

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ferriprox 500 mg film-coated tablets
Ferriprox 1000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ferriprox 500 mg film-coated tablets
Each tablet contains 500 mg deferiprone.

Ferriprox 1000 mg film-coated tablets
Each tablet contains 1000 mg deferiprone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Ferriprox 500 mg film-coated tablets
White to off-white, capsule-shaped, film-coated tablets imprinted “APO” bisect “500” on one side, plain on the other. The tablet is scored. The tablet can be divided into equal halves.

Ferriprox 1000 mg film-coated tablets
White to off-white, capsule-shaped, film-coated tablets imprinted “APO” bisect “1000” on one side, plain on the other. The tablet is scored. The tablet can be divided into equal halves.

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 half tablet. See tables below for recommended doses for body weights at 10 kg increments.

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

Dose table for Ferriprox 500 mg film-coated tablets

Body weight (kg)	Total daily dose (mg)	Dose (mg, three times/day)	Number of tablets (three times/day)
20	1500	500	1.0
30	2250	750	1.5
40	3000	1000	2.0
50	3750	1250	2.5
60	4500	1500	3.0
70	5250	1750	3.5
80	6000	2000	4.0
90	6750	2250	4.5

Dose table for Ferriprox 1000 mg film-coated tablets

Body weight (kg)	Total daily dose (mg)	Number of 1000 mg tablets*		
		Morning	Midday	Evening
20	1500	0.5	0.5	0.5
30	2250	1.0	0.5	1.0
40	3000	1.0	1.0	1.0
50	3750	1.5	1.0	1.5
60	4500	1.5	1.5	1.5
70	5250	2.0	1.5	2.0
80	6000	2.0	2.0	2.0
90	6750	2.5	2.0	2.5

*number of tablets rounded to nearest half tablet

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 deferoxamine 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.

Paediatric population

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

Method of administration

For 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. The patient's neutrophil count should be monitored every week.

In clinical trials, weekly monitoring of the neutrophil count has been effective in identifying cases of neutropenia and agranulocytosis. Neutropenia and agranulocytosis resolved once therapy was withdrawn. If the patient develops an infection while on deferiprone, therapy should be interrupted and the neutrophil count monitored more frequently. Patients should be advised to report immediately to their physician any symptoms indicative of infection such as fever, sore throat and flu-like symptoms.

Suggested management 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 absolute neutrophil count (ANC) is less than $1.5 \times 10^9/l$.

In the event of neutropenia:

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 recovers fully. 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.

In the event of severe neutropenia or agranulocytosis:

Follow the guidelines above and administer appropriate therapy such as granulocyte colony stimulating factor, beginning the same day that the event is identified; administer daily until the 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 Zn²⁺ concentration

Monitoring of plasma Zn²⁺ concentration, and supplementation in case of a deficiency, is recommended.

HIV positive or other immune-compromised patients

No data are available on the use of deferiprone in HIV positive or in other immune-compromised patients. Given that deferiprone can be associated with neutropenia and agranulocytosis, therapy in immune-compromised 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 renal or hepatic impairment. Since deferiprone is eliminated mainly via the kidneys, there may be an increased risk of complications in patients with impaired renal function. Similarly, as deferiprone is metabolised in the liver, caution must be exercised in patients with hepatic dysfunction. Renal and hepatic function should be monitored in this patient population 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.

Discoloration of urine

Patients should be informed that their urine may show a reddish/brown discoloration 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 Feriprox and deferasirox, and caution should be applied when considering the use of such combination.

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

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.

Women of childbearing potential must be advised to avoid pregnancy due to the clastogenic and teratogenic properties of the medicinal product. These women should be advised to take contraceptive measures and must be advised to immediately stop taking deferiprone if they become pregnant or plan to become pregnant (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 trials were nausea, vomiting, abdominal pain, and chromaturia, which were reported in more than 10% of patients. The most serious adverse reaction reported in clinical trials with deferiprone was agranulocytosis, defined as an absolute neutrophil count less than $0.5 \times 10^9/l$, 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 ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), not known (cannot be estimated from the available data).

SYSTEM ORGAN CLASS	VERY COMMON ($\geq 1/10$)	COMMON ($\geq 1/100$ 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 trials with deferiprone is agranulocytosis (neutrophils $< 0.5 \times 10^9/l$), with an incidence of 1.1% (0.6 cases per 100 patient-years of treatment) (see section 4.4). The observed incidence of the less severe form of neutropenia (neutrophils $< 1.5 \times 10^9/l$) 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 trials, post-marketing experience or published literature was consistent with that characterized for monotherapy.

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

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

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 **the national reporting system** listed in [Appendix V](#).

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: 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 to iron in a 3:1 molar ratio.

Pharmacodynamic effects

Clinical studies have demonstrated that Ferriprox is effective in promoting iron excretion and that a dose of 25 mg/kg three times 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 drug alone. Doses of Ferriprox in those studies ranged from 50 to 100 mg/kg/day and doses of deferoxamine from 40 to 60 mg/kg/day. However, chelation therapy may not necessarily protect against iron-induced organ damage.

Clinical efficacy and safety

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 stabilization 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 milliseconds 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 randomized 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 milliseconds in patients treated with Ferriprox compared with a change of about 1 millisecond 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 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 Ferriprox 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 assessment to last assessment (4% vs. 20%, $p=0.007$).

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

A randomized, placebo-controlled, double-blind trial evaluated the effect of concurrent therapy with Ferriprox and deferoxamine in patients with thalassaemia major, who previously received the standard chelation monotherapy with subcutaneous deferoxamine and had mild to moderate cardiac iron loading (myocardial T2* from 8 to 20 ms). Following randomization, 32 patients received deferoxamine (43.4 mg/kg/day for 5 days/week) and Ferriprox (75 mg/kg/day) and 33 patients received deferoxamine monotherapy (34.9 mg/kg/day for 5 days/week). After one year of study therapy, patients on concurrent chelation therapy had experienced a significantly greater reduction in serum ferritin (1574 $\mu\text{g/l}$ to 598 $\mu\text{g/l}$ with concurrent therapy vs. 1379 $\mu\text{g/l}$ to 1146 $\mu\text{g/l}$ 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 suprathreshold (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 msec (95% one-sided UCL: 5.01 msec), and between the LS means of the suprathreshold dose and placebo was 5.23 msec (95% one-sided UCL: 7.19 msec). 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 $\mu\text{mol/l}$) than in the fasting state (126 $\mu\text{mol/l}$), 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.

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 WBC, 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 vivo* 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

Ferriprox 500 mg film-coated tablets

Tablet core

Microcrystalline cellulose

Magnesium stearate

Colloidal silicon dioxide

Coating

Hypromellose

Macrogol

Titanium dioxide

Ferriprox 1000 mg film-coated tablets

Tablet core

Methylcellulose USP A15LV

Crospovidone

Magnesium stearate

Coating

Hypromellose 2910 USP/EP

Hydroxypropyl cellulose

Macrogol

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Ferriprox 500 mg film-coated tablets

5 years.

Ferriprox 1000 mg film-coated tablets

3 years.

For the bottle: After first opening use within 50 days.

6.4 Special precautions for storage

Ferriprox 500 mg film-coated tablets

Do not store above 30°C.

Ferriprox 1000 mg film-coated tablets

Do not store above 30°C.

For the bottle: Keep the bottle tightly closed in order to protect from moisture.

For the blister: Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Ferriprox 500 mg film-coated tablets

High density polyethylene (HDPE) bottles with child resistant closure (polypropylene).

Each pack contains one bottle of 100 tablets.

Ferriprox 1000 mg film-coated tablets

High density polyethylene (HDPE) bottle with a child resistant polypropylene cap and a desiccant.
Pack size of 50 tablets.

High density polyethylene (HDPE) bottle with a polypropylene screw cap and a desiccant.
Pack size of 100 tablets.

Perforated unit dose aluminium blisters.
Pack size of 50 tablets.

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

Apotex Europe B.V.
Darwinweg 20
2333 CR Leiden
Netherlands

8. MARKETING AUTHORISATION NUMBER

Ferriprox 500 mg film-coated tablets

EU/1/99/108/001

Ferriprox 1000 mg film-coated tablets

EU/1/99/108/004

EU/1/99/108/005

EU/1/99/108/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 August 1999

Date of latest renewal: 25 August 2009

10. DATE OF REVISION OF THE TEXT

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

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.

Dose table

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.

Body weight (kg)	Total daily dose (mg)	Dose (mg, three times/day)	ml of oral solution (three times/day)
20	1500	500	5.0
30	2250	750	7.5
40	3000	1000	10.0
50	3750	1250	12.5
60	4500	1500	15.0
70	5250	1750	17.5
80	6000	2000	20.0
90	6750	2250	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.

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.

Method of administration

For 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. The patient's neutrophil count should be monitored every week.

In clinical trials, weekly monitoring of the neutrophil count has been effective in identifying cases of neutropenia and agranulocytosis. Neutropenia and agranulocytosis resolved once therapy was withdrawn. If the patient develops an infection while on deferiprone, therapy should be interrupted and the neutrophil count monitored more frequently. Patients should be advised to report immediately to their physician any symptoms indicative of infection such as fever, sore throat and flu-like symptoms.

Suggested management 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 absolute neutrophil count (ANC) is less than $1.5 \times 10^9/l$.

In the event of neutropenia:

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 recovers fully. 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.

In the event of severe neutropenia or agranulocytosis:

Follow the guidelines above and administer appropriate therapy such as granulocyte colony stimulating factor, beginning the same day that the event is identified; administer daily until the 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 Zn²⁺ concentration

Monitoring of plasma Zn²⁺ concentration, and supplementation in case of a deficiency, is recommended.

HIV positive or other immune-compromised patients

No data are available on the use of deferiprone in HIV positive or in other immune-compromised patients. Given that deferiprone can be associated with neutropenia and agranulocytosis, therapy in immune-compromised 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 renal or hepatic impairment. Since deferiprone is eliminated mainly via the kidneys, there may be an increased risk of complications in patients with impaired renal function. Similarly, as deferiprone is metabolised in the liver, caution must be exercised in patients with hepatic dysfunction. Renal and hepatic function

should be monitored in this patient population 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.

Discoloration of urine

Patients should be informed that their urine may show a reddish/brown discoloration 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

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.

Women of childbearing potential must be advised to avoid pregnancy due to the clastogenic and teratogenic properties of the medicinal product. These women should be advised to take contraceptive measures and must be advised to immediately stop taking deferiprone if they become pregnant or plan to become pregnant (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 trials were nausea, vomiting, abdominal pain, and chromaturia, which were reported in more than 10% of patients. The most serious adverse reaction reported in clinical trials with deferiprone was agranulocytosis, defined as an absolute neutrophil count less than $0.5 \times 10^9/l$, 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 ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), not known (cannot be estimated from the available data).

SYSTEM ORGAN CLASS	VERY COMMON ($\geq 1/10$)	COMMON ($\geq 1/100$ 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 trials with deferiprone is agranulocytosis (neutrophils $< 0.5 \times 10^9/l$), with an incidence of 1.1% (0.6 cases per 100 patient-years of treatment) (see section 4.4). The observed incidence of the less severe form of neutropenia (neutrophils $< 1.5 \times 10^9/l$) 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 trials, post-marketing experience or published literature was consistent with that characterized for monotherapy.

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

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

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 **the national reporting system listed in [Appendix V](#)**.

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: 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 to iron in a 3:1 molar ratio.

Pharmacodynamic effects

Clinical studies have demonstrated that Ferriprox is effective in promoting iron excretion and that a dose of 25 mg/kg three times 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 drug alone. Doses of Ferriprox in those studies ranged from 50 to 100 mg/kg/day and doses of deferoxamine from 40 to 60 mg/kg/day. However, chelation therapy may not necessarily protect against iron-induced organ damage.

Clinical efficacy and safety

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 stabilization 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 milliseconds 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 randomized 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 milliseconds in patients treated with Ferriprox compared with a change of about 1 millisecond 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 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 assessment to last assessment (4% vs. 20%, $p=0.007$).

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

A randomized, placebo-controlled, double-blind trial evaluated the effect of concurrent therapy with Ferriprox and deferoxamine in patients with thalassaemia major, who previously received the standard chelation monotherapy with subcutaneous deferoxamine and had mild to moderate cardiac iron loading (myocardial T2* from 8 to 20 ms). Following randomization, 32 patients received deferoxamine (43.4 mg/kg/day for 5 days/week) and Ferriprox (75 mg/kg/day) and 33 patients received deferoxamine monotherapy (34.9 mg/kg/day for 5 days/week). After one year of study therapy, patients on concurrent chelation therapy had experienced a significantly greater reduction in serum ferritin (1574 $\mu\text{g/l}$ to 598 $\mu\text{g/l}$ with concurrent therapy vs. 1379 $\mu\text{g/l}$ to 1146 $\mu\text{g/l}$ 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 msec (95% one-sided UCL: 5.01 msec), and between the LS means of the supratherapeutic dose and placebo was 5.23 msec (95% one-sided UCL: 7.19 msec). 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 $\mu\text{mol/l}$) than in the fasting state (126 $\mu\text{mol/l}$), 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.

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 WBC, 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 vivo* 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
Hydrochloric acid, concentrated
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°C. 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

Apotex Europe B.V.
Darwinweg 20
2333 CR Leiden
Netherlands

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: 25 August 2009

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Apotex Nederland B.V.
Bio Science Park
Archimedesweg 2
2333 CN Leiden
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

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

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

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

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE OF 100 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Ferriprox 500 mg film-coated tablets
deferiprone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One tablet contains 500 mg deferiprone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.
Darwinweg 20
2333 CR Leiden
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/108/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ferriprox 500 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLES OF 250 ML AND 500 ML ORAL SOLUTION

1. NAME OF THE MEDICINAL PRODUCT

Ferriprox 100 mg/ml oral solution
Deferiprone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains Sunset Yellow (E110); see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

250 ml oral solution
500 ml oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening use within 35 days.

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.
Darwinweg 20
2333 CR Leiden
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ferriprox 100 mg/ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE OF 50 TABLETS
BOTTLE OF 100 TABLETS
BLISTER PACKS OF 50 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Ferriprox 1000 mg film-coated tablets
deferiprone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One tablet contains 1000 mg deferiprone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

50 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

For the bottle: After first opening use within 50 days.

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

For the bottle: Keep the bottle tightly closed in order to protect from moisture.

For the blister: Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Apotex Europe B.V.
Darwinweg 20
2333 CR Leiden
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/108/004	bottle of 50 film-coated tablets
EU/1/99/108/005	bottle of 100 film-coated tablets
EU/1/99/108/006	blisters, package of 50 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Ferriprox 1000 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Ferriprox 1000 mg film-coated tablets
deferiprone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Ferriprox 500 mg film-coated tablets

Deferiprone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- Attached to this leaflet you will find a patient/carer reminder card. You should detach, complete, read the card carefully and carry it with you.

What is in this leaflet

1. What Ferriprox is and what it is used for
2. What you need to know before you take Ferriprox
3. How to take Ferriprox
4. Possible side effects
5. How to store Ferriprox
6. Contents of the pack and other information

1. What Ferriprox is and what it is used for

Ferriprox contains the active substance deferiprone. Ferriprox is a medicine that removes iron from the body.

Ferriprox is used to treat iron overload caused by frequent blood transfusions in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate.

2. What you need to know before you take Ferriprox

Do not take Ferriprox

- if you are allergic to deferiprone or any of the other ingredients of this medicine (listed in section 6).
- if you have a history of repeated episodes of neutropenia (low white blood cell (neutrophil) count).
- if you have a history of agranulocytosis (very low white blood cell (neutrophil) count).
- if you are currently taking medicines known to cause neutropenia or agranulocytosis (see “Other medicines and Ferriprox”).
- if you are pregnant or breast-feeding.

Warnings and precautions

- the most serious side effect that may occur while taking Ferriprox is a very low white blood cell (neutrophil) count. This condition, known as severe neutropenia or agranulocytosis, has occurred in 1 to 2 out of 100 people who have taken Ferriprox in clinical studies. Because white blood cells help to fight infection, a low neutrophil count may place you at risk of developing a serious and potentially life-threatening infection. To monitor for neutropenia, your doctor will ask you to have a blood test (to check your white blood cell count) performed regularly, as frequently as every week, while you are being treated with Ferriprox. It is very important for you to keep all of these appointments. Please refer to the patient/carer reminder card attached to this leaflet. Report immediately to your doctor any symptoms of infection such as fever, sore throat or flu-like symptoms.

- if you are HIV positive or if your kidney or liver function is impaired, your doctor may recommend additional tests.

Your doctor will also ask you to come in for tests to monitor body iron load. In addition he or she might ask you to undergo liver biopsies.

Other medicines and Ferriprox

Do not take medicines known to cause neutropenia or agranulocytosis (see “Do not take Ferriprox”). Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines, including medicines obtained without a prescription.

Do not take aluminium-based antacids while taking Ferriprox.

Please consult with your doctor or pharmacist before taking vitamin C with Ferriprox.

Pregnancy and breast-feeding

Do not take this medicine if you are pregnant or if you are trying to become pregnant. This medicine could seriously harm your baby. You must use effective contraception while you are taking Ferriprox. Ask your doctor which method is best for you. If you become pregnant while taking Ferriprox, stop taking the medicine immediately and tell your doctor.

Do not use Ferriprox if you are breast-feeding. Please refer to the patient/carer reminder card attached to this leaflet.

Driving and using machines

Not relevant.

3. How to take Ferriprox

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. The amount of Ferriprox that you take will depend on your weight. The usual dose is 25 mg/kg, 3 times per day, for a total daily dose of 75 mg/kg. The total daily dose should not exceed 100 mg/kg. Take your first dose in the morning. Take your second dose midday. Take your third dose in the evening. Ferriprox can be taken with or without food; however, you may find it easier to remember to take Ferriprox if you take it with your meals.

If you take more Ferriprox than you should

There are no reports of acute overdose with Ferriprox. If you have accidentally taken more than the prescribed dose, you should contact your doctor.

If you forget to take Ferriprox

Ferriprox will be most effective if you do not miss any doses. If you do miss one dose take it as soon as you remember and take your next dose at its regularly scheduled time. If you miss more than one dose do not take a double dose to make up for forgotten individual doses, just continue with your normal schedule. Do not change your daily dose without first talking to your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most serious side effect of Ferriprox is a very low white blood cell (neutrophil) count. This condition, known as severe neutropenia or agranulocytosis, has occurred in 1 to 2 out of 100 people who have taken Ferriprox in clinical studies. A low white blood cell count can be associated with a serious and potentially life-threatening infection. Report immediately to your doctor any symptoms of infection such as: fever, sore throat or flu-like symptoms.

Very common side effects (may affect more than 1 in 10 people):

- abdominal pain
- nausea
- vomiting
- reddish/brown discolouration of urine

If you experience nausea or vomiting, it may help to take your Ferriprox with some food. Discoloured urine is a very common effect and is not harmful.

Common side effects (may affect up to 1 in 10 people):

- low white blood cell count (agranulocytosis and neutropenia)
- headache
- diarrhoea
- increase in liver enzymes
- fatigue
- increase in appetite

Not known (frequency cannot be estimated from the available data):

- allergic reactions including skin rash or hives

Events of joint pain and swelling ranged from mild pain in one or more joints to severe disability. In most cases, the pain disappeared while patients continued taking Ferriprox.

Neurological disorders (such as tremors, walking disorders, double vision, involuntary muscle contractions, problems with movement coordination) have been reported in children who had been voluntarily prescribed more than double the maximum recommended dose of 100 mg/kg/day for several years and have also been observed in children with standard doses of deferiprone. The children recovered from these symptoms after Ferriprox discontinuation.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ferriprox

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the label after EXP.

Do not store above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ferriprox contains

The active substance is deferiprone. Each tablet contains 500 mg deferiprone.

The other ingredients are:

Tablet core: Microcrystalline cellulose, Magnesium stearate, Colloidal silicon dioxide.

Coating: Hypromellose, Macrogol, Titanium dioxide.

What Ferriprox looks like and contents of the pack

Ferriprox tablets are white to off-white, capsule-shaped, film-coated tablets imprinted “APO” bisect “500” on one side, plain on the other. The tablets are scored and breakable in half. Ferriprox is packaged in bottles of 100 tablets.

Marketing Authorisation Holder and Manufacturer

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Darwinweg 20
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Manufacturing Authorisation Holder: Apotex Nederland B.V.
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Archimedesweg 2
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in .

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

Package leaflet: Information for the user

Ferriprox 100 mg/ml oral solution Deferiprone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- Attached to this leaflet you will find a patient/carer reminder card. You should detach, complete, read the card carefully and carry it with you.

What is in this leaflet

1. What Ferriprox is and what it is used for
2. What you need to know before you take Ferriprox
3. How to take Ferriprox
4. Possible side effects
5. How to store Ferriprox
6. Contents of the pack and other information

1. What Ferriprox is and what it is used for

Ferriprox contains the active substance deferiprone. Ferriprox is a medicine that removes iron from the body.

Ferriprox is used to treat iron overload caused by frequent blood transfusions in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate.

2. What you need to know before you take Ferriprox

Do not take Ferriprox

- if you are allergic to deferiprone or any of the other ingredients of this medicine (listed in section 6).
- if you have a history of repeated episodes of neutropenia (low white blood cell (neutrophil) count).
- if you have a history of agranulocytosis (very low white blood cell (neutrophil) count).
- if you are currently taking medicines known to cause neutropenia or agranulocytosis (see “Other medicines and Ferriprox”).
- if you are pregnant or breast-feeding.

Warnings and precautions

- the most serious side effect that may occur while taking Ferriprox is a very low white blood cell (neutrophil) count. This condition, known as severe neutropenia or agranulocytosis, has occurred in 1 to 2 out of 100 people who have taken Ferriprox in clinical studies. Because white blood cells help to fight infection, a low neutrophil count may place you at risk of developing a serious and potentially life-threatening infection. To monitor for neutropenia, your doctor will ask you to have a blood test (to check your white blood cell count) performed regularly, as frequently as every week, while you are being treated with Ferriprox. It is very important for you to keep all of these appointments. Please refer to the patient/carer reminder card attached to this leaflet. Report immediately to your doctor any symptoms of infection such as fever, sore throat or flu-like symptoms.

- if you are HIV positive or if your kidney or liver function is impaired, your doctor may recommend additional tests.

Your doctor will also ask you to come in for tests to monitor body iron load. In addition he or she might ask you to undergo liver biopsies.

Other medicines and Ferriprox

Do not take medicines known to cause neutropenia or agranulocytosis (see “Do not take Ferriprox”). Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines, including medicines obtained without a prescription.

Do not take aluminium-based antacids while taking Ferriprox.

Please consult with your doctor or pharmacist before taking vitamin C with Ferriprox.

Pregnancy and breast-feeding

Do not take this medicine if you are pregnant or if you are trying to become pregnant. This medicine could seriously harm your baby. You must use effective contraception while you are taking Ferriprox. Ask your doctor which method is best for you. If you become pregnant while taking Ferriprox, stop taking the medicine immediately and tell your doctor.

Do not use Ferriprox if you are breast-feeding. Please refer to the patient/carer reminder card attached to this leaflet.

Driving and using machines

Not relevant.

Ferriprox oral solution contains Sunset Yellow (E110)

Sunset Yellow (E110) is a colouring agent which may cause allergic reactions.

3. How to take Ferriprox

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. The amount of Ferriprox that you take will depend on your weight. The usual dose is 25 mg/kg, 3 times per day, for a total daily dose of 75 mg/kg. The total daily dose should not exceed 100 mg/kg. Use the measuring cup to measure the volume prescribed by your doctor. Take your first dose in the morning. Take your second dose midday. Take your third dose in the evening. Ferriprox can be taken with or without food however, you may find it easier to remember to take Ferriprox if you take it with your meals.

If you take more Ferriprox than you should

There are no reports of acute overdose with Ferriprox. If you have accidentally taken more than the prescribed dose, you should contact your doctor.

If you forget to take Ferriprox

Ferriprox will be most effective if you do not miss any doses. If you do miss one dose take it as soon as you remember and take your next dose at its regularly scheduled time. If you miss more than one dose do not take a double dose to make up for forgotten individual doses, just continue with your normal schedule. Do not change your daily dose without first talking to your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most serious side effect of Ferriprox is a very low white blood cell (neutrophil) count. This condition, known as severe neutropenia or agranulocytosis, has occurred in 1 to 2 out of 100 people who have taken Ferriprox in clinical studies. A low white blood cell count can be associated with a serious and potentially life-threatening infection. Report immediately to your doctor any symptoms of infection such as: fever, sore throat or flu-like symptoms.

Very common side effects (may affect more than 1 in 10 people):

- abdominal pain
- nausea
- vomiting
- reddish/brown discolouration of urine

If you experience nausea or vomiting, it may help to take your Ferriprox with some food. Discoloured urine is a very common effect and is not harmful.

Common side effects (may affect up to 1 in 10 people):

- low white blood cell count (agranulocytosis and neutropenia)
- headache
- diarrhoea
- increase in liver enzymes
- fatigue
- increase in appetite

Not known (frequency cannot be estimated from the available data):

- allergic reactions including skin rash or hives

Events of joint pain and swelling ranged from mild pain in one or more joints to severe disability. In most cases, the pain disappeared while patients continued taking Ferriprox.

Neurological disorders (such as tremors, walking disorders, double vision, involuntary muscle contractions, problems with movement coordination) have been reported in children who had been voluntarily prescribed more than double the maximum recommended dose of 100 mg/kg/day for several years and have also been observed in children with standard doses of deferiprone. The children recovered from these symptoms after Ferriprox discontinuation.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ferriprox

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the label after EXP.

After first opening use within 35 days. Do not store above 30°C. Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ferriprox contains

The active substance is deferiprone. Each ml of oral solution contains 100 mg deferiprone.

The other ingredients are: purified water; hydroxyethylcellulose; glycerol; hydrochloric acid, concentrated; artificial cherry flavour; peppermint oil; Sunset Yellow (E110); sucralose (E955).

What Ferriprox looks like and contents of the pack

Ferriprox oral solution is a clear, reddish orange coloured liquid. It is packaged in bottles of 250 ml or 500 ml.

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Manufacturing Authorisation Holder : Apotex Nederland B.V.
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in .

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

Package leaflet: Information for the user

Ferriprox 1000 mg film-coated tablets Deferiprone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- Attached to this leaflet you will find a patient/carer reminder card. You should detach, complete, read the card carefully and carry it with you.

What is in this leaflet:

1. What Ferriprox is and what it is used for
2. What you need to know before you take Ferriprox
3. How to take Ferriprox
4. Possible side effects
5. How to store Ferriprox
6. Contents of the pack and other information

1. What Ferriprox is and what it is used for

Ferriprox contains the active substance deferiprone. Ferriprox is a medicine that removes iron from the body.

Ferriprox is used to treat iron overload caused by frequent blood transfusions in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate.

2. What you need to know before you take Ferriprox

Do not take Ferriprox

- if you are allergic to deferiprone or any of the other ingredients of this medicine (listed in section 6).
- if you have a history of repeated episodes of neutropenia (low white blood cell (neutrophil) count).
- if you have a history of agranulocytosis (very low white blood cell (neutrophil) count).
- if you are currently taking medicines known to cause neutropenia or agranulocytosis (see “Other medicines and Ferriprox”).
- if you are pregnant or breast-feeding.

Warnings and precautions

- the most serious side effect that may occur while taking Ferriprox is a very low white blood cell (neutrophil) count. This condition, known as severe neutropenia or agranulocytosis, has occurred in 1 to 2 out of 100 people who have taken Ferriprox in clinical studies. Because white blood cells help to fight infection, a low neutrophil count may place you at risk of developing a serious and potentially life-threatening infection. To monitor for neutropenia, your doctor will ask you to have a blood test (to check your white blood cell count) performed regularly, as frequently as every week, while you are being treated with Ferriprox. It is very important for you to keep all of these appointments. Please refer to the patient/carer reminder card attached to

- this leaflet. Report immediately to your doctor any symptoms of infection such as fever, sore throat or flu-like symptoms.
- if you are HIV positive or if your kidney or liver function is impaired, your doctor may recommend additional tests.

Your doctor will also ask you to come in for tests to monitor body iron load. In addition he or she might ask you to undergo liver biopsies.

Other medicines and Ferriprox

Do not take medicines known to cause neutropenia or agranulocytosis (see “Do not take Ferriprox”). Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines, including medicines obtained without a prescription.

Do not take aluminium-based antacids while taking Ferriprox.

Please consult with your doctor or pharmacist before taking vitamin C with Ferriprox.

Pregnancy and breast-feeding

Do not take this medicine if you are pregnant or if you are trying to become pregnant. This medicine could seriously harm your baby. You must use effective contraception while you are taking Ferriprox. Ask your doctor which method is best for you. If you become pregnant while taking Ferriprox, stop taking the medicine immediately and tell your doctor.

Do not use Ferriprox if you are breast-feeding. Please refer to the patient/carer reminder card attached to this leaflet.

Driving and using machines

Not relevant.

3. How to take Ferriprox

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. The amount of Ferriprox that you take will depend on your weight. The usual dose is 25 mg/kg, 3 times per day, for a total daily dose of 75 mg/kg. The total daily dose should not exceed 100 mg/kg. Take your first dose in the morning. Take your second dose midday. Take your third dose in the evening. Ferriprox can be taken with or without food; however, you may find it easier to remember to take Ferriprox if you take it with your meals.

If you take more Ferriprox than you should

There are no reports of acute overdose with Ferriprox. If you have accidentally taken more than the prescribed dose, you should contact your doctor.

If you forget to take Ferriprox

Ferriprox will be most effective if you do not miss any doses. If you do miss one dose take it as soon as you remember and take your next dose at its regularly scheduled time. If you miss more than one dose do not take a double dose to make up for forgotten individual doses, just continue with your normal schedule. Do not change your daily dose without first talking to your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most serious side effect of Ferriprox is a very low white blood cell (neutrophil) count. This condition, known as severe neutropenia or agranulocytosis, has occurred in 1 to 2 out of 100 people who have taken Ferriprox in clinical studies. A low white blood cell count can be associated with a

serious and potentially life-threatening infection. Report immediately to your doctor any symptoms of infection such as: fever, sore throat or flu-like symptoms.

Very common side effects (may affect more than 1 in 10 people):

- abdominal pain
- nausea
- vomiting
- reddish/brown discolouration of urine

If you experience nausea or vomiting, it may help to take your Ferriprox with some food. Discoloured urine is a very common effect and is not harmful.

Common side effects (may affect up to 1 in 10 people):

- low white blood cell count (agranulocytosis and neutropenia)
- headache
- diarrhoea
- increase in liver enzymes
- fatigue
- increase in appetite

Not known (frequency cannot be estimated from the available data):

- allergic reactions including skin rash or hives

Events of joint pain and swelling ranged from mild pain in one or more joints to severe disability. In most cases, the pain disappeared while patients continued taking Ferriprox.

Neurological disorders (such as tremors, walking disorders, double vision, involuntary muscle contractions, problems with movement coordination) have been reported in children who had been voluntarily prescribed more than double the maximum recommended dose of 100 mg/kg/day for several years and have also been observed in children with standard doses of deferiprone. The children recovered from these symptoms after Ferriprox discontinuation.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ferriprox

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the label after EXP.

Do not store above 30°C.

For the bottle: Keep the bottle tightly closed in order to protect from moisture. After first opening use within 50 days.

For the blister: Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ferriprox contains

The active substance is deferiprone. Each 1000 mg tablet contains 1000 mg deferiprone.

The other ingredients are:

Tablet core: Methylcellulose, crospovidone, magnesium stearate.

Coating: Hypromellose, hydroxypropyl cellulose, macrogol, titanium dioxide.

What Ferriprox looks like and contents of the pack

Ferriprox 1000 mg tablets are white to off-white, capsule-shaped, film-coated tablets imprinted “APO” bisect “1000” on one side, plain on the other. The tablets are scored and breakable in half. Ferriprox is packaged in bottles of 50 tablets, bottles of 100 tablets, and blister packs of 50 tablets.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Apotex Europe B.V.
Darwinweg 20
2333 CR Leiden
Netherlands

Manufacturing Authorisation Holder: Apotex Nederland B.V.
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Archimedesweg 2
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

PATIENT/CARER REMINDER CARD

<p>((Front Cover))</p> <p>Important Safety Reminders for Patients taking Ferriprox (deferiprone)</p> <p>Prescribing doctor: _____</p> <p>Phone No: _____</p>	<p>((Back Cover))</p> <p>FOR WOMEN OF CHILD BEARING AGE</p> <p>Do not take Ferriprox if you are pregnant or if you are trying to become pregnant. If taken during pregnancy, Ferriprox may seriously harm the unborn baby.</p> <p>You must use effective contraception while you are taking Ferriprox. Ask your doctor which method is best for you. If you become pregnant while taking Ferriprox, stop taking the medicine immediately and tell your doctor. Do not take Ferriprox if you are breast-feeding.</p>
<p>((Inside 1))</p> <p>MONITORING YOUR WHITE BLOOD CELL COUNT WITH FERRIPROX</p> <p>There is a small chance that you may develop agranulocytosis (very low white blood cell count) while taking Ferriprox, which may lead to a serious infection. Even though agranulocytosis only affects 1 to 2 out of 100 users, it is important to monitor your blood on a regular basis.</p>	<p>((Inside 2))</p> <p>Make sure you do the following:</p> <ol style="list-style-type: none">1. Have your blood monitored on a weekly basis.2. Contact your doctor immediately if you develop a fever, sore throat or flu like symptoms

ANNEX IV

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS
OF THE MARKETING AUTHORISATION(S)**

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for deferiprone, the scientific conclusions of the CHMP are as follows:

During the review period of this PSUR (01/09/2015 - 31/08/2016), one relevant case has led to vary the terms of the MA:

Neurological disorders

A relevant case of neurological disorders in the literature (Economou M and al, 2016¹) has been identified: it concerns a 9 year-old girl with transfusion-dependent thalassaemia experiencing myalgia, arthralgia, behavioural changes, anxiety, hypotonia, inability to walk, hypertonia, dysthymia and loss of appetite during treatment with deferiprone. This girl had been receiving deferiprone at 75 mg/kg/day since the age of 7 years. Concomitantly, she received deferoxamine. The patient recovered after deferiprone discontinuation. She was symptom-free within 7 months under deferoxamine. When deferiprone was restarted due to serum ferritin (SF) increase, hypertonia and walking disability reoccurred within a few weeks. Her condition improved after permanent deferiprone discontinuation. Based on this relevant case and considering that this issue had already been closely monitored since the previous PSUR, an update of the product information has been recommended, adding a statement on the risk of “neurological disorders at recommended doses in children” under the recommended dose in sections 4.4 and 4.8 of the SmPC. The PL was updated accordingly.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considered that changes to the product information of medicinal products containing deferiprone were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for deferiprone the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing deferiprone is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation(s) should be varied.

¹ Economou M, et al. Neurological involvement in a thalassaemic child receiving deferiprone. Journal of Pediatric Hematology/Oncology 38: 406, No. 5, Jul 2016.