SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ferriprox 100 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral solution contains 100 mg deferiprone (25 g deferiprone in 250 ml and 50 g deferiprone in 500 ml).

Excipient with known effect

Each ml of oral solution contains 0.4 mg sunset yellow (E110).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

Clear, reddish orange-coloured liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Ferriprox in combination with another chelator (see section 4.4) is indicated in patients with thalassaemia major when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction (see section 4.2).

4.2 Posology and method of administration

Deferiprone therapy should be initiated and maintained by a physician experienced in the treatment of patients with thalassaemia.

Posology

Deferiprone is usually given as 25 mg/kg body weight, orally, three times a day for a total daily dose of 75 mg/kg body weight. Dose per kilogram body weight should be calculated to the nearest 2.5 ml. See table below for recommended doses for body weights at 10 kg increments.

To obtain a dose of about 75 mg/kg/day, use the volume of oral solution suggested in the following table for the body weight of the patient. Sample body weights at 10 kg increments are listed.

Table 1: Dose table for Ferriprox 100 mg/ml oral solution

Body weight (kg)	**Total daily dose (mg)**	**Dose (mg, three times/day)**	**ml of oral solution (three times/day)**
20	1 500	500	5.0
30	2 250	750	7.5
40	3 000	1 000	10.0
50	3 750	1 250	12.5
60	4 500	1 500	15.0
70	5 250	1 750	17.5
80	6 000	2 000	20.0
90	6 750	2 250	22.5

A total daily dose above 100 mg/kg body weight is not recommended because of the potentially increased risk of adverse reactions (see sections 4.4, 4.8, and 4.9).

Dose adjustment
The effect of Ferriprox in decreasing the body iron is directly influenced by the dose and the degree of iron overload. 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 the 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 therapy with deferiprone should be considered if serum ferritin falls below 500 µg/l.

Dose adjustments when used with other iron chelators
In patients for whom monotherapy is inadequate, Ferriprox may be used with deferoxamine at the standard dose (75 mg/kg/day) but should not exceed 100 mg/kg/day.

In the case of iron-induced heart failure, Ferriprox at 75-100 mg/kg/day should be added to deferoxamine therapy. The product information of deferoxamine should be consulted.

Concurrent use of iron chelators is not recommended in patients whose serum ferritin falls below 500 µg/l due to the risk of excessive iron removal.

Renal impairment
Dose adjustment is not required in patients with mild, moderate, or severe renal impairment (see section 5.2). The safety and pharmacokinetics of Ferriprox in patients with end stage renal disease are unknown.

Hepatic impairment
Dose adjustment is not required in patients with mildly or moderately impaired hepatic function (see section 5.2). The safety and pharmacokinetics of Ferriprox in patients with severe hepatic impairment are unknown.

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

<u>Method of administration</u>

Oral use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- History of recurrent episodes of neutropenia.
- History of agranulocytosis.
- Pregnancy (see section 4.6).
- Breast-feeding (see section 4.6).
- Due to the unknown mechanism of deferiprone-induced neutropenia, patients must not take medicinal products known to be associated with neutropenia or those that can cause agranulocytosis (see section 4.5).

4.4 Special warnings and precautions for use

Neutropenia/Agranulocytosis

Deferiprone has been shown to cause neutropenia, including agranulocytosis (see section 4.8 'Description of selected adverse reactions'). The patient's absolute neutrophil count (ANC) should be monitored every week during the first year of therapy. For patients whose Ferriprox has not been interrupted during the first year of therapy due to any decrease in the neutrophil count, the frequency of ANC monitoring may be extended to the patient's blood transfusion interval (every 2-4 weeks) after one year of deferiprone therapy.

The change from weekly ANC monitoring to monitoring at the time of transfusion visits after 12 months of Ferriprox therapy, should be considered on an individual patient basis, according to the physician's assessment of the patient's understanding of the risk minimization measures required during therapy (see section 4.4 below).

In clinical studies, weekly monitoring of the neutrophil count has been effective in identifying cases of neutropenia and agranulocytosis. Agranulocytosis and neutropenia usually resolve upon discontinuation of Ferriprox, but fatal cases of agranulocytosis have been reported. If the patient develops an infection while on deferiprone, therapy should be immediately interrupted, and an ANC obtained without delay. The neutrophil count should be then monitored more frequently.

Patients should be aware to contact their physician if they experience any symptoms indicative of infection (such as fever, sore throat and flu-like symptoms). Immediately interrupt deferiprone if the patient experiences infection.

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

Treatment with deferiprone should not be initiated if the patient is neutropenic. The risk of agranulocytosis and neutropenia is higher if the baseline ANC is less than 1.5×10^9/l.

For neutropenia events (ANC < 1.5×10^9/l and > 0.5×10^9/l):

Instruct the patient to immediately discontinue deferiprone and all other medicinal products with a potential to cause neutropenia. The patient should be advised to limit contact with other individuals in order to reduce the risk of infection. Obtain a complete blood cell (CBC) count, with a white blood cell (WBC) count, corrected for the presence of nucleated red blood cells, a neutrophil count, and a platelet count immediately upon diagnosing the event and then repeat daily. It is recommended that following recovery from neutropenia, weekly CBC, WBC, neutrophil and platelet counts continue to be obtained for three consecutive weeks, to ensure that the patient has fully recovered. Should any evidence of infection develop concurrently with the neutropenia, the appropriate cultures and diagnostic procedures should be performed, and an appropriate therapeutic regimen instituted.

For agranulocytosis (ANC < $0.5x10^9$/l):

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 condition resolves. Provide protective isolation and if clinically indicated, admit patient to the hospital.

Limited information is available regarding rechallenge. Therefore, in the event of neutropenia, rechallenge is not recommended. In the event of agranulocytosis, rechallenge is contraindicated.

Carcinogenicity/mutagenicity

In view of the genotoxicity results, a carcinogenic potential of deferiprone cannot be excluded (see section 5.3).

Plasma zinc (Zn^{2+}) concentration

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

Human immunodeficiency virus (HIV) positive or other immunocompromised patients

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

Renal or hepatic impairment and liver fibrosis

There are no data available on the use of deferiprone in patients with end stage renal disease or severe hepatic impairment (see section 5.2). Caution must be exercised in patients with end stage renal disease or severe hepatic dysfunction. Renal and hepatic function should be monitored in these patient populations during deferiprone therapy. If there is a persistent increase in serum alanine aminotransferase (ALT), interruption of deferiprone therapy should be considered.

In thalassaemia patients there is an association between liver fibrosis and iron overload and/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.

Discolouration of urine

Patients should be informed that their urine may show a reddish/brown discolouration due to the excretion of the iron-deferiprone complex.

Neurological disorders

Neurological disorders have been observed in children treated with more than 2.5 times the maximum recommended dose for several years but have also been observed with standard doses of deferiprone. Prescribers are reminded that the use of doses above 100 mg/kg/day are not recommended. Deferiprone use should be discontinued if neurological disorders are observed (see sections 4.8 and 4.9).

Combined use with other iron chelators

The use of combination therapy should be considered on a case-by-case basis. The response to therapy should be assessed periodically, and the occurrence of adverse events closely monitored. Fatalities and life-threatening situations (caused by agranulocytosis) have been reported with deferiprone in combination with deferoxamine. Combination therapy with deferoxamine is not recommended when

monotherapy with either chelator is adequate or when serum ferritin falls below 500 µg/l. Limited data are available on the combined use of Ferriprox and deferasirox, and caution should be applied when considering the use of such combination.

Excipients

Ferriprox oral solution contains the colouring agent sunset yellow (E110) which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the unknown mechanism of deferiprone-induced neutropenia, patients must not take medicinal products known to be associated with neutropenia or those that can cause agranulocytosis (see section 4.3).

Since deferiprone binds to metallic cations, the potential exists for interactions between deferiprone and trivalent cation-dependent medicinal products such as aluminium-based antacids. Therefore, it is not recommended to concomitantly ingest aluminium-based antacids and deferiprone.

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in men and women

Due to the genotoxic potential of deferiprone (see section 5.3), women of childbearing potential are recommended use effective contraceptive measures and avoid becoming pregnant while being treated with Ferriprox and for 6 months following the completion of treatment. .

Men are recommended to use effective contraceptive measures and to not father a child while receiving Ferriprox and for 3 months following completion of treatment.

Pregnancy

There are no adequate data from the use of deferiprone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Pregnant women must be advised to immediately stop taking deferiprone (see section 4.3).

Breast-feeding

It is not known whether deferiprone is excreted in human milk. No prenatal and postnatal reproductive studies have been conducted in animals. Deferiprone must not be used by breast-feeding mothers. If treatment is unavoidable, breast-feeding must be stopped (see section 4.3).

Fertility

No effects on fertility or early embryonic development were noted in animals (see section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions reported during therapy with deferiprone in clinical studies were nausea, vomiting, abdominal pain, and chromaturia, which were reported in more than 10% of patients. The most serious adverse reaction reported in clinical studies with deferiprone was agranulocytosis, defined as an absolute neutrophil count less than $0.5x10^9$/l, which occurred in approximately 1% of patients. Less severe episodes of neutropenia were reported in approximately 5% of patients.

Tabulated list of adverse reactions

Adverse reaction frequencies: very common (≥ 1/10), common (≥ 1/100 to < 1/10), not known (cannot be estimated from the available data).

Table 2: List of adverse reactions

System organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Frequency not known**
Blood and lymphatic system disorders		Neutropenia Agranulocytosis	
Immune system disorders			Hypersensitivity reactions
Metabolism and nutrition disorders		Increased appetite	
Nervous system disorders		Headache	
Gastrointestinal disorders	Nausea Abdominal pain Vomiting	Diarrhoea	
Skin and subcutaneous tissue disorders			Rash Urticaria
Musculoskeletal and connective tissue disorders		Arthralgia	
Renal and urinary disorders	Chromaturia		
General disorders and administration site conditions		Fatigue	
Investigations		Increased liver enzymes	

Description of selected adverse reactions

The most serious adverse reaction reported in clinical studies with deferiprone is agranulocytosis (neutrophils < $0.5x10^9$/l), with an incidence of 1.1% (0.6 cases per 100 patient-years of treatment) (see section 4.4). Data from pooled clinical studies in patients with systemic iron overload showed that 63% of the episodes of agranulocytosis occurred within the first six months of treatment, 74% within the first year and 26% after one year of therapy. The median time to onset of the first episode of agranulocytosis was 190 days (ranged 22 days- 17.6 years) and median duration was 10 days in clinical studies. A fatal outcome was observed in 8.3% of the reported episodes of agranulocytosis from clinical studies and post-marketing experience.

The observed incidence of the less severe form of neutropenia (neutrophils < $1.5x10^9$/l) is 4.9% (2.5 cases per 100 patient-years). This rate should be considered in the context of the underlying elevated incidence of neutropenia in thalassaemia patients, particularly in those with hypersplenism.

Episodes of diarrhoea, mostly mild and transient, have been reported in patients treated with deferiprone. Gastrointestinal effects are more frequent at the beginning of therapy and resolve in most patients within a few weeks without the discontinuation of treatment. In some patients it may be beneficial to reduce the dose of deferiprone and then scale it back up to the former dose. Arthropathy events, which ranged from mild pain in one or more joints to severe arthritis with effusion and significant disability, have also been reported in patients treated with deferiprone. Mild arthropathies are generally transient.

Increased levels of serum liver enzymes have been reported in some patients taking deferiprone. In the majority of these patients, the increase was asymptomatic and transient, and returned to baseline without discontinuation or decreasing the dose of deferiprone (see section 4.4).

Some patients experienced progression of fibrosis associated with an increase in iron overload or hepatitis C.

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

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 more than 2.5 times the maximum recommended dose of 100 mg/kg/day for several years. Episodes of hypotonia, instability, inability to walk, and hypertonia with inability of limb movement, have been reported in children in the post-marketing setting with standard doses of deferiprone. The neurological disorders progressively regressed after deferiprone discontinuation (see sections 4.4 and 4.9).

The safety profile of combination therapy (deferiprone and deferoxamine) observed in clinical studies, post-marketing experience or published literature was consistent with that characterised for monotherapy.

Data from the pooled safety database from clinical studies (1 343 patient-years exposure to Ferriprox monotherapy and 244 patient-years exposure to Ferriprox and deferoxamine) showed statistically significant ($p<0.05$) differences in the incidence of adverse reactions based on System Organ Class for “Cardiac disorders", "Musculoskeletal and connective tissue disorders” and "Renal and urinary disorders". The incidences of “Musculoskeletal and connective tissue disorders” and "Renal and urinary disorders" were lower during combination therapy than monotherapy, whereas the incidence of “Cardiac disorders" was higher during combination therapy than monotherapy. The higher rate of “Cardiac disorders" reported during combination therapy than monotherapy was possibly due to the higher incidence of pre-existing cardiac disorders in patients who received combination therapy. Careful monitoring of cardiac events in patients on combination therapy is warranted (see section 4.4).

The incidences of adverse reactions experienced by 18 children and 97 adults treated with combination therapy were not significantly different between the two age groups except in the incidence of arthropathy (11.1% in children vs. none in adults, $p=0.02$). Evaluation of rate of reactions per 100 patient-years of exposure showed that only the rate of diarrhoea was significantly higher in children (11.1) than in adults (2.0, $p=0.01$).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

United Kingdom (Northern Ireland): Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

Ireland: HPRA Pharmacovigilance Website: www.hpra.ie

4.9 Overdose

No cases of acute overdose have been reported. However, 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 more than 2.5 times the maximum recommended dose of 100 mg/kg/day for several years. The neurological disorders progressively regressed after deferiprone discontinuation.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: All other therapeutic products, iron chelating agents, ATC code: V03AC02

Mechanism of action

The active substance is deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one), a bidentate ligand which binds iron in a 3:1 molar ratio.

Pharmacodynamic effects

Clinical studies have demonstrated that Ferriprox is effective in promoting iron excretion and that a total dose of 75 mg/kg per day can prevent the progression of iron accumulation as assessed by serum ferritin, in patients with transfusion-dependent thalassaemia. Data from the published literature on iron balance studies in patients with thalassaemia major show that the use of Ferriprox concurrently with deferoxamine (coadministration of both chelators during the same day, either simultaneously or sequentially, e.g., Ferriprox during the day and deferoxamine during the night), promotes greater iron excretion than either medicinal product alone. Doses of Ferriprox in those studies ranged from 50 to 100 mg/kg/day and doses of deferoxamine from 40 to 60 mg/kg/day. However, chelation therapy may not necessarily protect against iron-induced organ damage.

Clinical efficacy and safety

Clinical efficacy studies were conducted with 500 mg film-coated tablets.

Studies LA16-0102, LA-01 and LA08-9701 compared the efficacy of Ferriprox with that of deferoxamine in controlling serum ferritin in transfusion-dependent thalassaemia patients. Ferriprox and deferoxamine were equivalent in promoting a net stabilisation or reduction of body iron load, despite the continuous transfusional iron administration in those patients (no difference in proportion of patients with a negative trend in serum ferritin between the two treatment groups by regression analysis; $p > 0.05$).

A magnetic resonance imaging (MRI) method, T2*, was also used to quantify myocardial iron load. Iron overload causes concentration-dependent MRI T2* signal loss, thus, increased myocardial iron reduces myocardial MRI T2* values. Myocardial MRI T2* values of less than 20 ms represent iron overload in the heart. An increase in MRI T2* on treatment indicates that iron is being removed from the heart. A positive correlation between MRI T2* values and cardiac function (as measured by left ventricular ejection fraction (LVEF)) has been documented.

Study LA16-0102 compared the efficacy of Ferriprox with that of deferoxamine in decreasing cardiac iron overload and in improving cardiac function (as measured by LVEF) in transfusion-dependent thalassaemia patients. Sixty-one patients with cardiac iron overload, previously treated with deferoxamine, were randomised to continue deferoxamine (average dose 43 mg/kg/day; N=31) or to

switch to Ferriprox (average dose 92 mg/kg/day N=29). Over the 12-month duration of the study, Ferriprox was superior to deferoxamine in decreasing cardiac iron load. There was an improvement in cardiac T2* of more than 3 ms in patients treated with Ferriprox compared with a change of about 1 ms in patients treated with deferoxamine. At the same time point, LVEF had increased from baseline by 3.07 ± 3.58 absolute units (%) in the Ferriprox group and by 0.32 ± 3.38 absolute units (%) in the deferoxamine group (difference between groups; p=0.003).

Study LA12-9907 compared survival, incidence of cardiac disease, and progression of cardiac disease in 129 patients with thalassaemia major treated for at least 4 years with Ferriprox (N=54) or deferoxamine (N=75). Cardiac endpoints were assessed by echocardiogram, electrocardiogram, the New York Heart Association classification and death due to cardiac disease. There was no significant difference in the percentage of patients with cardiac dysfunction at first assessment (13% for Ferriprox vs. 16% for deferoxamine). Of patients with cardiac dysfunction at first assessment, none treated with deferiprone compared with four (33%) treated with deferoxamine had worsening of their cardiac status (p=0.245). Newly diagnosed cardiac dysfunction occurred in 13 (20.6%) deferoxamine-treated patients and in 2 (4.3%) Ferriprox-treated patients who were cardiac disease-free at the first assessment (p=0.013). Overall, fewer Ferriprox-treated patients than deferoxamine-treated patients showed a worsening of cardiac dysfunction from first to last assessment (4% vs. 20%, p=0.007).

Data from the published literature are consistent with the results from the company-sponsored studies, demonstrating less heart disease and/or increased survival in Ferriprox-treated patients than in those treated with deferoxamine.

A randomized, placebo-controlled, double-blind study evaluated the effect of concurrent therapy with Ferriprox and deferoxamine in patients with thalassaemia major, who previously received the standard chelation monotherapy with subcutaneous deferoxamine and had mild to moderate cardiac iron loading (myocardial T2* from 8 to 20 ms). Following randomization, 32 patients received deferoxamine (34.9 mg/kg/day for 5 days/week) and Ferriprox (75 mg/kg/day) and 33 patients received deferoxamine monotherapy (43.4 mg/kg/day for 5 days/week). After one year of study therapy, patients on concurrent chelation therapy had experienced a significantly greater reduction in serum ferritin (1 574 µg/l to 598 µg/l with concurrent therapy vs. 1 379 µg/l to 1 146 µg/l with deferoxamine monotherapy, p<0.001), significantly greater reduction in myocardial iron overload, as assessed by an increase in MRI T2* (11.7 ms to 17.7 ms with concurrent therapy vs. 12.4 ms to 15.7 ms with deferoxamine monotherapy, p=0.02) and significantly greater reduction in liver iron concentration, also assessed by an increase in MRI T2* (4.9 ms to 10.7 ms with concurrent therapy vs. 4.2 ms to 5.0 ms with deferoxamine monotherapy, p<0.001).

Study LA37-1111 was conducted to evaluate the effect of single therapeutic (33 mg/kg) and supratherapeutic (50 mg/kg) oral doses of deferiprone on the cardiac QT interval duration in healthy subjects. The maximum difference between the LS means of the therapeutic dose and placebo was 3.01 ms (95% one-sided UCL: 5.01 ms), and between the LS means of the supratherapeutic dose and placebo was 5.23 ms (95% one-sided UCL: 7.19 ms). Ferriprox was concluded to produce no significant prolongation of the QT interval.

5.2 Pharmacokinetic properties

Absorption

Deferiprone is rapidly absorbed from the upper part of the gastrointestinal tract. Peak serum concentration occurs 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 deferiprone absorbed when it was given with food.

Biotransformation

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

Elimination

In humans, deferiprone is eliminated mainly via the kidneys; 75% to 90% of the ingested dose is reported as being recovered in the urine in the first 24 hours, in the form of free deferiprone, the glucuronide metabolite and the iron-deferiprone complex. A variable amount of elimination via the faeces has been reported. The elimination half-life in most patients is 2 to 3 hours.

Renal impairment

An open-label, non-randomized, parallel group clinical study was conducted to evaluate the effect of impaired renal function on the safety, tolerability, and pharmacokinetics of a single 33 mg/kg oral dose of Ferriprox film-coated tablets. Subjects were categorized into 4 groups based on estimated glomerular filtration rate (eGFR): healthy volunteers (eGFR ≥ 90 mL/min/1.73m^2), mild renal impairment (eGFR 60-89 mL/min/1.73m^2), moderate renal impairment (eGFR 30–59 mL/min/1.73m^2), and severe renal impairment (eGFR 15–29 mL/min/1.73m^2). Systemic exposure to deferiprone and to its metabolite deferiprone 3-*O*-glucuronide was assessed by the PK parameters C_{max} and AUC.

Regardless of the degree of renal impairment, the majority of the dose of Ferriprox was excreted in the urine over the first 24 hours as deferiprone 3-*O*-glucuronide. No significant effect of renal impairment was seen on systemic exposure to deferiprone. Systemic exposure to the inactive 3-*O*-glucuronide increased with decreasing eGFR. Based on the results of this study, no adjustment of the Ferriprox dose regimen is required in patients with impaired renal function. The safety and pharmacokinetics of Ferriprox in patients with end stage renal disease is unknown.

Hepatic impairment

An open-label, non-randomized, parallel group clinical study was conducted to evaluate the effect of impaired hepatic function on the safety, tolerability, and pharmacokinetics of a single 33 mg/kg oral dose of Ferriprox film-coated tablets. Subjects were categorized into 3 groups based on the Child-Pugh classification score: healthy volunteers, mild hepatic impairment (Class A: 5– 6 points), and moderate hepatic impairment (Class B: 7– 9 points). Systemic exposure to deferiprone and to its metabolite deferiprone 3-*O*-glucuronide was assessed by the PK parameters C_{max} and AUC. Deferiprone AUCs did not differ between treatment groups, but C_{max} was decreased by 20% in mildly or moderately hepatically impaired subjects compared with healthy volunteers. Deferiprone-3-*O*-glucuronide AUC was decreased by 10% and C_{max} by 20% in mildly and moderately impaired subjects compared with healthy volunteers. A serious adverse event of acute liver and renal injury was seen in one subject with moderate hepatic impairment. Based on the results of this study, no adjustment of the Ferriprox dose regimen is required in patients with mildly or moderately impaired hepatic function.

The influence of severe hepatic impairment on the pharmacokinetics of deferiprone and deferiprone 3-*O*-glucuronide has not been evaluated. The safety and pharmacokinetics of Ferriprox in patients with severe hepatic impairment is unknown.

5.3 Preclinical safety data

Non-clinical studies have been conducted in animal species including mice, rats, rabbits, dogs and monkeys.

The most common findings in non-iron-loaded animals at doses of 100 mg/kg/day and above were hematologic effects such as bone marrow hypocellularity, and decreased white blood cell (WBC), red blood cell (RBC) and/or platelet counts in peripheral blood.

Atrophy of the thymus, lymphoid tissues, and testis, and hypertrophy of the adrenals, were reported at doses of 100 mg/kg/day or greater in non-iron-loaded animals.

No carcinogenicity studies in animals have been conducted with deferiprone. 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 *in vitro* assays and in animals.

Deferiprone was teratogenic and embryotoxic in reproductive studies in non-iron-loaded pregnant rats and rabbits at doses at least as low as 25 mg/kg/day. No effects on fertility or early embryonic development were noted in non-iron-loaded male and female rats that received deferiprone orally at doses of up to 75 mg/kg twice daily for 28 days (males) or 2 weeks (females) prior to mating and until termination (males) or through early gestation (females). In females, an effect on the oestrous cycle delayed time to confirmed mating at all doses tested.

No prenatal and postnatal reproductive studies have been conducted in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Purified water
Hydroxyethylcellulose
Glycerol (E422)
Concentrated hydrochloric acid (for pH adjustment)
Artificial cherry flavour
Peppermint oil
Sunset yellow (E110)
Sucralose (E955)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

After first opening, use within 35 days.

6.4 Special precautions for storage

Do not store above 30 ºC. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Amber polyethylene terephthalate (PET) bottles with child resistant closure (polypropylene), and a graduated measuring cup (polypropylene).

Each pack contains one bottle of 250 ml or 500 ml oral solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

8. MARKETING AUTHORISATION NUMBER

EU/1/99/108/002
EU/1/99/108/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 August 1999
Date of latest renewal: 21 September 2009

10. DATE OF REVISION OF THE TEXT

09/2022

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.