SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 1 June 2004. For scientific information on procedures after this date please refer to module 8B.

1. Introduction

Thalassaemia major (TM) is a rare hereditary disease (< 20,000 patients in the European Union) characterised by severe anaemia, requiring a life-long program of periodic blood transfusions to sustain growth, normal physiological development and extend survival. Frequent blood transfusions result in iron overload, which may also be aggravated by inappropriate increases in iron absorption from the gastrointestinal tract. As there are no natural means for the body to eliminate the excessive iron, these patients inexorably develop a clinically significant haemosiderosis. In the absence of treatment with iron chelators to decrease the iron deposition, the excess iron results in damage to the heart, liver, endocrine organs and death ultimately occurs, mainly due to cardiac haemosiderosis during the second decade of life. Prior to the marketing authorization of Ferriprox, the only therapy approved in the European Union for the treatment of iron overload in thalassemia was deferoxamine (Desferal, DFO). Over the past two decades, this therapy has been shown to ameliorate hepatic, cardiac and endocrine dysfunction, improve growth and sexual maturation, and prolong survival in iron-overloaded thalassemia major patients. However, DFO must be administered by subcutaneous infusion up to 12 hours a day a minimum of 5 times a week. This inconvenient method of administration is difficult for some patients and access to an alternative chelation regimen such as deferiprone (Ferriprox, L1) is a therapeutic option. Another treatment alternative is bone marrow transplantation.
Ferriprox contains deferiprone, a bidendate chelating agent that chelates trivalent iron cations (Fe^{3+}) in a 3:1 (deferiprone:iron) ratio. It is indicated for the treatment of iron overload in patients with TM for whom deferoxamine therapy is contra-indicated. The most serious undesirable effect of Ferriprox treatment reported in clinical trials is agranulocytosis; the mechanism of Ferriprox-induced agranulocytosis and of milder forms of neutropenia is unknown.
Deferiprone had a very unusual development programme. Indeed, toxicological evaluation of this agent in animals did not follow the customary pattern; having been administered to humans before the full, formal toxicological evaluation had been obtained in animals. Progress on the drug was curtailed in 1993 by Ciba-Geigy due to the toxic effects observed in non-clinical studies. The main toxic effect of the drug was bone marrow suppression that was observed in all non-iron loaded animal species, which were investigated. In contrast, the status of deferiprone was also reviewed at this time by clinical investigators from the International Study Group on Oral Iron Chelators, which clearly recommended expansion of the clinical evaluation (Hershko, 1993). Since then, a number of further studies have been undertaken on the drug, and its development has been re-instated by Apotex due to the effectiveness of chelation achieved in humans.

The Department of Health in India in December 1994 approved for clinical use another formulation of deferiprone, called Kelfer®. The marketing authorisation holder is Cipla.

Ferriprox is given orally as 25-mg/kg body weights, three times a day for a total daily dose of 75-mg/kg body weights. Dosage per kilogram body weight should be calculated to the nearest half tablet. Doses above 100 mg/kg/day are not recommended because of the potentially increased risk of adverse reactions.

There are limited data available on the use of Ferriprox in children between 6 and 10 years of age, and no data on Ferriprox use in children under 6 years of age.

2. Chemical, pharmaceutical and biological aspects

Composition and product development

Ferriprox is a capsule-shaped, film-coated tablet, bisect on one side, containing 500 mg of deferiprone, a new active substance used in the treatment of iron overload.

The choice of the formulation, which contains a large amount of the active ingredient, is well justified.

The formulation and development are unremarkable and standard. The formulation used in clinical studies was practically the same as the one proposed for marketing: pink-coated tablets (250 mg and 500 mg) were changed to white film coated, scored tablet, containing 500 mg of Deferiprone. The amount of coating was increased slightly in the retained composition.

Tablets are packaged in HDPE bottles with white polypropylene caps.

Active substance

The description of the process is adequate.

No catalysts or class 1 solvents (as defined by the ICH guideline "Residual solvents") are used in the manufacturing process. One class 2 solvent is used. Quality control during manufacture is adequate.

The active ingredient is relatively pure as the maximum level of impurities observed range from 0.01% to 0.1%. The impurity limits in the specification for the active substance have been tightened and are justified by toxicology studies.

The quality of the active ingredient is controlled with suitable specifications and validated analytical methods with respect of the guidelines regarding known related substances (<0.1%) and residual solvents. No polymorphism has been detected in deferiprone batches examined by X-ray diffraction and differential scanning calorimetry.

The proposed specifications are supported by the batch analysis results.

Stability studies have been carried out under stress, accelerated and real-time conditions.

Excipients

All excipients are tested in accordance with the Ph. Eur. In addition all excipients are tested in compliance with USP for Organic Volatile Ingredient (OVI test).

Finished product

The product is being manufactured in a facility that holds the necessary Manufacturing Authorisation (see Annex II of the Opinion).

The identification, quantification and uniformity of the deferiprone content are carried out by means of a HPLC method that is adequately described.

The proposed monograph and specifications for the control of deferiprone tablets are sufficient to ensure batch quality and reproducibility as well as the consistency of pilot and industrial scale batches. The microbiological test is in accordance with the Ph. Eur.

The batch analysis results confirm satisfactory compliance with specifications and uniformity of the product at release.

Due to the good stability of both the finished product and the active ingredient, a three-year shelf life is acceptable, as defined in the SPC. Ferriprox should be stored below 30^{o}C.

A BSE statement is supplied for the magnesium stearate. It is confirmed that any BSE risk is improbable.

In summary, the documentation of substances, materials, methods of production as well as the quality controls is sufficient to ensure a product of appropriate and consistent quality.

3. Toxico-pharmacological aspects

Pharmacodynamics

Deferiprone is a bidentate chelating agent that preferentially chelates trivalent iron cations (Fe^{3+}) in a 3:1 (deferiprone: iron) complex. This is unlike the binding activity of deferoxamine, the currently available therapy, which forms a 1:1 complex. Both the free ligand and the deferiprone-iron complex are uncharged at physiological pH.

The efficacy of a chelator depends not only upon its stability as a chelator, but also on the rate of biotransformation and elimination of the chelate-iron complex.

Deferiprone-induced iron clearance has been documented in animal studies. Deferiprone demonstrated iron mobilisation from both hepatocellular and reticuloendothelial iron stores.

The iron excretion efficiency of deferiprone and deferoxamine were compared using the molar binding ratio of the iron-chelator complexes. Deferiprone was 0.43 times as efficient as deferoxamine in non-iron loaded rats and 0.4 times as efficient in the iron-loaded *Cebus* monkeys. A similar level of iron excretion was observed in iron-loaded humans and iron-loaded *Cebus* monkeys even though the relative proportion of iron excreted in the urine of humans was considerably higher.

Interactions between deferiprone and other drugs have not been explicitly investigated or reported. Since this compound binds to cations that may be essential for the pharmacology of some drugs, antagonistic interactions between deferiprone and cation-dependent drugs may arise.

Pre-clinical pharmacodynamic studies using deferiprone have shown promising iron excretion in iron-loaded animals.

The effective clearance of iron from hepatic parenchyma (HP) and the reticuloendothelial (RE) system in iron-loaded experimental animals supports therapeutic efficacy in clearing iron deposition in thalassemic individuals.

In order to assess the risk on liver fibrosis the following publication has been reviewed: The iron chelator L1 potentiates oxidative DNA damage in iron-loaded liver cells, L. Cragg, Blood, 1998

This publication shows that deferiprone's potential toxicity is highly dependent on the L1: iron ratio. *In vitro* studies examining iron-mediated ascorbate oxidation in the presence of L1 showed that an L1: iron ratio must be at least 3 to 1 for L1 to inhibit the generation of free radicals; at lower concentrations of L1 increased oxygen radical generation occurs. In the clinical setting, such potentialisation of iron-catalysed oxidative DNA damage at low L1:iron ratios may lead to long-term toxicities.

This experimental study demonstrates the interaction between several chelators and iron on tissue damage. There is a correlation between high iron overload and visceral toxicity of the chelators, especially L1. This has been taken into account for limiting the indication.

Although this publication in Blood provides a mechanistic explanation for tissue damage by deferiprone a causal relationship has not been shown in practice. Most patients die because of cardiac causes (71%), and only a small minority due to liver problems (6%).

Pharmacokinetics

Studies have been performed in rabbits and in dogs.

The half-life of the drug in non-iron-loaded animals is short, ranging from 61-75 min in rabbits and 29-58 min (mean 39.9 min) in dogs. A longer half-life of 31-82 min (mean 54.2 min) is reported in iron-loaded dogs, which is consistent with a slower rate of elimination.

The glucuronide metabolite accounted for 44 % of the administered dose, while the methylated metabolite accounted for 1% and the unchanged drug accounted for 10.5%. Fifty-five and a half percent of the intravenous dose of deferiprone was identified in the urine of non-iron-loaded rats during the first 72 hrs

following dosing.

Most available pre-clinical pharmacokinetic data show significant inter and intra-species variability in pharmacokinetic profiles. In light of this, any extrapolation of absorption, metabolism, or excretion studies from rats or dogs to humans must be done with caution.

Toxicology

Single dose toxicity

The single-dose toxicity of deferiprone was assessed using lethal dose studies in both mouse and rat models. Albino male mice (BALB/c) aged 6 to 8 weeks and rats were given a range of single intravenous doses. Death occurred at high doses within 2-8 hours after deferiprone administration. The mode of death suggested a CNS-related cause, with death being immediately preceded by convulsions.

Additional information was derived from a 14-day oral toxicity study in non-iron-loaded dogs. Lethality was seen at a dose of 600 mg/kg. There was no mortality at doses of 25-400 mg/kg in the same study.

Repeated dose studies

The following studies have been conducted:

Subacute toxicity

Table 1: Toxicity after repeated dose: subacute toxicity

Species	Duration	Route	Doses (mg/kg)	Results
Mouse; T/O albino n = 3 Iron-loaded	24 days	2 groups : daily oral or intraperitoneal	300	No mortality and no apparent ill effects in either group.
Mouse ; BALB/c non-iron-loaded and iron-loaded mice	5 days/week for 60 days	daily intraperitoneal	200	No mortality in iron overloaded group and 33 % mortality in non-iron-loaded group. Both groups exhibited equivalent blood chemistry, slightly reduced haemoglobin, platelets and body weight gain and a significant drop in WBC (changes less pronounced in iron-loaded group). Histology of major organs was essentially normal.
Mouse ; BALB/c	5 days/week for 84 days	daily intraperitoneal	200	Significant reductions were observed at 84 days in white cell counts, haemoglobin, red cell counts and bone marrow cellularity. These changes were not observed after 14 days or 42 days.

Mouse ; n = 3 per group	5 days/week for 55 days and twice daily for next 22 days	2 groups : daily oral or intraperitoneal	250	The six animals survived throughout the administration period and the one-month recovery period.
Rat n = 6	13 days	3 subcutaneous infusions/day	300	All animals treated with deferiprone survived and exhibited similar body weight gain and liver weights to the control group.
Rat Sprague-Dawley (n = 10 per group)	28 days	daily oral or intraperitoneal	75, 150, 300 ip 300 oral	Hyperactivity, weight loss and hypersalivation were observed in the 300 mg/kg groups. Pathological observations included atrophy of thymus, spleen and testes and hypertrophy of adrenals at 150 and 300 mg/kg. WBC, RBC, and haemoglobin reduced by close to 50 % in the 300 mg/kg groups
Rat	3 months	oral	100, 200	Mortality was observed at 200 mg/kg and reduced red and white blood cell counts at 100 mg/kg. Atrophy of thymus and other organs at 100 mg/kg and above.
Rat	90 days followed by 60 days	oral	200 followed by 2 x 200	Significant drop in the white blood cell count and haemoglobin was reported at 30 and 150 days of testing. The effect on platelets and weight gain was minimal.
Dog ; Pure-bred Beagle n = 4 per group	14 days	oral	25, 50, 100, 200, 400, 600	Mortality observed in the four dogs of the 600 mg/kg group between days 7 and 12. Toxicity observed at doses ≥ 100 mg/kg which included anorexia, emaciation, decreased activity, hypothermia, salivation and tremors. At 14 days, decreased white cell counts and platelets were found in most animals at 200 and 400 mg/kg. Hypertrophy of adrenal glands and atrophy of testes observed in some animals at ≥ 400 mg/kg. No treatment related effects found at doses of 25 and 50 mg/kg.

Monkey ; Cynomolgus	3 months	daily oral	40 and 150 - 250	Mortality observed in high dose group in 6/13 animals. Reduced red and white blood cell counts and organ atrophy reported at 150 mg/kg or higher. Minor toxic effects to the bone marrow were observed at 40 mg/kg. Organ atrophy was seen in the monkeys at doses of 150 mg/kg or more.
Rat Sprague-Dawley n = 12	28 days	daily oral or intraperitoneal	300	-Animals treated intraperitoneally: slower rate of growth in body weight, red cell count reduced significantly after a week of treatment. -All treated animals : bone marrow suppression, haemoglobin and hematocriet reduced, marked atrophy of thymus.

Chronic toxicity

Table 2: Toxicity after repeated dose: chronic toxicity

Species	Duration	Route	Doses mg/kg	Results
Rat n = 12	5 days a week for 12 months	oral	200	Mortality was observed in 2/12 animals (similar to saline control group) with a substantial decrease in white blood cell counts between months 1 and 4 (males and females). Hypocellularity of white hypertrophy were also reported in animals treated with deferiprone.

Genotoxicity

The genotoxic potential of deferiprone was evaluated in a set of in *vitro* and *in vivo* tests. Deferiprone did not show direct mutagenic properties however, it did display clastogenic characteristics in non-iron-loaded systems. A study in patients is to be undertaken to assess the relevance of the clastogenic effects in animals.

Carcinogenicity

Chronic carcinogenicity studies have not been undertaken. This is reflected in the SPC.

Reproductive and development toxicity studies

Deferiprone was embryotoxic and teratogenic in non-iron-loaded rats and rabbits, at doses as low as 25 mg/kg/day.

Ecotoxicity/Environmental risk assessment

It is expected that deferiprone will react with and chelate free iron (Fe^{3+}). It would be expected that deferiprone released into soils or aquatic environments would chelate with cations and be sequestered in the local environment. The active ingredient of Ferriprox, deferiprone, is sparingly soluble in water (12.95

mg/ml) and, less than 10% of the ingested dose is excreted as the active form, the majority of the drug being excreted as the inactive glucuronide metabolite.

The amount of drug in the environment is anticipated to be small as Thalassaemia is an orphan disease and due to the genetic screening of populations at risk, the percentage of Thalassemia patients is decreasing.

4. Clinical aspects

One phase III and two-phase II trials have been conducted involving a total of 283 patients (ITT Population), of which 247 received deferiprone.
The pivotal and a supportive clinical trial were performed according to GCP standards and agreed ethical principles.

Clinical pharmacology

Pharmacodynamics

The mechanism of action is based on the formation of a complex of three molecules of deferiprone with one atom of iron. This complex is excreted mainly in urine and a net negative iron balance is achieved if the iron excreted is greater than the iron accumulated from transfused blood (0.5 mg/kg/day). The affinity of deferiprone for essential divalent cations like copper and zinc is considerably lower than for Fe^{3+}. The efficacy of a chelator depends not only upon the stability as a chelate, but also on the rate of biotransformation and elimination of the chelate-iron complex.

Dose finding studies

No formal dose finding studies have been carried out. A dose of 75 mg/kg/day in three divided doses has been selected. Doses of 100 mg/kg/day were associated with increased incidence of adverse events and doses of 50 mg/kg/day were unable to obtain a negative iron balance.

Pharmacokinetics

Study LA-01 characterised the pharmacokinetic profile of the Apotex formulation of deferiprone, Ferriprox, in seven patients who were fed.

Deferiprone has been reported to be rapidly absorbed from the upper part of the gastrointestinal tract, appearing in the blood within 5-10 minutes. Peak serum concentrations are reached 45 to 60 minutes following administration of 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 drug absorbed when given with food.

The serum protein binding of deferiprone in normal serum is lower than 10% over the concentration range of 0.01 - 0.2 mM.

Deferiprone is metabolised predominantly to a glucuronide conjugate. This metabolite lacks iron-binding capacity because of inactivation of the 3-hydroxy group of deferiprone. Peak serum concentrations of the glucuronide occur 2 to 3 hours after administration of Ferriprox.

In humans, deferiprone is eliminated mainly via the kidneys with reports of 75% to 90% of the ingested dose being recovered in the urine during the first 24 hours, in the form of free deferiprone, the glucuronide metabolite and the iron-deferiprone complex.

A variable amount of elimination into the faeces has been reported.

Clinical experience

Efficacy

Efficacy data concerning deferiprone in patients with thalassemia major concern 247 patients provided by three trials conducted by Apotex. In addition published data are available:

Table 3: Efficacy data

Study number	*Design*	*Dura - tion*	*Number of patients*	*Primary end-point*	*Efficacy result*
LA-01	Pivotal, open phase III, deferiprone vs. deferoxamine, multicentre, in patients 10 years of age or older, modified to 6 years, 10 months by protocol modification, in Thalassemia Major	2 years	Ferriprox: 35 (7 withdrawn); DFO:36 (4 withdrawn)	Serum ferritin	Mean serum ferritin in deferiprone treated-patients and in deferoxamine-treated patients is approximately similar. Mean hepatic iron concentration in deferiprone-treated patients seems to increase more than in deferoxamine treated patients.
LA-02/ LA-06 (follow-up)	Supportive, open, non-comparative, single treatment safety and efficacy study in patients 10 years of age or older in Thalassemia Major	1 year	187 (25 patients withdrawn)	Serum ferritin, neutrophil counts	Deferiprone allows to maintain serum ferritin values at pre-study levels. A subgroup analysis showed that in the more heavily iron-loaded patients (baseline >5000 µg/l), the mean ferritin values decreased progressively with time.
LA-03	Compassionate use	6 years	25 (4 withdrawn)	As this study was for compassionate use, no main efficacy endpoint	During the first 2 years of treatment, decrease in mean serum ferritin values. After this period values stabilised.

Statistical methods

Study LA-01
The original hypothesis to be tested in this study was that the efficacy of Ferriprox was within 20 % of the efficacy of deferoxamine after 24 months of treatment as measured by hepatic iron concentration (HIC). Due in part to poor compliance with the study procedures, this hypothesis could not be tested. In its place the measurement used to evaluate efficacy was the sequential monitoring of serum ferritin.

An analysis of covariance (ANCOVA) was to compare the difference between baseline and subsequent iron concentration for the two groups.

The correlation between urinary iron excretion and trough concentration of Ferriprox, serum ferritin, and liver iron were to be studied by multivariate analysis.

Study LA-02
A descriptive statistical approach was planned including establishment of 95 % confidence interval around the rate of occurrence of agranulocytosis. An approximate incidence rate of 0.4 % to 1 % was anticipated.

The sample size was sufficient to permit a rate of up to 2% to be detected with 95% confidence, using not more than 250 patients.

Study LA-03
As this study was for the compassionate use of deferiprone, no sample size calculation was performed. Since there was no a priori statistical plan in the protocol, the analysis presented is based on analysis of variance (ANOVA) and analysis of covariance (ANCOVA) assessments of serum ferritin and HIC over time.

Study populations

Table 4: Baseline characteristics of patients

	Mean age ± sd (years) (range)	**Gender**	**ethnic origin**	**Number of withdrawals**
LA-01 randomised, open-label, comparative n = 71 35 deferiprone 36 deferoxamine	Ferriprox 16.1±5.5 (6.9-30.8)	Male 51% Female 49%	Greek 25.7% Italian 22.8% Guyanese 2.8% Asian 42.8% Arabic 5.7%	7
	deferoxamine 17.1±6.5 (6.9-28.1)	Male 50% Female 50%	Greek 25% Italian 27.8% African 2.8% Asian 38.9% Arabic 5.6%	4
LA-02/LA06 (follow-up) open-label, single treatment safety study; n = 187	18.4±5.6 (10-41)	Male 49.7% Female 50.2%	Greek 1% Italian 98% Asian 1%	25 before one year treatment
LA-03 compassionate use n = 25	22.7±7.1 (6.9-40)	Male 60 % Female 40 %	Greek 20% Italian 24% African 4% Asian 32% Arabic 20%	4

Clinical studies in specific populations
No study was performed in patients with renal or hepatic impairment. In the case of renal impairment no toxicity is expected due to accumulation of deferiprone, because of the low fraction of unchanged drug excreted in the urine. The relation between hepatic function and drug elimination is complex and not well understood. The applicant commits to provide pharmacokinetic studies in patients with cirrhosis. Appropriate warnings have been included in the SPC.

The effect of age on deferiprone was not studied owing to the young age of the study population.

Safety

Patient exposure

There are data from the three studies mentioned and from other sources, especially data reported in the literature. It has been estimated that more than 2000 patients have been treated with deferiprone since 1987, albeit for a number of disorders at a variety of doses and duration of therapy.

Adverse events, including laboratory findings and serious adverse events

Among 247 patients who were enrolled in the Apotex-sponsored studies, 21 patients had serious adverse experiences. They included neutropenia, agranulocytosis, polyarticular arthritis, and nausea/vomiting.

The most serious adverse reactions are agranulocytosis and neutropenia. The incidence of agranulocytosis (neutrophils $<0.5x10^9/l$) is 1.2% (0.6 cases per 100 patient years of treatment). Agranulocytosis is potentially severe, occurring with a highly variable delay (from 0.5 to 21 months). During the Apotex-sponsored studies, agranulocytosis occurred during the first five months on therapy with deferiprone. It is therefore recommended that a patient's absolute neutrophil count (ANC) be monitored every week. This precaution for use may prevent agranulocytosis, and may decrease its severity by allowing an early discontinuation of Ferriprox and initiation of appropriate therapy with a granulocyte growth factor. The risk of agranulocytosis justifies the interruption of Ferriprox in cases of ANC values under 1.5 x 109/l. This information is included in the SPC in section 4.4. In addition patients with a history of agranulocytosis are contra-indicated. A strong educational effort by the applicant directly to haematologists and indirectly through patients through the Thalassemia International Federation (TIF) will be used to ensure that physicians and their patients are aware of the importance of weekly monitoring. To fortify the prescribers' and patients' compliance with the ANC monitoring, the drug will be packaged in units of approximately 1-week supply.

In total 15 fatalities have been reported, 13 fatalities in literature data and two additional cases. However, only two cases were considered to be related to deferiprone, one case of systemic lupus erythematosus, and one case of agranulocytosis and diphtheria-like infection.

The most common adverse reaction reported in patients treated with Ferriprox was reddish/brown urine. The event is attributed to the excretion of the iron-deferiprone complex that is a chromophore. Similar events are reported for patients taking deferoxamine, and no patient discontinued any study as a result of the reddish urine.

Apart from the reddish discoloration of the urine, the most frequently reported adverse reactions were related to the body as a whole, the digestive and musculoskeletal system. Gastrointestinal disorders such as nausea, vomiting, are the second cause for withdrawals and occurred in 16% of treated patients. Arthralgia and arthropathy are most often mild or moderate.

Agranulocytosis, neutropenia and gastrointestinal disorders are probably deferiprone-specific adverse reactions.

Transient fluctuations in liver enzymes have been reported in some patients treated with deferiprone. In the majority of the patients, the increase was asymptomatic and returned to baseline values without discontinuation or decreasing the dose of deferiprone. In some cases the abnormality was considered related to post-transfusion hepatitis. In one patient with evidence of previous hepatitis C infection, fluctuating levels of ALT were considered related to deferiprone. The clinical significance of increased ALT observed in some treated patients is unclear, due to the underlying disease.

Table 5: Frequency of adverse reactions

Adverse Reaction	Rate of Event (Per 100 Patient Years)	Percentage of Patients Affected
Red Urine	29.2	53.8
Nausea	8.6	15.9
Abdominal Pain	7.6	14.1
Vomiting	7.2	13.3
Arthralgia	5.1	9.4
Increased ALT	3.7	6.8
Neutropenia	3.5	6.5
Increased Appetite	2.9	5.4
Agranulocytosis	0.6	1.2

Liver fibrosis

A study has been published in the literature (New Eng J Med 1998; 339:417-23) in which the authors concluded that deferiprone might worsen hepatic fibrosis. As reported in the correspondence section of the journal (New Eng J Med 1998; 339:1710-14) this topic is controversial as other published studies concluded that deferiprone was not associated with hepatic fibrosis.

The study performed by Berdoukas et al (unpublished data) included 12 deferiprone treated patients and 22 deferoxamine treated patients. In the deferiprone treated group there was an increased chance of having progression of hepatic fibrosis, even over a short period of time.

However, the results of this study are inconclusive due to a number of methodological problems. And therefore do not provide additional information that might have altered the benefit/risk ratio.

Although the number of patients is low in above-mentioned studies and the findings are not derived from a randomised comparison, there is still doubt that deferiprone may worsen hepatic fibrosis, based on all available information. In thalassemia 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. This has been reflected in the SPC.

5. Overall conclusions and benefit-risk assessment

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Pre-clinical pharmacology and toxicology

Toxicological evaluation is particularly difficult to interpret because of differences between humans and animals: difference in metabolic pathways, difference in iron turnover and the inability to totally mimic in animals the iron overload seen in humans.

Deferiprone is genotoxic in 3/4 tests. The CPMP concluded that deferiprone did not show direct mutagenic properties, however, it did display clastogenic characteristics in non-iron-loaded systems. Therefore, genotoxic and carcinogenic effects in humans therefore cannot be ruled out. The applicant addressed this point in the oral explanation and committed to provide data on the relevance of these

clastogenic findings to humans by performing a study to examine chromosomal aberrations and chromatic breaks in patients on deferiprone treatment.

A statement has been included in the SPC that deferiprone is mutagenic and that its carcinogenicity cannot be excluded.

In conclusion, the toxicological data and the preclinical safety profile of deferiprone support only a strictly limited indication at this time.

Efficacy

Because of the deficiencies in the comparative study, the only data available for assessment of efficacy are uncontrolled. It is recognised that it would be difficult to perform a new prospective, randomised, comparative study in view of the limited number of patients. In addition, new oral iron chelators are under development and only a second line indication has been applied for.
Concern was also expressed about the results of a study, published in the literature (Hoffbrand AV, Al-Refaie F, Davis B, et al. Long-term trial of deferiprone in 51 transfusion-dependent iron overloaded patients. Blood 1998; 91: 295-300) in which some patients presented a less favourable response to deferiprone compared with the results of trial LA-06. This difference can be explained by the quality of chelation at baseline.

Data on long term hepatic iron concentrations are available only for very few patients. Deferiprone 75 mg/kg/day stabilises iron balance in regularly transfused patients, but it has not been shown that a negative iron-balance is reached in the long term. Because there are no adequate data to show that deferiprone reverses end-organ damage and because the leading cause of death in iron-loaded patients is cardiac iron loading, the ability to deferiprone to prolong life and prevent damage to vital organs such as the heart is crucial. There are no indications that deferiprone might worsen cardiac function. No death from congestive heart failure was reported in patients who had been treated long term with deferiprone. Several individual data show an improvement in cardiac function. Deferiprone has not been associated with a worsening of height growth curve. No increased incidence of iron-induced endocrine complications has been associated with deferiprone.

Despite the limitations in the data the CPMP concluded that the product was efficacious. The data support a restricted indication.

Safety

As mentioned before, a comparison between the pre-clinical data and the safety data is very difficult in this case. The most important adverse reactions are agranulocytosis and neutropenia whose incidence are 1.2% and 6% respectively. The amount of long-term data is limited, but in view of the indication this was accepted. As a weekly monitoring of blood counts is included in the SPC, the safety of the product is acceptable. There is still doubt that deferiprone may worsen hepatic fibrosis.

Benefit/risk assessment

Taking into account the fact that thalassemia major is a rare disease, where the lifetime of patients (currently only treated by deferoxamine which can induce toxic and in some cases allergic reactions) depends on iron overload, the CPMP considered that, despite the safety concerns raised with respect to agranulocytosis and insufficient information on clastogenicity, deferiprone offers an acceptable second-line alternative.

Only a restricted indication is accepted due to:

- limited comparative efficacy data with deferoxamine,
- the lack of data showing that a negative iron-balance is reached in the long term,
- its possible clastogenic properties,
- and the risk of agranulocytosis.

In conclusion, based on the available data on quality, safety and efficacy, the CPMP concluded by consensus that the benefit/risk profile of Ferriprox is favourable in the treatment of iron overload in

patients with thalassemia major for whom deferoxamine therapy is contra-indicated or who present serious toxicity with deferoxamine therapy. The CPMP, considering the fact that thalassemia major is a rare disease, where the lifetime of patients (currently only treated by deferoxamine which can induce toxic and in some cases allergic reactions) depends on iron overload, and having taking into account the conclusions of the ad-hoc expert group, recommended, the granting of a Marketing Authorisation under exceptional circumstances in accordance with Article 13 (2) of Council Regulation (EEC) No 2309/93, as amended, and Part 4 G of the annex to Council Directive 75/318/EEC.

6. Extension of the indication in patients for whom deferoxamine therapy is inadequate

Introduction

The very restricted indication currently approved for "the treatment of iron overload in patients with thalassemia major for whom DFO therapy is contraindicated or who present serious toxicity with DFO therapy" was adopted by the CPMP under exceptional circumstances in 1999. Consequently, the MAH undertook a series of studies in order to fulfill a number of specific obligations and follow-up measures. Further to the provision of these data, which included encouraging results pertaining to the safety of deferiprone, the exceptional circumstances were removed in May 2002.

Recent iron balance studies have demonstrated that the combined use of DFO and L1 could have an additive effect on total body iron excretion in thalassemia patients. Furthermore, preliminary data also indicate that spleen iron content may be decreased during therapy with L1. These data suggest that L1 and DFO may chelate iron from different body iron pools. Based on this hypothesis, an optimal chelation regimen could be the combination of lower doses of L1 and DFO. This regimen may avoid the toxicity associated with higher doses of either chelator and, on the other hand, by inducing chelation of different iron pools, it may promote a greater reduction in total body iron than either chelator alone.

The MAH applied for a wider, unrestricted indication in the treatment of iron overload in thalassemia patients and patients with other forms of secondary iron overload inadequately treated with conventional therapy.

Clinical aspects.

Independent investigators have conducted studies to evaluate liver histology changes during therapy with deferiprone and with the exception of one single retrospective study in 14 patients, no evidence of deferiprone-induced liver fibrosis was observed in the analysis of the scientific literature. A recent analysis of the largest collection of liver biopsies reported to date demonstrated lack of progression of liver fibrosis in 56 patients receiving deferiprone therapy for a mean of 3.1 years (Wanless IR, Sweeney G, Dhillon AP, et al. Lack of progressive hepatic fibrosis during long-term therapy with deferiprone in subjects with transfusion-dependent beta-thalassemia. Blood 2002;100(5):1566-9), confirming the conclusions of previous studies that there is no evidence of chelator-induced hepatic fibrosis. Based on all available scientific information, the concern of hepatic fibrosis was alleviated by the CPMP along with all other specific obligations.

In support of this application the MAH has provided results taken from one randomised study comparing the alternating therapy with deferiprone and deferoxamine *versus* the monotherapy with deferoxamine, and from various published studies, notably a multi-centre, randomised, active controlled study by Maggio *et al* comparing the efficacy of Ferriprox to that of DFO.

Study LA-08-9701

A multi-centre, randomised, open label, controlled, parallel clinical trial to compare the efficacy and safety of *alternating* therapy with deferiprone and DFO *versus* the *monotherapy* with DFO (current standard therapy) for 12 months in 60 TM patients already undergoing DFO therapy.

Patients in arm A (L1+DFO) received s.c. DFO on 2 consecutive days a week (DFO - 20-60mg/kg - 9±1 hour infusion) followed by 5 consecutive days of L1 (25mg/kg body weight t.i.d for a total daily dose of 75 mg/kg body weight). Patients in Arm B (DFO alone) received DFO s.c. 5 - 7 days a week (20-60 mg/kg - 9±1 hour infusion).

The most relevant *inclusion criteria* were TM patients ≥10 years of age with serum ferritin concentration 1000 - 4000 µg/l (initially between 1500 and 3500 µg/l and later amended) receiving chelation therapy (DFO only), and females of childbearing potential who have negative pregnancy tests prior to enrolment in the study and are out of risk of pregnancy. The *exclusion criteria* were mainly being diagnosed with anaemia other than TM, cardiac dysfunction requiring treatment, hepatic failure, previously diagnosed liver cirrhosis, previously diagnosed chronic active hepatitis or renal failure, patients who previously discontinued therapy with L1 or DFO because of an adverse reaction to either chelator, and patients with disorders associated with neutropenia or thrombocytopenia in the previous year.

The efficacy of both therapy arms was assessed by i) the quantification of body iron, determined by serum ferritin, hepatic iron concentration (HIC) and spleen iron concentration in non-splenectomized patients, ii) the difference between treatment groups in mean body stores of iron, as determined by the serum ferritin concentration and Superconducting Quantum Interference Device (SQUID), and iii)the tolerability of the regimen assessed by the incidence of adverse reactions . Thus, the *primary efficacy endpoint* was the change in serum ferritin concentration from baseline to the end of the study. The secondary efficacy endpoints were the hepatic and spleen (in non-splenectomised patients) iron concentrations, as measured by SQUID. Due to the difficulties associated with liver biopsies and the small number (4) of existing SQUIDs, only limited data are available on the changes in hepatic iron during chelation therapy in transfusion-dependent patients.

The *safety* of both therapy arms was evaluated by the incidence of adverse events (AEs) and adverse drug reactions (ADRs) reported during the study, the changes in physical examination and in laboratory values from baseline.

Regarding *statistical methods*, the study was designed to test the hypothesis that the two therapies have the same efficacy in the treatment of iron overload. A total of 60 patients were planned for the study, based on previous experience (LA-02 study). In the analysis of the primary endpoint, both "study completers" and "intent-to-treat" (ITT) approaches were employed. A two-sample t-test was performed to compare the mean change of the two regimens. In addition, ANOVA taking into account the site effect and the effects of splenectomy or baseline serum ferritin concentration (<2500 or >2500 µg/l), were also performed to determine the statistical significance of the difference between the two regimens in the presence of these covariates. Trend analysis of serum ferritin concentration data was performed using the repeated measures ANOVA approach. The proportion of patients with a negative or a positive trend in serum ferritin during the study was also determined by simple regression and compared between the two regimens by the Chi-square test.

The distribution of gender, splenectomy status, hepatits C virus infection status (HCV) and serum ferritin level >2500 µg/l between the two groups of patients at baseline was compared by the Chi-square test.

Results

The study was finally conducted in 3 centres. Fifty-nine (59) of the 60 patients enrolled finally completed the study (30 patients in the DFO cohort and 29 patients in DFO + L1 cohort). The DFO dose received was slightly smaller as compared to the usually prescribed one and the mean DFO dose during the study

period was significantly different between the two therapies: 37.77±8.92 mg/kg/day in the DFO arm, and 33.30±6.64 mg/kg/day in the experimental therapy group.

The following table shows the baseline characteristics of the two treatment arms,

Table 1: *Patients' characteristics at baseline*

	DFO	**DFO+L1**
Patient numbers	30	29
Age (years)	19.8±6.1	18.7±4.8
Female (%)	60	45
Splenectomized (%)	23.3	17.2
DFO dose (mg/kg/day)	34.77±8.85	36.04±5.75
HCV positive (%)	46.7	41.4
Serum ferritin concentration > 2500 µg/l (%)	40.0	27.6

Efficacy

Regarding the primary endpoint, the mean serum ferritin was similar for both groups at baseline (2048 ± 685 µg/l for the DFO+L1 therapy and 2257 ± 748 µg/l for DFO alone, p = 0.2682). At the end of the study, the value decreased to 1800 ± 887 µg/l for DFO + L1 therapy and 1877 ± 840 µg/l for DFO arm. Both therapies resulted in a statistically similar decrease in serum ferritin (-248 ± 791 for the L1+DFO arm versus –349 ± 573 µg/l for the DFO arm; p = 0.5802). The results of the trend analysis of the monthly serum ferritin data indicated that overall, there was a significant negative trend of serum ferritin concentration over time (p = 0.0469). The rate of decline was estimated to be -24.8 ± 12.4 µg/l/month (mean ± SD). In the DFO group, 24/30 (80%) patients had a negative trend in serum ferritin concentration whereas in the DFO + L1 group, 23/29 (79.3%) patients had a negative trend in serum ferritin. There was no statistically significant difference in the proportion of patients with a negative trend between the two therapy groups (p = 0.9475).

Regarding the splenectomy status**, t**he ANOVA on the change in serum ferritin concentration from baseline to the end of study showed that it has no effect on the non-significant difference in change in serum ferritin concentration between the two therapies (p = 0.5203).

There was no significant difference on Red Blood Cell Consumption between the two treatment arms (p = 0.8151).

The results of the ITT analysis were similar to those from 'Study Completer' analysis

Regarding secondary endpoints, the HIC declined from the baseline of 1625 ± 642 to 1386 ± 537 µg/g in DFO patients and from a baseline of 1629 ± 744 to 1565 ± 657 µg/g (N = 9) in DFO + L1 patients (N = 29) at the end of the study. Overall, there was no statistically significant difference (-239 ± 474 vs. -65 ± 615 µg/g) between the two therapies (p = 0.2263). The decrease was statistically significant from zero for the DFO patients (p = 0.0099) but non-significant for the DFO + L1 therapy patients (p = 0.5761). The effect of splenectomy status on HIC revealed that the highest mean change from baseline was found in splenectomized patients from DFO + L1 cohort; however, the difference was not statistically significant. Overall, there was no significant difference in HIC between splenectomized and non-splenectomized patients (p = 0.0844).

Of the total of 47 non-splenectomized patients, only eight patients had baseline assessment of spleen iron concentration and only 5/8 patients had their spleen iron concentration evaluated at the end of study. Due to the extremely small number of patients with spleen iron concentration data, no meaningful statistical comparison between the two regimens could be performed.

There was no statistically significant difference in the change of Non-Transferrin Bound Iron concentration between the DFO and DFO + L1 therapies (p = 0.5775).

Safety

Twenty-three (76.7%) of the 30 DFO patients reported 161 adverse events (AE) during the study, while 27 (93.1%) of the 29 DFO + L1 patients reported 149 AEs. The difference was not statistically significant (p = 0.1455).

Table 2. Incidence and distribution of AEs categorised into different body systems

	Number of reports of AEs	
Body system	**DFO**	**DFO+L1**
Body as a whole	80	49
Cardiovascular	3	1
Digestive	9	49
Endocrine system	0	1
Haemic and Lymphatic	1	2
Metabolic and nutritional	1	3
Musculoskeletal	1	1
Nervous	1	1
Respiratory	46	36
Skin	5	1
Special senses	4	4
Urogenital	10	1

When the AEs were categorised into different (COSTART) body systems, the frequency of patients with AEs was still not statistically significant between the two groups for all body systems.

Three AEs were considered as severe (pyelectasis) or moderate (renal colic, pharyngitis) in the DFO monotherapy group but the relationship on each case was considered doubtful and all resolved. In the DFO+L1 group all the adverse events were mild and all resolved.

Although the vast majority of AEs were not thought related, statistical analysis of the events showed an association between therapy and the distribution of reports by body system ($p<0.0001$). Patients in the DFO arm experienced more AEs in the “body as a whole” (back pain and headache) and “urogenital” (mainly dysmenorrhoea) systems whilst patients in the DFO + L1 arm reported more “digestive system” events (diarrhoea and vomiting).

The Cochrane-Mantel-Haenszel test revealed a statistically significant general association between therapy and the distribution of the number of AE reports among body systems ($p < 0.0001$). Patients in the DFO group experienced more AEs in the BODY AS A WHOLE (back pain and 20 headache) and UROGENITAL (mainly dysmenorrhoea) systems, whereas the patients in DFO + L1 group reported more AEs in the DIGESTIVE system (16 diarrhoea and 27 vomiting).

When the events considered to be adverse drug reactions (ADRs) were reviewed, two (6.7%) of the 30 DFO monotherapy patients reported a total of 3 ADRs compared with seven (24.1%) of the 29 DFO + L1 therapy patients, who between them experienced 40 ADRs during the study. The difference was not statistically significant (p = 0.0797). All reports had a favourable outcome.

Table 3. Number of individual ADR in the DFO+L1 and DFO arms

		Number of reports of ADR	
Body system	**COSTART Term**	**DFO**	**DFO+L1**
Body as a whole	Abdominal pain	0	5
	Allergic reaction	2	0
	Abscess	1	0
Digestive	Vomit	0	25
	Diarrhoea	0	5
	Nausea	0	2
Haemic and lymphatic	Decreased ANC	0	1
Metabolic and nutritional	Increased ALT	0	2

There was no significant difference in the incidence of ADRs between the two therapy groups with the exception of vomiting ($p = 0.0237$), which was probably related to the oral administration of L1.

There was a statistically significant general association between therapy and the distribution of the number of adverse drug reaction reports among COSTART terms ($p < 0.0001$). Allergic reactions (2 reports from 1 patient) were observed only with DFO monotherapy, whereas nausea, vomiting, diarrhoea, and increased ALT were observed only in patients using combination therapy.

There were no deaths in either treatment group and there were no relevant findings regarding serious adverse events.

Treatment interruptions

Five patients (16.7%) using DFO monotherapy and 12 patients receiving DFO+L1 combination (40%) experienced a total of 5 and 36 treatment interruptions, respectively, due to AEs. Reasons for interruptions in the DFO group were laryngotracheitis, gastroenteritis, flu, renal colic and worldwide travels where required monitoring of blood counts could not be assured, and n the second group, reasons for interruptions were digestive disorders in 10 cases (mostly diarrhoea), hepatic disorders in 2 cases (increased ALT), neuralgia in one case, and pharyngitis, cold, flu or chicken pox in the remaining cases. The total interruption for DFO monotherapy was 27 days (range 1 - 15 days) and for the L1 + DFO group was 207 days (range 4 - 39 days).

A more detialed review of the data carried out by the MAH at the request of the CPMP showed that site research personnel were much more cautious with the investigational product (Ferriprox) than with the standard therapy (DFO) and treated the same AE differently, depending on the therapy.

Clinical Laboratory Evaluation: ***ALT***

There was no statistically significant difference in mean ALT levels between the two patient groups either at baseline ($p = 0.7667$) or at the end of the treatment period ($p = 0.1886$). Slight, but non-significant increases from baseline occurred in both groups (DFO 2.0 ± 29.3 U/l ($p = 0.7160$) (N =30), and DFO + L1 20.9 ± 70.5 U/l (0.1214) (N = 29). Trend analysis of the monthly ALT data revealed that there was no significant difference in trend between the two therapy groups ($p = 0.3030$). Overall, there was no significant trend in ALT over time ($p = 0.2325$).

The effect of baseline HCV was investigated.

Table 8: *Mean baseline ALT values in patients according to HCV status*

Therapy	HCV	
	Positive	**Negative**
DFO	48.3±39.9 U/l (N=14)	30.4±19.0 U/l (N=16)
DFO+L1	52.8±50.4 U/l (N=12)	24.4±14.2 U/l (N=17)

As expected, HCV+ patients had higher baseline ALT levels. However, the difference in baseline ALT level between HCV+ and HCV- patients was not statistically significant in the ANOVA ($p = 0.0601$).

The changes in ALT from baseline to the end of the study *according to HCV status* are shown below:

Table 9: *Changes in ALT from baseline to the end of the study according to HCV status*

Therapy	HCV	
	Positive	**Negative**
DFO	-3.9 ± 19.5 U/l (N=14)	+7.1 ± 35.7 U/l (N=16)
DFO+L1	+44.9 ± 105.4 U/l (N=12)	+3.9 ± 17.4 U/l (N=17)

None of the changes in ALT was significantly different from zero ($p > 0.05$), nor were the changes significantly different between the two therapies, regardless of HCV infection status. Overall, there was no significant difference between HCV positive and negative patients ($p = 0.4196$).

Frequency of ALT above 2 or 3 Times the Upper Normal Limit (ULN)

The baseline frequency of patients with their ALT above two or three times ULN was similar for both therapy groups, even after adjusting for baseline HCV status. At the end of the study, there was a similar incidence between the two therapy groups of patients with ALT 2xULN and of patients with ALT 3xULN, even after adjusting for their baseline HCV status.

The percentage of patients with ALT levels >2xULN was examined over time. The percentage ranged from 0 - 13.3% (DFO) and 3.4 - 17.2% (DFO + L1). The following table summarises the effect of baseline HCV status on the percentage of patients with ALT >2xULN at each point in time:

Table: % of patients with ALT >2xULN at each point in time

	Baseline HCV-	**Baseline HCV+**
DFO group	0-6.3%	0-21.4%
DFO + L1 group	0-17.6%	0-33.3%

These results show that there was a significant effect of baseline HCV status on the incidence of ALT >2xULN, especially in the DFO + L1 therapy group.

The following table summarises the effect of baseline HCV status on the percentage of patients with ALT >3xULN at each point in time:

Table: % of patients with ALT >3xULN at each point in time

	Baseline HCV-	**Baseline HCV+**
DFO group	0- 6.3%	0-7.1%
DFO + L1 group	0-5.9%	0-33.3%

There was a significant association between baseline HCV status and the frequency of ALT >3xULN, after adjusting for therapy (p = 0.0002). Similarly, a significant association between therapy and the frequency of ALT >3xULN was detected, after adjusting for HCV status (p = 0.0054). A statistically significant difference in the overall frequency of ALT >3xULN was observed between the DFO monotherapy (2.55%) and the DFO + L1 (8.33%) therapy groups for HCV+patients (p = 0.0134). In HCV- patients, however, this difference was not significant (p = 0.3734).

Published Studies

The MAH has provided results from several published studies, including a multi-center, randomised, active controlled study by Maggio *et al* comparing the efficacy of L1 to that of DFO.

Deferiprone versus deferoxamine in patients with thalassemia major: a randomized clinical trial. Maggio et al. Blood cells, molecules, and disease: 1998; 28(2): 196-208.

This was a multi-centre, randomised, active controlled study comparing the efficacy of L1 to that of DFO. One hundred forty-four (144) consecutive TM patients previously treated with DFO and and with serum ferritin concentration ≤ 3000 ng/ml were randomly assigned to L1 (75 mg/kg/day) (n=71) or DFO (50 mg/kg/day) (n=73) for one year.

The study objective was to compare the reduction of iron overload or the prevention of its increase in the 2 treatments groups. The main measure of the treatment efficacy was the difference between the serum ferritin concentration before and after one year of treatment. Secondary efficacy measures were (i) the variation in HIC measured as µg/g of dry weight in patients willing to undergo liver biopsy prior to and after the treatment period, (ii) the variation in liver and heart iron content estimated by magnetic resonance, and (iii) heart function.

The sample size estimation was based on an expected mean reduction in serum ferritin concentration of 250 ng/ml at the end of 1 year of treatment, based on previous experience showing that in patients with initial serum ferritin <3000 ng/ml and treated with s.c. DFO, the mean reduction in serum ferritin after 1 year of therapy was 250 ng/ml, with a standard deviation of 65 ng/ml. The authors assumed that a difference > 30 ng/ml with respect to this expected ferritin reduction with DFO would be clinically significant. Therefore, to detect a 30 ng/ml difference (i.e. from 250 to 220), 70 patients per group were included (two sided test; □= 0.05; □=0.80).

The following table shows serum ferritin values, HIC, urinary iron excretion (UIE) and liver NMR at baseline and at the end of the study.

	L1 (n=71)			**DFO (n=73)**		
	Baseline	**End**	**Difference**	**Baseline**	**End**	**Difference**
Serum Ferritin (ng/ml)	**2283±754**	2061±853	222±783	**2019±678**	1787±893	232±619
HIC (µg/g/dry weight)	**3363±5490**	2341±2197	1022±3511	**3516±2974**	3166±2519	350±524
Urinary Iron excretion (mg/24h)	**11.4±8.5**	15.8±10.9	-4.4±13.2	**15.7±12.8**	19.9±13.6	-4.2±12.5
Liver NMR	**0.83±0.32**	0.89±0.26	-0.06±0.38	**0.85±0.36**	0.98±0.35	-0.13±0.28

There was no significant difference between treatments in the mean reduction in serum ferritin concentration (p=0.81). A statistically significant increase in intensity signal ratio (ISR) was found after

both treatments for all the magnetic resonance measurements. This increase was not significant for the liver in the L1 group. Assessment of heart function by ultrasound did not show appreciable variation with either treatment after the study period.

An analysis of possible confounding factors showed that the two variables independently associated with a higher serum ferritin reduction were female sex (p=0.036) and the number of blood units transfused in the year before randomisation (p=0.033)

Hepatic fibrosis scores increased in 7/21 patients in the L1 group and in 4/15 patients in the DFO group. The mean fibrosis scores, however, did not change with respect to their baseline values. Regarding AEs, 24 patients in the L1 group developed side effects requiring temporary dose reduction or treatment withdrawal, or withdrawal compared to 11 DFO treated patients who continued on DFO after temporary dosage reduction or treatment withdrawal.

Reanalysis of the data
Since study LA-08 study did not specifically address the comparison between DFO and deferiprone as monotherapies, the CPMP asked for a reanalysis of this published study targeting this comparison. Further to this request, the MAH obtained the complete data package of this trial and conducted a *post-hoc* analysis of Maggio's study to determine whether or not it had the statistical power to accomplish its stated objective.

This trial was designed to exclude inferiority of L1 compared to DFO with a power of 0.80 and a non-inferiority margin of 30 ng/ml. Sample size calculation was based on a standard deviation in endpoint value of 65 ng/ml. It appears from the data that variance was in fact affected by more than a 100-fold increase (standard deviations were multiplied by more than ten: 848 ng/ml and 1028 ng/ml in deferiprone and DFO groups, respectively). *Post-hoc* calculation of power (less than 0.10) leads to consider that this study fails to demonstrate any non-inferiority. In addition, the MAH's interpretation of the trial results based on Hwang's criteria is not acceptable as this *post-hoc* analysis uses an unusual non-inferiority criterion (percentage of patients in whom ferritin decreases or remains stable) with a large margin (a 23% difference). Thus, observing statistically significant ferritin concentration decreases in both arms that do not statistically differ when treatments are compared does not allow to consider that the two treatments are equivalent.

- *Comparative effects of deferiprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis (study LA-12) – Piga et al. Haematologica 2003; 88: 489-496.*

The MAH sponsored a retrospective comparative case-history review of the occurrence of cardiac disease and of the survival of all subjects with TM ≥ 5-year-old treated with L1 or DFO at the University of Turin since 1 January 1995. The retrospective design of this study was agreed upon by the CPMP in September 1999, taking into account the non-feasibility of an equivalent prospective study, the monocentric design, and need to obtain these data in the defined time frame.

The prevalence of cardiac disease was similar for both therapy groups at the first cardiac assessment of the study [6/55 (11%) on deferiprone v.s. 11/79 (14%) on deferoxamine]. During the 4-year study period, an improvement of the cardiac function was observed in 3/6 deferiprone patients (50%) and in 3/11 deferoxamine patients (27%) with cardiac dysfunction diagnosed at the first assessment (p = 0.6). A worsening of the cardiac disease was diagnosed in three (5%) deferiprone-treated patients and in 12 (15%) deferoxamine-treated patients (p = 0.075). Three patients in the DFO group died during the study period, with all 3 deaths due to cardiac disease. Kaplan-Meier analysis indicates a significant difference (p = 0.015) in the cardiac disease free survival between the two groups.
This study was actually assessed in November 2000 as part of the 1st annual reassessment of Ferriprox. The CPMP concluded the following:

- Both therapies were administered at the recommended dosages.
- With regard to the mean HIC elevation, it was noted that SQUID had evaluated only 17/78 DFO patients versus 46/48 deferiprone patients, therefore leading to a low value for this comparison. With regard to the liver biopsies, 37/48 patients were evaluated in the deferiprone subgroup versus none patient in the DFO subgroup.
- Considering the results, there was no suggestion of a higher risk of prevalent cardiac disease among deferiprone patients as compared with DFO patients during the study period.

Subsequently, the MAH provided updated information and a new analysis of study LA-12 in May 2001. These data confirmed that a reduction or stable maintenance of the patients' body iron load could be achieved with the use of deferiprone as well as a reduction on the incidence of cardiac disease that would inevitably occur in those patients unable or unwilling to take DFO. It was thus concluded that the new data confirm previous results and that deferiprone therapy may be associated with further reduction in iron-induced cardiac disease. Several clinical communications agree with the data submitted and would suggest a specific chelator effect of deferiprone on myocardial tissue.

Comparison of effects of oral deferiprone and subcutaneous desferrioxamine on myocardial iron concentrations and ventricular function in beta-thalassemia. Anderson et al; Lancet 2002; 360: 43-47.

This was an investigator -sponsored single centre and retrospective study comparing myocardial iron content and cardiac function in 15 patients receiving long-term L1 treatment with 30 matched TM controls on long-term treatment with DFO (2DFO controls per L1 patient). Myocardial iron concentrations were measured by a new magnetic-resonance T2* technique, which shows values inversely related to tissue iron concentration. Patients who received chelation with L1 alone for longer than 3 years (mean duration 5.7 years) were included. The mean administered L1 dose was 80.5 mg/kg divided into 3 doses per day.

Patients' characteristics were compared by means of Student's t test (age and serum ferritin) or Fisher's exact test (presence or absence of diabetes mellitus, hypopituitarism, hepatitis C). Myocardial and liver iron values were positively skewed in all groups, and non-parametric analyses were used for comparison of these variables. Paired comparisons were made between the L1 and DFO groups with each L1 patient paired to the mean value of the two matched DFO patients.

The L1 treated group had significantly less myocardial iron than the DFO-treated group (median myocardial T2* 34.0 versus 11.4 ms, p=0.02). The L1 group also had a higher mean left-ventricular ejection fraction (p=0.004) and less left ventricular dilatation in systole (p=0.03) and diastole (p=0.01). The left-ventricular mass index was lower, but not significantly so, in the L1 patients (p=0.09). Excess myocardial iron (myocardial T2* <20 ms) was noted in 4 (27%) L1 patients compared with 20 (67%) DFO treated patients (p=0.025), and severe iron overload (T2*<10 ms) was seen in one (7%) and 11 (37%) patients, respectively. The odds ratio for excess myocardial iron was 5.5 (95% CI 1.2-28.8) in the DFO versus the L1 group. Finally, the L1 group had significantly higher HIC than the DFO group (median 5.1 versus 3.5 mg/g liver dry weight, p=0.03).

Comparison between desferrioxamine and combined therapy with desferrioxamine and deferiprone in iron overloaded thalassemia patients. Mourad et al. Br J Haematol 2003; 121 (1): 187-9.(short report).

This was a single-centre, randomised, active controlled study conducted in 25 patients with TM over 12 months; 11 patients received combined therapy (DFO 2g/day twice weekly + L1) and 14 patients received DFO alone.

Serum ferritin levels decreased from 5506±635 µg/l to 4856±699 µg/l at 6 months (p=0.07) and to 3998±604 µg/l at 12 months (p<0.001) in the 14 DFO patients, and from 4153±517µg/l to 3005±393 µg/l at 6 months (p<0.02) and to 2805±327 µg/l at 12 months (p<0.001) in the 11 patients receiving DFO+L1.

No patient showed any change in physical examination, ANC, serum urea, creatinine or liver biochemistry. The most common side-effects in patients receiving DFO alone was pain, itching, erythema, swelling and indurations at the site of infusion, and in patients receiving DFO+L1 it was nausea, joint pain, stiffness and swelling.

The results taken indicate that the DFO (at a dose of 2g/day twice weekly) and L1 combination therapy was globally well tolerated in TM patients who were initially non compliant with DFO and with serum ferritin concentration > 3000 ng/ml.

Monitoring long-term efficacy of iron chelation therapy by deferiprone and desferrioxamine in patients with beta-thalassemia major: application of SQUID biomagnetic liver susceptometry. Fischer et al. Br J Haematol 2003; 121: 938-48.

This was a non-randomised study comparing HIC (as measured by the SQUID technique) in 54 L1-treated patients with 51 patients treated with DFO. The authors concluded that the relative change in HIC with respect to baseline after 2 years of treatment with L1 appeared to depend significantly on the initial HIC. After a comparable period of time, the mean HIC of patients treated with DFO increased from 1076±567-µg/g liver to 1260±770-µg/g liver (p=NS). During the study period, L1 treated patients had received greater iron accumulation (24.4±5.3 mg of iron per day) than DFO-treated patients (18.9±4.7 mg of iron per day). The total body iron excretion (TBIE) was also calculated and was 22.9±6.5 mg/day for L1, and 18.5±mg/day for DFO.

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

This was a prospective study comparing 11 TM patients unwilling or unable to use DFO and treated with L1 with 13 TM patients treated with DFO. Efficacy of the chelation treatment was determined by (i) the decrease of serum ferritin concentration to <2500 µg/l, (ii) the decrease of HIC to <4.6 µg/g of liver, (iii) the decrease of gross signal intensity (SI) in the cardiac and hepatic systems measured by MRI, or (iv) the increase of cardiac functions determined by the left ventricular ejection fraction (LVEF). Safety was determined by monitoring the patients for physical or physiological conditions encountered in other studies and included a weekly side-effect report for the first 3 months and a monthly report for the following 3 months.

The mean serum ferritin level declined from 4652 to 2792 ng/ml (L1, p=0.043) and from 4109 to 2612 ng/ml (DFO, p=0.067) after 36 months of therapy. In the L1 group, the final serum ferritin levels in 5/11 patients were <2500 ng/ml, compared with 6/10 patients in the DFO group. However, the mean HIC decreased from 115 to 83 µmol/g in the DFO group (p=0.048) and from 141.4 to 99.1 µmol/g in the L1 group (p<0.005). Post therapeutic MR images in 5 patients (45.4%) of the L1 group showed a marked recovery of SI in the cardiac region. A slight improvement in SI was detected in 2 DFO patients (20%). The increase in cardiac function measured by LVEF in the L1 group (from 58.6±6.8 to 65.2±7.1%, p=0.02) was more prominent than that in the DFO group (from 63.3±6.3 to 64.6±7%, p=0.36).
Moreover, pathohistological examination showed a distinct reduction in grades of haemosiderosis, although with individual variability, in the liver specimens following DFO and L1 treatment.

Comparison between deferoxamine and deferiprone (L1) in iron-loaded thalassemia patients. Taher et al. Eur J Haematol 2001; 67: 30-34.

Fifty-seven (57) patients with transfusion-dependent thalassaemia were studied; 17 received L1 and 40 received DFO. The efficacy of both chelators was assessed by periodic measurements of serum ferritin concentrations over a 24-month follow-up period. In patients on L1, a 24h urinary iron excretion (UIE) assessment was performed initially 1 week after starting the drug and at 6 and 12 months.

The mean serum ferritin level in the 16 patients receiving L1 (1 patient was not compliant and was lost for follow-up) showed a decline with time from an initial mean±SEM of 3663±566 µg/l (range 1005-9787) to 2599±314 (range 575-4206) at 6 months, and 2716±461 (range 944-7117) at 24 months ($p<0.03$ and $p<0.05$, respectively). UIE one week after starting L1 therapy was 20.7±3.2 mg/24h (range 0.3-42.7) and dropped to 10.5±1.7 (range 0.07-25) and 13.7±1.8 (range 0.3-28) at 6 and 12 months. There was a positive correlation between initial serum ferritin level and UIE, but this correlation did not persist over the follow-up period.

In the 40 DFO patients, mean serum ferritin level showed a decrease with time from an initial mean±SEM of 3480±417 µg/l (range 829-10 540) to 3143±378 (range 591-11734) at 6 months, and 2819±292 (453-8602) at 24 months.

Taken together, the data indicate that L1 seems to be effective in increasing UIE in patients with transfusional iron overload. However, although patients received comparable doses of L1, UIE varied considerably from patient to patient. Moreover, UIE dropped abruptly at 6 months and then appeared to plateau. This was not observed in the DFO arm, where serum ferritin levels showed a regular decrease with time. It is possible that a higher dosage of L1 may be needed.

Combined oral and parenteral iron chelation in beta thalassemia major. Balveer et al. Med J Malaysia 2000; 55 (4): 493-497.

This non-randomised study evaluated the efficacy and safety in TM patients of the administration of L1 alone (10 patients) or DFO+ L1 (7 patients). In all patients, there was a fall in serum ferritin after 12 months of treatment. The mean HIC in all patients was 19.6 µg/g dry weight at the beginning of the trial and after 12 months of treatment, the reduction was to 18.2 µg/g dry weight only (statistically non significant). The combined therapy was found to increase the UIE in 7 patients from 13.66 (6.43-32.67) mg/day to 27.38 (11.12-53.36) mg/day. Liver fibrosis deteriorated in one patient only.

Overall Discussion

The currently approved indication is very restricted since at the time of its approval there were limited comparative efficacy data with Desferal and serious safety concerns.

Regarding *efficacy*, serum ferritin concentration represents the most commonly used parameter to monitor response to chelation therapy in transfusion-dependent patients. This parameter was chosen as the main efficacy variable in the LA-08 pivotal study. According to the provided results, both therapies globally resulted in a similar decrease in the primary and secondary endpoints over the 1-year study, leading the MAH to claim non-inferiority of DFO+L1 with respect to the standard treatment DFO. However, the identification of a non-statistically significant difference between the two groups does not automatically lead to formally conclude that there is no real difference in efficacy between these medicinal products. The statistical non-significance of the difference in decline of serum ferritin between the two therapies should be interpreted with caution since the coefficient of variation (CoV) for the change in serum ferritin concentration was over 150% for both therapy groups. This is above the expected CoV of 35%, which

would have provided a power of 80% for the sample size used in the study. Therefore, as mentioned by the MAH, another study of much larger sample size would be needed to conclude, with at least 80% power, that the same efficacy truly exists between the two therapies.

With both therapies, the magnitude of the response was dependent on the patients' initial (baseline) body iron load. Depending on the status of this parameter, one may observe improved, comparable or lesser response in serum ferritin and/or HIC changes. Although there was no significant difference in baseline serum ferritin concentration between both arms, the mean concentration was higher in patients receiving DFO monotherapy, which could have favoured the DFO monotherapy. Furthermore, even if data indicate that both arms resulted in a statistically similar decrease in serum ferritin in non-splenectomised patients, there was a clear trend in favour of the DFO arm, as the experimental therapy appeared to be 29% less effective. This trend was also observed in the decrease in HIC, where the experimental therapy seems to be 72.8% less effective than DFO alone. Although a decrease in HIC with the combination therapy over only a 1-year follow-up is in itself encouraging. In conclusion, this study does not demonstrate that Ferriprox use 5 days per week, supplemented with DFO 2 days per week, is as efficacious in controlling iron overload in thalassaemia patients as DFO alone.

The other study most relevant to the efficacy of Ferriprox is the one conducted by Maggio et al, given it is a relatively large (>70 patients per group) randomised study addressing most of the current doubts on the comparative efficacy of deferiprone and deferoxamine in a clinical in a head-to-head clinical trial. As requested by the CPMP, the MAH provided more detailed results from the study and a new analysis of the data. There is unfortunately insufficient power in this study to demonstrate that deferiprone and DFO are comparable; specifically, the comparison in serum ferritin response failed to show that deferiprone is non-inferior to DFO at the 30 ng/ml level. Thus, Maggio's study does not establish non-inferiority at a level that would be close enough to provide confidence of comparability or equivalency.

A number of published studies suggest that L1 may serve as a shuttle, entering cells and bringing iron from tissue compartments to the blood stream where it is transferred to DFO, simultaneously administered, and excreted bound to DFO. However, most of the data provided were difficult to interpret due to the rather short follow-up and the small number of enrolled patients.

Regarding *safety*, the listing of AEs and ADRs in LA-08 does not raise major safety concerns. Data on neutropenia occurring in this study are not worrying. Nonetheless, 40 ADR reports, mostly regarding digestive intolerance such as diarrhoea and vomiting, were collected in patients using combination therapy whereas only 3 ADR reports are mentioned in the DFO monotherapy arm.

Safety results from the provided published studies are reassuring since they suggest that the use of Ferriprox might have a beneficial impact on the prevention of cardiac disease, and that the incidence of agranulocytosis seems to be lower than expected. Moreover, some studies have not observed drug-induced progression of liver fibrosis associated with the use of Ferriprox and suggested that the increase in fibrosis observed in some patients was most likely related to hepatitis C infection and/or to the hepatic iron load.

To conclude, taking into account the clinical data provided and the digestive safety concerns, the CPMP considers that the risk-benefit for the claimed unrestricted indication in the "treatment of iron overload in thalassemia patients and patients with other forms of secondary iron overload inadequately treated with conventional therapy" is negative. Nonetheless, considering that the pre-clinical information is now more comprehensive, that several hundred patients have been followed-up for several years and a few more comparative trials with DFO are now available, the CPMP believes that the current indication may be too restrictive, based on reassuring safety data and despite the fact that the data submitted do not provide sufficient reliable information concerning the comparative efficacy with deferoxaminee. Therefore, the following indication, i.e. the treatment of iron overload in patients with thalassemia major when deferoxamine therapy is contraindicated or inadequate, is more appropriate.

7. Other changes to the SPC

Several statements have been deleted from section 4.4 of the SPC ("Special warnings and special precautions for use") further to the evaluation of data provided in order to fulfil the Specific Obligations and Follow-up measures undertaken by the MAH at the time of the granting of the Marketing Authorisation, and to the evidence arising from subsequent clinical trials and published articles, such as those reviewed in this assessment report. These include "information to be made available in the future", and statements regarding the lack of data on cardiac function and the possible worsening of hepatic fibrosis.

The suggested monitoring frequency for the assessment of iron overload has been amended in line with current recommendations from the Thalassemia International Federation, which recommends that serum ferritin be assessed every 3 months. Iron accumulation in thalassaemia major patients ranges from 0.3 to 0.5 mg/kg/day. No significant change in body iron overload is expected to occur in less than 2-3 months in those patients. More frequent assessments do not provide additional benefits to the management of these patients.