1. NAME OF THE MEDICINAL PRODUCT

Ferriprox Tablets 500 mg
Ferriprox Tablets 1000 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ferriprox Tablets 500 mg
Each tablet contains 500 mg deferiprone.

Ferriprox Tablets 1000 mg
Each tablet contains 1000 mg deferiprone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Ferriprox Tablets 500 mg
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 Tablets 1000 mg
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 is indicated for the treatment of iron overload in patients over 6 years old with thalassaemia major in whom deferoxamine therapy is contraindicated or inadequate.

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 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 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 Tablets 500 mg

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 Tablets 1000 mg

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 deferiprone should be considered if serum ferritin falls below 500 μg/l.

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

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

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

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

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

Treatment with deferiprone should not be initiated if the patient is neutropenic. The risk of agranulocytosis and neutropenia is higher if the baseline ANC is less than $1.5x10^9$/l.

For neutropenia events (ANC < $1.5x10^9$/l and > $0.5x10^9$/l):
Instruct the patient to immediately discontinue deferiprone and all other medicinal products with a potential to cause neutropenia. The patient should be advised to limit contact with other individuals in order to reduce the risk of infection. Obtain a complete blood cell (CBC) count, with a white blood cell

(WBC) count, corrected for the presence of nucleated red blood cells, a neutrophil count, and a platelet count immediately upon diagnosing the event and then repeat daily. It is recommended that following recovery from neutropenia, weekly CBC, WBC, neutrophil and platelet counts continue to be obtained for three consecutive weeks, to ensure that the patient 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.

For agranulocytosis (ANC < $0.5x10^9$/l):
Follow the guidelines above and administer appropriate therapy such as granulocyte colony stimulating factor, beginning the same day that the event is identified; administer daily until the condition resolves. Provide protective isolation and if clinically indicated, admit patient to the hospital.

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

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

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

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

Renal or hepatic impairment and liver fibrosis
There are no data available on the use of deferiprone in patients with 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 these patient populations during deferiprone therapy. If there is a persistent increase in serum alanine aminotransferase (ALT), interruption of deferiprone therapy should be considered.

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

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).

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

No studies on the effects on the ability to drive and use machines have been performed.

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 0.5×10^9/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 (≥1/10), Common (≥1/100 to <1/10), not known (cannot be estimated from the available data).

SYSTEM ORGAN CLASS	**VERY COMMON (≥1/10)**	**COMMON (≥1/100 to <1/10)**	**FREQUENCY NOT KNOWN**
Blood and lymphatic system disorders		Neutropenia Agranulocytosis	
Immune system disorders			Hypersensitivity reactions
Metabolism and nutrition disorders		Increased Appetite	
Nervous system disorders		Headache	
Gastrointestinal disorders	Nausea Abdominal Pain Vomiting	Diarrhoea	
Skin and subcutaneous tissue disorders			Rash Urticaria
Musculoskeletal and connective tissue disorders		Arthralgia	
Renal and urinary disorders	Chromaturia		
General disorders and administration site conditions		Fatigue	
Investigations		Increased liver enzymes	

Description of selected adverse reactions

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

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

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

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

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

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

Neurological disorders (such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, hand movements and axial hypotonia) have been observed in children who had been voluntarily prescribed more than 2.5 times the maximum recommended dose of 100 mg/kg/day for several years. Episodes of hypotonia, instability, inability to walk, and hypertonia with inability of limb movement, have been reported in children in the post-marketing setting with standard doses of deferiprone. The neurological disorders progressively regressed after deferiprone discontinuation (see sections 4.4 and 4.9).

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

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 Ferriproxis 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. 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 thalassemia 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 ms represent iron overload in the heart. An increase in MRI T2* on treatment indicates that iron is being removed from the heart. A positive correlation between MRI T2* values and cardiac function (as measured by Left Ventricular Ejection Fraction (LVEF)) has been documented.

Study LA16-0102 compared the efficacy of Ferriprox with that of deferoxamine in decreasing cardiac iron overload and in improving cardiac function (as measured by LVEF) in transfusion-dependent thalassemia 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 ms in patients treated with Ferriprox compared with a change of about 1 ms in patients treated with deferoxamine. At the same time point, LVEF had increased from baseline by 3.07 ± 3.58 absolute units (%) in the Ferriprox group and by 0.32 ± 3.38 absolute units (%) in the deferoxamine group (difference between groups; $p=0.003$).

Study LA12-9907 compared survival, incidence of cardiac disease, and progression of cardiac disease in 129 patients with thalassemia 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.

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

5.2 Pharmacokinetic properties

Absorption
Deferiprone is rapidly absorbed from the upper part of the gastrointestinal tract. Peak serum concentration occurs 45 to 60 minutes following a single dose in fasted patients. This may be extended to 2 hours in fed patients.

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

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

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

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 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 Tablets 500 mg
Tablet core
Microcrystalline cellulose
Magnesium stearate
Colloidal silicon dioxide

Coating
Hydroxypropyl methylcellulose
Polyethylene glycol
Titanium dioxide
Purified water

Ferriprox Tablets 1000 mg
Tablet core
Methylcellulose A15LV
Crospovidone
Magnesium stearate vegetable sourrce

Coating
Hydroxyproyl methylcellulose 2910E5
Hydroxypropyl cellulose (LF)
Polyethylene Glycol 8000
Titanium Dioxide
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Ferriprox Tablets 500 mg
After first opening use within 100 days.

Ferriprox Tablets 1000 mg
After first opening use within 50 days.

6.4 Special precautions for storage

Ferriprox Tablets 500 mg
Do not store above 30ºC.

Ferriprox Tablets 1000 mg
Do not store above 30ºC.
Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Ferriprox Tablets 500 mg
High density polyethylene (HDPE) bottle with a child resistant polypropylene cap.
Pack size of 100 tablets.

Ferriprox Tablets 1000 mg
High density polyethylene (HDPE) bottle with a child resistant polypropylene cap and a desiccant.
Pack size of 50 tablets.

6.6 Special precautions for disposa

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

7. MANUFACTURER:

Apotex Inc., Canada
50 Steinway Boulevard, Etobicoke, Ontario M9W 6Y3,
Canada

8. LICENSE HOLDER AND IT'S ADDRESS:

Lapidot Medical Import and Markeeting Ltd.,
8 Hashita St., Industrial Zone Caesarea 3088900

9. REGISTRATION NUMBER:

Ferriprox Tablets 500 mg: 139-68-31585-00
Ferriprox Tablets 1000 mg: 163-83-35170-00

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