Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. Circulation 2009; 120: 1961-8.

[29] Wood JC. History and current impact of cardiac magnetic resonance imaging on the management of iron overload. Circulation 2009; 120: 1937-9.

major.[25,27,30,31] Considering the infeasibility of conducting prospective randomized studies on morbidity and survival, the epidemiology data that have been collected over the past 10 years by independent studies in different countries are consistent that deferiprone treated patients have less cardiac disease and survive longer than patients treated with deferoxamine.[19,30,31,32] In fact, the relevance of these studies' results, which are consistent that deferiprone use is associated with lower incidence of iron induced cardiac disease and with increased survival, has been acknowledged by the European Medicine Agency and the European Ferriprox Summary of Product Characteristics (SmPC) has been modified to include the following statement: "Data from the published literature are consistent with the results from the Apotex studies, demonstrating less heart disease and/or increased survival in Ferriprox treated patients than in those treated with deferoxamine." Update of the SmPC to include the information on survival is underway in other jurisdictions.

While reduction of cardiac iron concentrations can be achieved with the use of any of the iron chelators currently available, only deferiprone has demonstrated greater efficacy than desferrioxamine in cardiac iron reduction, improved cardiac function and decreased iron induced cardiac morbidity and mortality.[19,26,27,25,30,31,33,34,35,36] Although Exjade is approved for first line use, no data are available on its ability in decreasing iron induced morbidity and/or increasing survival in patients with thalassaemia major.

In the randomized trial LA-16, the target dose for DFO was 50 mg/kg/day for at least 5 days per week. The actual dose prescribed for DFO during the LA-16 trial was 43 mg/kg for 5.7 d/wk, which is equivalent to the recommended dose, 35 mg/kg/day, in the Australian Desferal PI for patients with serum ferritin levels between 2000 and 3000 μg/L. The recommended DFO dose for patients with a serum ferritin level <2000 μg/L is 25 mg/kg day. The Desferal PI also recommends that the lowest effective dose should be used. It is unknown if DFO at doses higher than the recommended dose would promote cardiac benefits similar to those obtained with deferiprone at doses within the recommended dose range approved by the EMA and most other countries. The mean iron overload, as assessed by serum ferritin in patients treated with deferiprone, in the LA-12 trial was 2033 ± 919 μg/L, whereas the mean serum ferritin in patients treated with deferiprone in the LA-16 trial was 1791 ± 1029 μg/L.

Extension to first line

The sponsor concurred with the Delegate that Ferriprox has similar efficacy to DFO in controlling the total body iron load, as assessed by serum ferritin or liver iron concentration. However, there is a body of evidence that deferiprone is superior to DFO in

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[30] Piga A, et al. Comparative effects of deferiprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis. Haematologica 2003; 88: 489-96.

[31] Modell B, et al. Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2008; 10: 42

[32] Telfer P, et al. Survival of medically treated thalassemia patients in Cyprus. Trends and risk factors over the period 1980-2004. Haematologica 2006; 91: 1187-92.

[33] Telfer P. Update on survival in thalassemia major. Hemoglobin 2009; 33: S76-S80.

[34] Ceci A, et al. Risk factors for death in patients with beta-thalassemia major: results of a case-control study. Haematologica 2006; 91: 1420-1.

[35] Maggio A., et al. Improving survival with deferiprone treatment in patients with thalassemia major: A prospective multicenter randomised clinical trial under the auspices of the Italian Society for Thalassemia and hemoglobinopathies. Blood Cells Mol Dis 2009; 42: 247-251.

[36] Anderson LJ, et al. Comparison of effects of oral deferiprone and subcutaneous desferrioxamine on myocardial iron concentrations and ventricular function in beta-thalassaemia. Lancet 2002; 360: 516-20.

reducing cardiac iron overload, which is the main cause of death in patients with thalassaemia major.[25,27,36] In addition, there is ample evidence that deferiprone is superior to DFO in improving cardiac function, decreasing iron-induced cardiac morbidity and in increasing survival of patients with thalassaemia major.[19,26,30,31,32,33,34,35] There is no evidence that Ferriprox-induced iron excretion would differ in subjects with transfusional iron overload conditions other than thalassaemia.

Increased maximum dose

The sponsor disagreed with the Delegate's views that there is no justification for the 100 mg/kg/day dose of deferiprone and that the safety of this dose has not been defined.

As with all other iron chelators, deferiprone induced iron excretion is dose dependant.[37,38,39,40,41,42] Doses of deferiprone up to 100 mg/kg/day have been used in clinical trials since 1987.[43] Deferiprone at 100 mg/kg/day is not associated with higher incidence of adverse reactions than 75 mg/kg/day, with the exception of gastrointestinal intolerance such as transient nausea and vomiting when therapy is initiated at the higher dose. There were no new serious or unexpected adverse events in subjects dosed with 100 mg/kg/day compared to subjects dosed with 75 mg/kg/day. Agranulocytosis, which is the most serious adverse reaction to deferiprone, is an idiosyncratic event and it is not dose dependent within the recommended doses up to 100 mg/kg/day range. Clinical manifestations of overdose, which do not include agranulocytosis, have been reported only with doses of 200-250 mg/kg/day for longer than 1-2 years, as described in the current Ferriprox PI.

The recommended initial dose of Ferriprox is 75 mg/kg/day. This dose can prevent net iron accumulation in most patients whose transfusion iron accumulation does not exceed 0.5 mg/kg/day. Higher doses are required for those patients with higher rates of transfusional iron accumulation. Dose adjustments should be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of the iron burden). Doses up to 100 mg/kg/day are approved in all countries, except Australia, since its first market authorization in 1999. Restricting the dose of Ferriprox to the minimum recommended dose will deny the treating physicians in Australia the possibility of making dose adjustments, as with all iron chelators, based on individual patient's needs. As stated earlier, doses up to 100 mg/kg/day are not associated with higher incidence of agranulocytosis or other serious adverse events.

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[37] Al-Refaie FN, Wonke B, Hoffbrand AV, Wickens DG, Nortey P, Kontoghiorghes GJ. Efficacy and possible adverse effects of the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one (L1) in thalassemia major. Blood. 1992; 80: 593-9.

[38] 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: 918-22.

[39] Al-Refaie FN, Hershko C, Hoffbrand AV, Kosaryan M, Olivieri NF, Töndury P, et al. Results of long-term deferiprone (L1) therapy: A report by the international study group on oral iron chelators. Br J Haematol 1995; 91: 24-9.

[40] Grady RW, Hilgartner MW, Giardina PJV. Deferiprone: its effectiveness relative to that of desferrioxamine. Proceedings of the 6th International Conference on Thalassaemia and the Haemoglobinopathies; 1997 Apr 5-10; St. Paul's Bay, Malta. p. 2.

[41] Agarwal MB, Gupte SS, Viswanathan C et al. Long-term assessment of efficacy and safety of L1, an oral iron chelator, in transfusion dependent thalassaemia: Indian trial. Br J Haematol 1992; 82: 460-6.

[42] Addis A, Loebstein R, Koren G, Einarson TR. Meta-analytic review of the clinical effectiveness of oral deferiprone (L1). Eur J Clin Pharmacol 1999; 55: 1-6.

[43] Kontoghiorghes GJ, Aldouri MA, Hoffbrand AV et al. Effective chelation of iron in b thalassaemia with the oral chelator 1,2-dimethyl-3-hydroxypyrid-4-one. BMJ 1987; 295: 1509-12.

As described in the Treatment section of the Borgna-Pignatti et al publication, "the usual dose of deferiprone was 75 mg/kg body weight, given daily in 3 divided doses."

Possible bias

As identified by the Delegate, the large study by Borgna-Pignatti et al also supported the cardiac efficacy of Ferriprox in comparison to DFO. In this study, a potential for length bias exists favouring Ferriprox. However, the average duration of deferiprone treatment in this study was 4 years and it would be surprising if the bias were strong enough to explain why there were no events with 750 subject years of exposure on more than 150 patients.

The degree of iron overload favoured patients maintained on DFO in the Borgna-Pignatti study. The ferritin levels were significantly higher in patients switched to deferiprone (1870 µg/L; 532-10632 µg/L) than in patients maintained on DFO (1461 µg/L; 160-9458 µg/L) (p < 0.001). Nonetheless the higher iron load in deferiprone treated patients, all 52 cardiac events, including 15 cardiac deaths, occurred in patients treated with DFO.

Carryover effects when treatment was changed from DFO to Ferriprox and vice versa were in fact taken into account. An additional analysis conservatively assumed that a lack of protection of deferiprone from cardiac events may extend up to 2 years beyond the end of deferiprone. This was modeled by keeping the group assignment of deferiprone for an additional 2 years of exposure (unless end of follow up is reached earlier) for all patients who received deferiprone. Under this assumption, one of the 6 cardiac events that occurred after deferiprone treatment (20 months after end of deferiprone) would be attributed to deferiprone. In this analysis, the hazard ratio on deferiprone compared with DFO was 0.08 (CI 0.011, 0.57; P = 0.012).

The 516 patients were exposed to a total of 3610 person-years on DFO (average patient exposure: 7 years), in which 52 cardiac events occurred. The 157 receiving deferiprone were exposed to 750 person years on deferiprone (average patient exposure, 4.8 years), in which no cardiac event occurred. The normalization of cardiac events by exposure demonstrated higher incidence in patients treated with DFO (1.4 events per 100 person years; CI 1.1, 1.9) than in patients treated with deferiprone (0 events per 100 person years; CI 0, .0.5). When assuming Poisson processes for both rates and comparing those rates, they are significantly different (P < 0.002).

As reported by the authors, the study may have had a patient selection bias against deferiprone, because, at least initially, deferiprone was experimental and was given mainly to patients with higher body iron load as measured by their serum ferritin levels or liver iron concentration. Conversely, since deferiprone was not approved in Italy until the year 2000, some physicians might have been reluctant in prescribing deferiprone to their sicker patients, biasing results in favour of deferiprone. Given that the time of initiating deferiprone shows a fairly uniform distribution over the 9 year interval of the study, neither consideration appears to have strongly biased the results of the study.

Adverse effects

The sponsor noted that it is not surprising that an oral drug would be associated with greater incidence of gastrointestinal adverse events such as nausea, vomiting, abdominal pain and eructation than a parenteral administered drug. Those gastrointestinal events were generally mild and resolved despite continued Ferriprox therapy. Increased serum liver enzymes were also generally mild and resolved despite continued Ferriprox therapy.

There is no evidence that the risk of deferiprone induced agranulocytosis is higher in patients with conditions other than thalassaemia major. It is important to note that the causal association of 2 of the 3 episodes of agranulocytosis in patients with conditions other than thalassaemia major is uncertain. The episode of agranulocytosis in the sickle

cell patient was assessed by the patient's physician as not related to Ferriprox use. However ApoPharma assessed this case as possibly related to deferiprone and has included this case in the agranulocytosis section. One of the episodes of agranulocytosis in a patient with myelodysplastic syndrome was also classified by the patient's physician as doubtfully related to deferiprone use. Upon resolution of the event, deferiprone was re-initiated and the patient has not experienced recurrence of agranulocytosis up to the cut-off date of this response, which represents 4.9 years upon re-initiation of deferiprone.

The withdrawal rate should be considered in the context of the longer duration of patient follow up during Ferriprox therapy (up to 14 years) than during DFO therapy (up to 2 years). Within controlled studies, the rate of withdrawals between Ferriprox and DFO-treated subjects were comparable (LA-01: 23% for Ferriprox vs 17% for DFO; LA08-9701 and LA10-9902: 0% for both groups; LA16 0102: 7% for Ferriprox vs 9% for DFO).

Agranulocytosis is not dose dependent within the recommended therapeutic dose, that is, up to 100 mg/kg/day, and no specific risk factors for agranulocytosis have been identified other than that most episodes have occurred during the first year of therapy. To ensure that Ferriprox is discontinued at the earliest sign of neutropenia and thus reduce the risk of agranulocytosis, weekly monitoring of the neutrophil count and other precautions are recommended for all patients treated with deferiprone.

Risk Management Plan

The issues identified by the OPR have been addressed.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission to increase the maximum dose for the current indication:

For the treatment of iron overload in patients with thalassaemia major who are unable to take desferrioxamine therapy or in whom desferrioxamine therapy has proven ineffective.

In making this recommendation the ACPM considered dose adjustments could be of potential benefit to the prescriber in the current population.

ACPM also made some recommendations concerning the PI and the Consumer Medicines Information (CMI) but these are beyond the scope of this AusPAR.

ACPM recommended rejection of the submission for an extension of indications from a second line treatment to a first line treatment for iron overload and to broaden the patient population beyond those with thalassaemia major on the grounds that the safety of Ferriprox in the wider population had not been established.

In making this recommendation the ACPM advised that the treatment population in terms of degree of iron overload has not been defined and the rates of agranulocytosis and neutropenia reported in the treatment population compared to controls was of concern and would require monitoring. There was also insufficient exposure to establish the safety of the 100 mg/kg dose in the wider population.

The committee noted that despite creatinine being monitored in most studies there was no information provided on treatment in renal impairment.

Initial Outcome

Based on a review of quality, safety and efficacy, TGA approved an increase in the maximum dose to 100 mg/kg/day for Ferriprox tablets 500 mg and solution 25 g/250 mL and 50 g/500 mL containing deferiprone for the current indication.

The full indications remain as follows:

Treatment of iron overload in patients with thalassaemia major who are unable to take desferrioxamine therapy or in whom desferrioxamine therapy has proven ineffective.

As a specific condition of registration, the deferiprone Risk Management Plan (RMP), version 3, dated 15 March 2011, and any subsequent revisions, as agreed with the TGA and its Office of Product Review must be implemented.

Final Outcome

Following the initial decision described above, the sponsor appealed under Section 60 of the Therapeutic Goods Act whereby a review of the initial decision was conducted by the Minister.

The Delegate of the Minister noted that Section 25(1)(d) of the Act requires that applications under section 25 of the Act are to be evaluated having regard to whether the quality, safety, and efficacy of the products, for the purposes for which they are to be used, have been satisfactorily established.

The Delegate of the Minister noted the following findings on material facts and evidence:

1.   Ferriprox is currently registered for the indication of:

for the treatment of iron overload in patients with thalassaemia major who are unable to take desferrioxamine therapy; or in whom desferrioxamine therapy has proven ineffective.

2.   In this application the sponsor proposed to broaden the patient population to be treated with Ferriprox by changing the indication to:

for the treatment of patients with transfusional iron overload due to chronic blood transfusions (transfusional haemosiderosis).

3.   The clinical evaluation report (CER) did "<u>not</u> recommend approval of the application to change the patient group for whom Ferriprox is indicated by removing the restrictions in the currently approved indication." The report in its discussion stated that:

"However, any cardioprotective benefit that DFP therapy has over DFO therapy is outweighed by the considerable safety risk of agranulocytosis and neutropenia that is associated with DFP treatment of patients with transfusional iron overload due to chronic blood transfusions."

4.   On 3 November 2010 the sponsor responded to the CER providing comments on the CER. This response raised the sponsor's concerns that the reviewer had minimised deferiprone's benefits and exaggerated its risks. It also raised a concern that the reviewer had "neglected" the supporting information for the wider patient group.

5.   On 17 December 2010 the TGA provided the sponsor with the Delegate's proposed action which included the request for ACPM advice. It indicated that the Delegate's draft decision was to reject the application to extend the indication as requested by the sponsor. It stated that "I do not recommend extending the population to be treated with Ferriprox until the drug's safety is better characterised."

6.   On 6 January 2011 the sponsor responded to the TGA Delegate's Request for ACPM advice and the Delegate of the Minister noted that this included a summary of worldwide market authorisation status showing that deferiprone was not currently approved by the FDA or Canada, and that all its market authorisation approvals, less Turkey, were for the current TGA approved indication only. It concluded that "Orphan Australia strongly believes that Ferriprox merits an indication comparable to those of

the currently marketed iron chelators, DFO and deferasirox – first line treatment of transfusional haemosiderosis, in this small patient population."

7. On 3 and 4 February 2001 ACPM met and considered the submission and in its minutes recommended rejection for an extension of indication. It stated:

"In making this recommendation the ACPM advised that the treatment population in terms of degree of iron overload has not been defined and the rates of agranulocytosis and neutropenia reported in the treatment population compared to controls was of concern and would require monitoring. There was also insufficient exposure to establish safety of the 100 mg dose in the wider population. The committee noted that despite creatinine being monitored in most studies there was no information provided on treatment in renal impairment."

8. On 17 March 2011 the Delegate provided a decision letter on deferiprone which rejected the submission for extension for indication and attached a Statement of Reasons for this rejection. In this he stated the reasons for rejection being:

"There were significant gaps in the safety data for Ferriprox and a relatively high incidence of agranulocytosis. Therefore, the safety of Ferriprox in the proposed wider population has not been established.

Efficacy data for Ferriprox were minimal for patients with anaemias other than thalassaemia major. Therefore, the efficacy of Ferriprox has been established in only part of the proposed wider population, first line treatment of transfusional iron overload in patients with thalassaemia major."

9. On 14 June 2011 the sponsor wrote to the Parliamentary Secretary for Health and Ageing appealing against the Delegate's decision on the basis that:

    1. The Delegate had not kept in perspective:

        §   The rarity of the relevant conditions;
        §   The frequent and invasive monitoring that is common in chronically transfused patients;
        §   The extensive safety data available for Ferriprox from more than 23 years of clinical experience;
        §   The scarcity of alternative treatments and the risks associated with their use; and
        §   The body of evidence indicating the particular value of Ferriprox treatment in lowering the burden of cardiac disease and premature death.

    2. The Delegate seems to have erred in his interpretation of the results of study LA16.

    3. When the Delegate pointed out there were minimal data for patients with anaemias other than thalassaemia and possibly an increased risk of agranulocytosis in these patients, he had failed to take into consideration that:

        §   Iron overload leads to increased mortality and morbidity irrespective of the primary disease;
        §   The favourable benefit/risk of Ferriprox, despite the risk of agranulocytosis; and
        §   The toxicities associated with alternative chelators.

10. Included in the appeal was the statement of a potential alternative outcome:

"in the event that the TGA still considers that the case in support for a first line indication for Ferriprox in transfusional siderosis does not presently extend to MDS and SCD, Orphan Australia requests that TGA designates Ferriprox as a second line treatment of iron overload in non-thalassaemia patients, to enable ready access for such patients to Ferriprox when desferrioxamine and deferasirox prove to be inadequate."

The Delegate of the Minister noted that in making his decision he was bound by Section 25(1)(d) of the Act that requires that applications under section 25 of the Act are to be evaluated having regard to whether the quality, safety and efficacy of the product, for the purposes for which they are to be used, has been satisfactorily established. In this case there are no issues with the quality of the product.

Efficacy

In the view of the Delegate of the Minister there was insufficient evidence to satisfy him that this product is efficacious for the broader patient group requested. The Delegate of the Minister noted that the Delegate, in his Statement of Reasons, had acknowledged that the "efficacy of Ferriprox has been established in only part of the proposed wider population, first line treatment of transfusional iron overload in patients with thalassaemia major." The Delegate of the Minister agreed with the Delegate in regard to this statement.

In the data provided by the sponsor the vast majority of clinical trial patients had thalassaemia major with only small numbers with other conditions, for example, in LA 16 all had thalassaemia major; in LA 12 all had transfusion dependent β-thalassaemia; in Borgna-Pignatti et al all had thalassaemia major. In the appeal documentation, the sponsor stated "information on the use of Ferriprox in patients with transfusional siderosis other than thalassaemia major is *limited (the Delegate of the Minister italics)*".

Furthermore the sponsor indicated that in the pooled analysis only 77 subjects who received deferiprone suffered from other transfusion dependent anaemias (that is, those other than thalassaemia major) and the Delegate of the Minister noted from a table provided by the sponsor that only 5 had sickle cell disease and 14 myelodysplasia. Noting that there are 15 different disease diagnoses, and hence processes, in the table for the other transfusion dependent anaemias there are insufficient subjects in these other anaemias to provide appropriate efficacy evidence.

The Delegate of the Minister observed that the sponsor noted that "transfusion dependent thalassaemia can be considered a model disease for transfusional overload...." however the sponsor did not provide any evidence that this proposition was broadly accepted and hence its relevance is uncertain.

Safety

In the view of the Delegate of the Minister there was insufficient evidence to satisfy him that this product is safe for the broader patient group requested.

As mentioned above the clinical trial data is from trials which were predominantly on subjects with thalassaemia major with only 77 subjects with other transfusion dependent anaemias drawn from 15 different diagnoses. This alone did not provide significant data to convince the Delegate of the Minister that the product is safe in each of these groups, which would all be included in the new indication the sponsor has requested.

The main safety issues are the incidence of agranulocytosis and neutropenia with this product. The Delegate of the Minister observed that the sponsor noted that "the most important risk for patients treated with Ferriprox is the development of agranulocytosis...observed at a rate of approximately 1-3% of patients". The sponsor also

noted that the "prevalence of agranulocytosis has been compared between thalassaemia and non-thalassaemia patients, and there appears to be no significant difference between the two populations." The sponsor also acknowledged that neutropenia also occurs in some of these patients. Although the sponsor noted that frequent and invasive monitoring may identify patients with agranulocytosis or neutropenia early these conditions are themselves potentially serious and would require intervention. As deferiprone is the only one of the three iron chelators compared that has this as a significant risk, there are the alternative chelators which do not have such a significant risk of these conditions.

The Delegate of the Minister also noted that the ACPM recommended rejection of the submission stating "the rates of agranulocytosis and neutropenia reported in the treatment population compared to controls was of concern and would require monitoring."

Taking the above into consideration and the small number of non-thalassaemia major subjects in the clinical trials (all with a variety of diagnoses), in the view of the Delegate of the Minister the safety in the broader patient groups requires further study.

General

In response to the sponsor's comments that the following issues had not been given adequate consideration by the Delegate, the Delegate of the Minister made the following comments:

· The rarity of the relevant conditions

Although the conditions might be rare there still needs to be evidence to satisfactorily support the efficacy and safety of the medicine for each condition. In the view of the Delegate of the Minister, sufficient evidence has not been provided for anything other than thalassaemia major.

· The frequent and invasive monitoring that is common in chronically transfused patients

The Delegate of the Minister commented on this aspect above.

· The extensive safety data available for Ferriprox from more than 23 years of clinical experience

The Delegate of the Minister assumed these data are predominantly from use in thalassaemia major, as this is the only approved indication shown in the current international regulatory status table provided by the sponsor in its pre-ACPM response.

· The scarcity of alternative treatments and the risks associated with their use

In the view of the Delegate of the Minister, the sponsor is required to prove that Ferriprox is safe and efficacious in its own right.

· The body of evidence indicating the particular value of Ferriprox treatment in lowering the burden of cardiac disease and premature death

This appears to be from the information provided by the sponsor and is predominantly in patients with thalassaemia major and not the other conditions. Also the Delegate of the Minister noted that the Australian guidelines put out by a group of Australian haematologists which the sponsor used to support some issues also stated that the drug of choice in patients with impaired cardiac function is intravenous desferrioxamine, with a combination of deferiprone and desferrioxamine as a potential second line treatment.

Overall

Taking into account the concerns of the Delegate of the Minister on the efficacy and safety of the use of deferiprone in the broader patient group requested he was not satisfied that the risk/benefit of deferiprone in the broader patient group has been satisfactorily established.

For the same reasons he was also not satisfied that the alternative outcome suggested in the appeal has been satisfactorily established.

The Delegate of the Minister decided to affirm the initial decision to reject the application to extend the indications of deferiprone (Ferriprox).
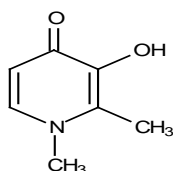
Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

FERRIPROX®
deferiprone 500 mg tablet
deferiprone 100 mg/mL oral solution

NAME OF THE MEDICINE

Deferiprone

DESCRIPTION

Deferiprone is an orally active synthetic iron chelator. Chemically, deferiprone is designated as 3-hydroxy-1,2-dimethyl-4(1H)-pyridone. Deferiprone is a white to off-white crystalline powder with a molecular formula of $C_7H_9NO_2$ and a molecular weight of 139.15. It has a melting range of 272ºC to 278ºC. Deferiprone does not show stereoisomerism. The CAS Registry Number for deferiprone is 30652-11-0.

Deferiprone is sparingly soluble in water, very slightly soluble in acetone and slightly soluble in methanol.

FERRIPROX film-coated tablets are formulated as white, capsule-shaped, film coated tablets, imprinted "APO" bisect "500" on one side, plain on the other. The tablets are scored and breakable in half.

Each tablet contains 500 mg deferiprone as active substance and the following excipients: microcrystalline cellulose, magnesium stearate, silicon dioxide, hypromellose, macrogol 3350 and titanium dioxide. Each bottle contains 100 tablets.

FERRIPROX oral solution is a clear, reddish-orange coloured liquid with a peppermint and cherry-flavoured aroma.

Each mL of oral solution contains 100 mg deferiprone as active substance and the following excipients: purified water, hydroxyethyl cellulose, glycerol, hydrochloric acid, artificial cherry flavour, peppermint oil, sunset yellow FCF and sucralose. The 250 mL bottle contains a total dose of 25 g of deferiprone and the 500 mL bottle contains a total dose of 50 g of deferiprone.

PHARMACOLOGY

Pharmacodynamic properties
Deferiprone is a bidentate iron (III) chelator (pFe^{3+}=19.4) that forms a 3:1 (deferiprone iron) complex. Deferiprone is uncharged at physiological pH and is rapidly absorbed from the gut. Deferiprone has been shown to mobilise iron from primary cultures of cells derived from

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organs affected clinically by iron overload, including cardiomyocytes, hepatocytes and reticuloendothelial cells.

Pharmacokinetic properties

Absorption
Deferiprone is rapidly absorbed from the upper part of the gastro-intestinal tract.

Peak serum concentration is reported to occur 45 to 60 minutes following a single dose in fasted patients. This may be extended to 2 hours in fed patients.

Following a dose of 25 mg/kg, lower peak serum concentrations have been detected in patients in the fed state (85 µmol/L) than in the fasting state (126 µmol/L), although there was no decrease in the amount of substance absorbed when given with food.

Distribution
The protein binding of deferiprone is low (<10%). Following oral administration of deferiprone, the volume of distribution is at least 1.73 L/kg in thalassaemia patients.

Metabolism
Deferiprone is cleared from plasma by metabolism, predominantly to a glucuronide metabolite. The rate of clearance has not been determined. The glucuronide metabolite lacks iron binding capacity because of inactivation of the 3-hydroxy group of deferiprone. Peak concentrations of the glucuronide metabolite occur 2 to 3 hours after administration of deferiprone.

Elimination
In humans, deferiprone is eliminated mainly via the kidneys with reports of 75% to 90% of the ingested dose being recovered in the urine in the first 24 hours, mainly in the form of the glucuronide metabolite and the iron-deferiprone complex. Only 5% of an administered dose of deferiprone is excreted unchanged in the urine. A variable amount of elimination into the faeces has been reported. The elimination half-life in most patients is 2 to 3 hours

CLINICAL TRIALS

In a randomised study (LA-01), the efficacy of Ferriprox (25 mg/kg three times per day) was compared with desferrioxamine (50 mg/kg/day, 4 to 7 times/week) in the treatment of iron overload in patients with thalassaemia major for about two years. There were 35 patients in the Ferriprox group and 36 in the desferrioxamine group. At the completion of the second year of the study, no significant change from baseline was observed in serum ferritin concentration or hepatic iron concentration of patients treated with either therapy. The power to detect a 20% difference in serum ferritin or hepatic iron concentration between groups was less than 80% due to the variability of the data and a relatively small sample size.

An uncontrolled multicentre prospective iron chelation study (LA-02) was performed in 187 transfusion-dependent thalassaemia patients over a year. Patients were aged ≥ 10 years and had previously been regularly chelated with desferrioxamine. Ferriprox 25 mg/kg orally three times per day was not associated with an increase in body iron stores (as assessed by serum ferritin) after changing from desferrioxamine.

On completion of the study, 84 patients continued Ferriprox treatment in an extension study (LA-06) for a total treatment duration of 4 years. Ferriprox maintained stable body iron stores.

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In a randomised, open-label, parallel-group trial (LA-16) in patients with thalassaemia major who had received chelation therapy with desferrioxamine for at least 5 years, 29 patients were switched to Ferriprox and 31 remained on desferrioxamine. Subjects wre aged 18 to 35 years. The mean dose of Ferriprox was 92 mg/kg/day and desferrioxamine 43 mg/kg/day (mean 5.7 days per week in the case of desferrioxamine). After 12 months, there were no significant differences between Ferriprox and desferrioxamine in reduction in serum ferritin or liver iron concentration.

INDICATIONS

FERRIPROX is indicated for the treatment of iron overload in patients with thalassaemia major who are unable to take desferrioxamine or in whom desferrioxamine therapy has proven ineffective.

CONTRAINDICATIONS

FERRIPROX is contraindicated in patients who:

♦ have demonstrated hypersensitivity to the active substance or any of the excipients
♦ have a history of recurrent episodes of neutropenia
♦ have a history of agranulocytosis
♦ are pregnant or breast-feeding.

PRECAUTIONS

General
Ferriprox may be associated with significant toxicity including agranulocytosis, which may lead to development of serious and potentially life-threatening infection.

Allergic Reactions
Ferriprox oral solution contains the colouring agent Sunset Yellow (E110) which may cause allergic reactions.

QT Prolongation
No significant inhibition of hERG K^+ channels was seen at deferiprone concentrations up to 3,000 µM, and no effect on QT interval or other cardiovascular and electrocardiographic parameters were noted in iron-loaded and non iron-loaded monkeys that received deferiprone for up to 12 months. However, the tested concentrations and doses were low, limiting the predictive value of negative findings. One episode of Torsades de Pointes during therapy with Ferriprox was observed in a patient with a history of QT prolongation. Ferriprox should be administered with caution to patients who may be at increased risk of prolongation of the cardiac QT interval (e.g., those with congestive heart failure, bradycardia, use of a diuretic, cardiac hypertrophy, hypokalemia or hypomagnesemia). Any patient taking Ferriprox who experiences symptoms suggestive of an arrhythmia (such as palpitations, dizziness, lightheadedness, syncope, or seizures) should seek medical attention immediately.

Neutropenia/Agranulocytosis
Ferriprox has been shown to cause neutropenia, including agranulocytosis. It is recommended that a patient's neutrophil count be monitored every week.

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The most serious adverse effect of therapy reported in clinical trials with Ferriprox is agranulocytosis (absolute neutrophil count $<0.5 \times 10^9$/L) with an incidence of 1.9% (0.9 cases per 100 patient-years of treatment). The observed incidence of the less severe form of neutropenia (absolute neutrophil count $<1.5 \times 10^9$/L but $>0.5 \times 10^9$/L) is 6.4% (3.6 cases per 100 patient years). This rate should be considered in context of the underlying elevated incidence of neutropenia in thalassaemia patients, particularly in those with hypersplenism.

Based on clinical trials, it is recommended that neutrophil counts be monitored weekly to enable prompt detection of neutropenia and agranulocytosis. In the event of neutropenia or agrnulocytosis, Ferriprox treatment should be stopped (see below for guidelines on re-initiating treatment).

If the patient develops an infection, Ferriprox therapy should be interrupted and the neutrophil count monitored more frequently. Patients should be advised to report immediately to their physician any symptoms indicative of infection such as: fever, sore throat and flu-like symptoms.

Suggested management for cases of neutropenia is outlined below. It is recommended that such a management protocol be in place prior to initiating any patient on Ferriprox treatment.

Treatment with Ferriprox should not be initiated if the patient is neutropenic**.**

In the event of neutropenia:
Instruct the patient to immediately discontinue Ferriprox and all other medications with a potential to cause medicinal product-associated neutropenia. The patient should be advised to limit contact with other individuals in order to reduce the risk of potential infection. Obtain a complete blood cell count immediately upon diagnosing the event and then repeat daily. It is recommended that following recovery of the neutrophil count, weekly complete blood cell count continue to be obtained for three consecutive weeks, to ensure that the patient recovers fully. Should any evidence of infection develop concurrent with the neutropenia, the appropriate cultures and diagnostic procedures should be performed and an appropriate antibiotic regimen instituted.

In the event of severe neutropenia or agranulocytosis:
Follow the guidelines above and administer appropriate therapy such as granulocyte colony stimulating factor, beginning the same day that the event is identified; administer daily until the neutrophil count recovers. Provide protective isolation and if clinically indicated, admit patient to hospital.

Limited data are available regarding rechallenge. Therefore in the event of neutropenia rechallenge is not recommended. In the event of agranulocytosis a rechallenge is contra-indicated.

Renal or hepatic impairment and liver fibrosis
Renal impairment
Currently there is no available data in patients with renal impairment. Since Ferriprox and its metabolites are excreted by the kidney, there may be an increased risk of complications in patients with impaired renal function. Caution must be used when treating patients with renal impairment.

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Hepatic impairment
There are limited data on the safety and efficacy of Ferriprox in patients with hepatic impairment. Ferriprox is metabolized by the liver and therefore caution should be exercised in such patients and hepatic function should be monitored.

In thalassaemia patients there is an association between liver fibrosis and hepatitis C. Special care must be taken to ensure that iron chelation in patients with hepatitis C is optimal. In these patients careful monitoring of liver histology is recommended.

Ferriprox has been associated with hepatotoxicity (increased ALT) in some patients. If there is a persistent increase in serum ALT, interruption of Ferriprox therapy should be considered.

Patient Monitoring
Serum ferritin concentrations/ plasma Zn^{2+}
It is recommended that serum ferritin concentrations be monitored regularly (every two to three months) to assess the long-term effectiveness of the chelation regimen in controlling the body iron load. Interruption of therapy with Ferriprox should be considered if serum ferritin measurements fall below 500 µg/L.

Monitoring of plasma Zn^{2+}, and supplementation in case of a deficiency is recommended.

HIV positive or other immune compromised patients
No data are available on the use of Ferriprox in HIV positive or in other immune compromised patients. Given that Ferriprox is associated with neutropenia and agranulocytosis, therapy in immune compromised patients should not be initiated unless potential benefits outweigh potential risks.

Discoloration of urine
Patients should be informed that a reddish/brown discoloration of the urine is commonly associated with Ferriprox use; the discolouration is due to the excretion of the iron-Ferriprox complex, which is a chromophore.

Effects on fertility
No effect on fertility or early embryonic development, and no effect on reproductive performance were noted in naive (non iron-loaded) male and female rats that received deferiprone orally at 75 mg/kg twice daily (0.3 times the clinical dose based on body surface area) for 28 days (males) or 2 weeks (females) prior to mating and until termination (males) or through early gestation (females).

Atrophy of the testis was reported at oral doses of greater than or equal to 400 mg/kg/day in non-iron loaded dogs, corresponding to about 3 times the recommended initial human dose of 75 mg/kg/day, based on body surface area.

Use in pregnancy (Category D)
Reproductive studies in non iron-loaded rats and rabbits have indicated that Ferriprox is teratogenic and embryotoxic at doses corresponding to human-equivalent doses (on a body surface area basis) considerably below the recommended daily dose in patients

Women of childbearing potential should be advised to avoid pregnancy due to the potential mutagenic, clastogenic and teratogenic properties identified in pre-clinical studies with Ferriprox. Women should be counselled to take contraceptive measures and should be advised to immediately stop taking Ferriprox should they become pregnant or plan to become pregnant.

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Use in lactation
There is no relevant data on the use of Ferriprox in nursing mothers. No perinatal/post-natal reproductive studies have been conducted in animals. Ferriprox should not be used in nursing mothers.

Paediatric use
The safety and efficacy of Ferriprox for paediatric use was evaluated in 220 children aged 1 to 15 years old with transfusion dependent anaemias. The data show that Ferriprox was effective in decreasing body iron load as measured by serum ferritin concentrations and it was not associated with new health concerns in this patient population. The effects of Ferriprox on growth are unknown.

Carcinogenicity
The carcinogenic potential of deferiprone has not been adequately investigated in long-term animal studies. In view of the genotoxicity results a carcinogenic potential of deferiprone cannot be excluded.

Genotoxicity
The genotoxic potential of deferiprone was evaluated in a set of *in vitro* and *in vivo* tests. Deferiprone was shown to be clastogenic in mouse micronucleus assays, as well as mutagenic and clastogenic *in vitro* in mammalian cells. Deferiprone was non-mutagenic in the bacterial reverse mutation assay.

A comparative study on the assessment of lymphocyte clastogenicity in patients with thalassaemia treated with deferiprone or with desferrioxamine did not show a significant difference in chromosomal aberration frequency between the two therapies.

Interactions with other medicines
Due to the unknown mechanism of Ferriprox-induced neutropenia, patients should not take medicinal products known to be associated with neutropenia or those that can cause agranulocytosis.

Interactions between Ferriprox and other medicinal products have not been reported. However, since this compound binds to some metallic cations, the potential exists for interactions between Ferriprox and trivalent cation-dependent medicinal products such as aluminium-based antacids. Therefore, it is not recommended to concomitantly ingest aluminium-based antacids with Ferriprox.

The safety of concurrent use of Ferriprox and vitamin C has not been formally studied. Based on the reported adverse interaction that can occur between desferrioxamine and vitamin C, caution should be used when administering concurrent Ferriprox and vitamin C.

Studies *in vitro* and in animals suggest that Ferriprox does not increase the risk of opportunistic Yersinia infections in iron overload conditions.

Effect on ability to drive and use machines
There is no evidence that Ferriprox affects the ability of patients to drive or use machinery.

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ADVERSE EFFECTS

Adverse effect information for Ferriprox represents the pooled data collected from 590 subjects with chronic iron overload secondary to transfusion-dependent anemias, primarily subjects with thalassemia major, who participated in single arm or active-controlled clinical studies.

System Organ Class (MedDRA classification)	VERY COMMON (>=1/10)	COMMON (>=1/100 to 1/10)	UNCOMMON (>=1/1,000 to 1/100)
Blood And Lymphatic System Disorders	None	Agranulocytosis, Neutropenia	Blood Disorder, Hypersplenism, Leukopenia, Thrombocytopenia
Cardiac Disorders	None	None	Arrhythmia, Torsade De Pointes
Ear And Labyrinth Disorders	None	None	Deafness, Ear Pain, Tinnitus, Vertigo
Gastrointestinal Disorders	Nausea, Vomiting	Abdominal Discomfort, Abdominal Pain, Abdominal Pain Upper, Diarrhoea, Dyspepsia	Abdominal Distension, Abdominal Pain Lower, Aphthous Stomatitis, Constipation, Epigastric Discomfort, Eructation, Gastritis, Reflux Oesophagitis, Stomach Discomfort
General Disorders And Administration Site Conditions	None	Oedema Peripheral	Asthenia, Chest Pain, Discomfort, Fatigue, Influenza Like Illness, Malaise, Pyrexia, Thirst
Hepatobiliary Disorders	None	None	Hepatic Pain, Hepatitis, Hepatomegaly, Jaundice, Liver Tenderness
Immune System Disorders	None	None	Hypersensitivity
Infections And Infestations	None	None	Cytomegalovirus Hepatitis, Diabetic Foot Infection, Gastroenteritis, Gastroenteritis Viral, Influenza, Nasopharyngitis, Sepsis, Upper Respiratory Tract Infection, Yersinia Infection
Injury, Poisoning And Procedural Complications	None	None	Epicondylitis, Transfusion Reaction
Investigations	None	Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Neutrophil Count Decreased, Weight Increased, White Blood Cell Count Decreased	Blood Bilirubin Increased, Blood Creatinine Increased, Blood Lactate Dehydrogenase Increased, Blood Phosphorus Increased, Blood Zinc Decreased, Electrocardiogram T Wave Inversion, Gamma-Glutamyltransferase Increased, Hepatic Enzyme Increased, Platelet Count Decreased, Platelet Count Increased, Weight Decreased
Metabolism And Nutrition Disorders	None	Anorexia, Increased Appetite	Decreased Appetite, Fluid Retention

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System Organ Class (MedDRA classification)	VERY COMMON (>=1/10)	COMMON (>=1/100 to 1/10)	UNCOMMON (>=1/1,000 to 1/100)
Musculoskeletal And Connective Tissue Disorders	Arthralgia	Arthropathy, Back Pain, Joint Swelling, Pain In Extremity	Arthritis, Bone Pain, Joint Crepitation, Joint Effusion, Joint Range Of Motion Decreased, Joint Stiffness, Metatarsalgia, Muscle Spasms, Muscular Weakness, Musculoskeletal Chest Pain, Musculoskeletal Pain, Myalgia, Polyarthritis, Synovial Cyst
Nervous System Disorders	None	Headache	Dizziness, Hypogeusia, Migraine, Somnolence
Renal And Urinary Disorders	Chromaturia (red/brown)	None	Pollakiuria
Reproductive System And Breast Disorders	None	None	Amenorrhoea, Menstruation Irregular
Respiratory, Thoracic And Mediastinal Disorders	None	None	Asthma, Dry Throat, Oropharyngeal Pain
Skin And Subcutaneous Tissue Disorders	None	None	Alopecia, Hyperhidrosis, Pruritus, Rash, Rash Generalised, Rash Pruritic, Skin Hypopigmentation, Urticaria, Xeroderma

Gastrointestinal effects are more frequent at the beginning of therapy with Ferriprox and in most patients are resolved within a few weeks without the discontinuation of treatment. In some patients it may be beneficial to reduce the dose of Ferriprox and then scale it back up to the total 25 mg/kg three times per day.

Arthropathy events ranged from mild pain in one or more joints to severe arthritis with effusion and significant disability. Mild arthropathies are generally transient.

Increased ALT levels have been reported in some patients taking Ferriprox. This increase, which occurred most frequently during the first 3 months of therapy, was generally mild, and resolved either without discontinuation or after decreasing the dosage of Ferriprox in the majority of patients.

Some patients experienced progression of liver fibrosis associated with an increase in iron overload or hepatitis C. Special care must be taken to ensure that iron chelation in patients with hepatitis C is optimal. In these patients careful monitoring of liver histology is recommended.

Low plasma zinc levels have been associated with Ferriprox, in a minority of patients. The levels normalised with oral zinc supplementation.

Postmarketing Experience
The following adverse experiences have been reported in patients receiving Ferriprox worldwide since its first market authorization in 1999. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: Agranulocytosis and mild/moderate neutropenia, febrile neutropenia, thrombocytopenia, thrombocythemia, leukopenia, granulocytopenia, pancytopenia.

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Cardiac disorders: atrial fibrillation, cardiac disorder, cardiac failure congestive cardiac failure, sinus tachycardia.

Congenital, familial and genetic disorders: congenital anomaly, hypospadia, non acute porphyria,

Eye disorders: diplopia, papilledema, eye movement disorder, periorbital oedema, retinal toxicity visual impairment.

Gastrointestinal disorders: cecitis, enterocolitis, rectal hemorrhage, gastric ulcer, vomiting, nausea, diarrhea, abdominal pain, stomatitis, pancreatitis, dysphagia, parotid gland enlargement

General disorders and administration site conditions: asthenia, chills, difficulty in walking, face edema, hyperpyrexia, pyrexia, fatigue, edema peripheral, multi-organ failure.

Hepatobiliary disorders: hepatic function abnormal, jaundice, hepatomegaly.

Immune system disorders: anaphylactic shock, hypersensitivity.

Infections and infestations: cryptococcal cutaneous infection, encephalitis enteroviral, neutropenic sepsis, parapharyngeal abscess, *yersinia* infection, bacterial infection, septic shock, pneumonia, infection, sepsis, parapharyngeal abscess, furuncle, subcutaneous abscess, tonsillitis urinary tract infection.

Investigations: anti-HBs antibody positive, blood arsenic increased, blood bilirubin increase, hemoglobin decrease, alanine aminotransferase increased, aspartate aminotransferase increased, blood corticotrophin decreased, blood cortisol decreased, hepatic enzymes increased, neutrophil count decreased, urine colour abnormal

Metabolism and nutrition disorders: metabolic disorders, dehydration.

Musculoskeletal and connective tissue disorders: arthralgia, arthritis, bone pain, joint effusion, joint swelling pain in extremity, chondropathy, osteoarthritis, myositis polyarthritis.

Neoplasms benign, malignant and unspecified (including cysts and polyps): hepatic neoplasm malignant.

Nervous system disorders: cerebellar syndrome, cerebral hemorrhage, convulsion, coordination abnormal, dystonia, febrile convulsion, hypotonia, intracranial pressure increased, nystagmus, psychomotor skills impaired, headache, depressed level of consciousness, dizziness, balance disorder.

Pregnancy, puerperium and perinatal conditions: intra-uterine death

Psychiatric disorders: depression, obsessive-compulsive disorder.

Renal and urinary disorders: renal failure, haemoglobinuria, glycosuria, chromaturia

Reproductive system and breast disorders: balanitis.

Respiratory, thoracic and mediastinal disorders: respiratory acidosis, hemoptysis, dyspnea, lung disorder, pulmonary embolism, epistaxis, oropharyngolaryngeal pain, pharyngeal erythema.

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Skin, subcutaneous tissue disorders: photosensitivity reaction, pruritis, urticaria, rash erythematous, rash, Henoch-Schonlein purpura, rash maculo-papular.

Vascular disorders: hypotension, hypertension.

DOSAGE AND ADMINISTRATION

Therapy with FERRIPROX should be initiated and maintained by a physician experienced in the treatment of patients with transfusional haemosiderosis.

The effect of Ferriprox in decreasing the body iron is influenced by the dose and the degree of iron overload. Ferriprox is given as 25 mg/kg to 33 mg/kg body weight, orally, three times a day for a total daily dose of 75 mg/kg to 100 mg/kg body weight. The recommended initial total daily dose of Ferriprox is 75 mg/kg body weight. After starting Ferriprox therapy, it is recommended that serum ferritin concentrations or other indicators of body iron load be monitored every two to three months to assess the long-term effectiveness of the chelation regimen in controlling body iron load. Dose adjustments should be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). Interruption of Ferriprox therapy should be considered if serum ferritin falls below 500 µg/L.

Doses above 100 mg/kg/day are not recommended because of the limited experience with these higher doses of Ferriprox.

Dosage per kilogram body weight should be calculated to the nearest half tablet or to the nearest 2.5 mL. See Dosage Table below.

Dosage Table for 75 mg/kg/day

To obtain a dose of about 75 mg/kg/day, use the dose suggested in the following table for the body weight of the patient.

Body Weight (kg)	Total Daily Dose (mg)	Dose (mg, three times/day)	500 mg film-coated tablets	100 mg/mL oral solution
			Number of tablets (three times/day)	mL (three times/day)
20	1500	500	1.0	5.0
30	2250	750	1.5	7.5
40	3000	1000	2.0	10.0
50	3750	1250	2.5	12.5
60	4500	1500	3.0	15.0
70	5250	1750	3.5	17.5
80	6000	2000	4.0	20.0
90	6750	2250	4.5	22.5

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Dosage Table for 100 mg/kg/day

To obtain a dose of about 100 mg/kg/day, use the dose suggested in the following table for the body weight of the patient.

Body Weight (kg)	Total Daily Dose (mg)	Dose (mg, three times/day)	500 mg film-coated tablets Number of tablets (three times/day)	100 mg/mL oral solution mL (three times/day)
20	2000	667	1.5	7.5
30	3000	1000	2	10.0
40	4000	1333	2.5	15.0
50	5000	1667	3.5	17.5
60	6000	2000	4	20.0
70	7000	2333	4.5	25.0
80	8000	2667	5.5	27.5
90	9000	3000	6	30.0

Due to the nature of the serious adverse events, which can occur with the use of Ferriprox, special monitoring is required for all patients. Treatment with Ferriprox should not be initiated if the baseline absolute neutrophil count (ANC) is low. Caution must be used when treating patients with renal insufficiency or hepatic dysfunction (See PRECAUTIONS).

Renal and hepatic impairment

Currently there are no available data in patients with renal impairment and limited data on the use of Ferriprox in patients with hepatic impairment. Caution must be used when treating patients with renal insufficiency or hepatic dysfunction (See PRECAUTIONS, Renal or hepatic impairment and liver fibrosis).

OVERDOSAGE

Acute Toxicity and Symptoms

There have been no reports of acute overdose with Ferriprox.

Neurological disorders (such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, hand movements and axial hypotonia) have been observed in children who had been voluntarily prescribed approximately 3 times the maximum recommended dose for several years. The neurological disorders progressively regressed after Ferriprox discontinuation.

Management and Treatment

In case of overdosage, close clinical supervision of the patient is required.

For advice on the management of overdosage, please contact the Poisons Information Centre (telephone 13 11 26).

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PRESENTATION

FERRIPROX tablets are available in HDPE containers of 100 tablets with child resistant closures.

FERRIPROX oral solution is available in 250 mL and 500 mL round amber polyethylene terephthalate (PET) bottles with white polypropylene child resistant pictorial caps. Only the 250 mL presentation is currently marketed. Each pack contains one re-closable bottle and one graduated 30 mL plastic dosing cup.

Storage Condition
Ferriprox film-coated tablets: Store below 25°C.

Ferriprox oral solution: Store below 30°C, protect from light. After first opening, store at 2°C to 8°C (Refrigerate. Do not freeze.), and use within 35 days.

NAME AND ADDRESS OF THE SPONSOR

Orphan Australia Pty Ltd
(a member of the Aspen Australia group of companies)
34-36 Chandos Street
St Leonards NSW 2065
Australia

POISON SCHEDULE

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FERRIPROX® is a registered trademark of Apotex Inc.

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