SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ferriprox 100 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral solution contains 100 mg deferiprone.

Excipient:
Each ml of oral solution contains 0.4 mg Sunset Yellow (E110).
For a 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 is indicated for the treatment of iron overload in patients with thalassaemia major when deferoxamine therapy is contraindicated or inadequate.

4.2 Posology and method of administration

For oral use.

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

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.

Doses above 100 mg/kg/day are not recommended because of the potentially increased risk of adverse reactions; chronic administration of more than 2.5 times the maximum recommended dose has been associated with neurological disorders (see sections 4.4, 4.8, and 4.9).

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.

Due to the serious nature of agranulocytosis, that can occur with the use of deferiprone, special monitoring is required for all patients. Caution must be used when the patients' absolute neutrophil count (ANC) is low, as well as when treating patients with renal insufficiency or hepatic dysfunction. (see section 4.4).

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

History of recurrent episodes of neutropenia.

History of agranulocytosis.

Pregnancy or 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 $1.5x10^9$/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, a rechallenge is contraindicated.

Carcinogenicity/mutagenicity/effects on fertility
In view of the genotoxicity results, a carcinogenic potential of deferiprone cannot be excluded (see section 5.3). No animal studies to evaluate the potential effects of deferiprone on fertility have been reported.

Serum ferritin concentration/plasma Zn^{2+} concentration
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. Interruption of therapy with deferiprone should be considered if serum ferritin measurements fall below 500 µg/l.

Monitoring of plasma Zn^{2+} 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.

Chronic overdose and neurological disorders
Neurological disorders have been observed in children treated with 2.5 to 3 times the recommended dose for several years. Prescribers are reminded that the use of doses above 100 mg/kg/day are not recommended (see sections 4.2, 4.8 and 4.9).

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

Interactions between deferiprone and other medicinal products have not been reported. However, 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.

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).

4.6 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 counselled 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).

Lactation
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.

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

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). 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 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. The neurological disorders progressively regressed after deferiprone discontinuation (see sections 4.2, 4.4 and 4.9).

Adverse reaction frequencies: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100).

SYSTEM ORGAN CLASS	VERY COMMON (≥1/10)	COMMON (≥1/100 to <1/10)	UNCOMMON (≥1/1,000 to <1/100)
Investigations		Increased liver enzymes	
Blood and lymphatic system disorders		Neutropenia Agranulocytosis	
Nervous system disorders		Headache	
Gastrointestinal disorders	Nausea Abdominal Pain Vomiting	Diarrhoea	
Renal and urinary disorders	Chromaturia		
Musculoskeletal and connective tissue disorders		Arthralgia	
Metabolism and nutrition disorders		Increased Appetite	
General disorders and administration site conditions		Fatigue	

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

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.

Clinical studies have demonstrated that deferiprone 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. However, chelation therapy may not necessarily protect against iron-induced organ damage.

Deferiprone has been investigated in 247 patients in two phase III trials and a compassionate use programme. Serum ferritin was chosen as the primary efficacy criterion in the studies. In one study of two-year duration deferiprone was compared to deferoxamine. The mean serum ferritin levels were not significantly different in the two treatment groups, but mean hepatic iron concentration in deferiprone treated patients seems to increase more than in deferoxamine treated patients. Therefore deferiprone at the recommended dose could be less effective than deferoxamine.

The other study was a supportive open, non-comparative study. In this study patients maintained serum ferritin values at pre-study levels. The primary end-point was the incidence of agranulocytosis, which occurred at a frequency of 1.2%.

5.2 Pharmacokinetic properties

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

Following a dose of 25 mg/kg, lower peak serum concentrations have been detected in patients in the fed state (85 µmol/l) than in the fasting state (126 µmol/l), although there was no decrease in the amount of 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 rats and rabbits at doses at least as low as 25 mg/kg/day. 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

No special requirements

7. MARKETING AUTHORISATION HOLDER

Apotex Inc., 150 Signet Drive, Toronto, Ontario, Canada, M9L 1T9

8. MARKETING AUTHORISATION NUMBER

1C 116/52 (NC)

9. DATE OF REVISION OF THE TEXT

August 30, 2013

PATIENT INFORMATION LEAFLET

Ferriprox® Oral Solution

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicinal product has been prescribed for you personally. Never give it to anyone else. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What Ferriprox is and what it is used for
2. Before you take Ferriprox
3. How to take Ferriprox
4. Possible side effects
5. Storing Ferriprox

Ferriprox 100 mg/mL oral solution
Deferiprone

The active substance is deferiprone 100 mg/mL of oral solution.

The other ingredients are:
Purified water; Hydroxyethylcellulose; Glycerol; Hydrochloric acid, concentrated; Artificial cherry flavour; Peppermint oil; Sunset Yellow (E110); Sucralose (E955)

1. WHAT FERRIPROX IS AND WHAT IT IS USED FOR

Deferiprone is a medicine that removes iron from the body.

Ferriprox oral solution is a clear, reddish orange coloured liquid. It is packaged in bottles of 250 mL or 500 mL. Not all pack sizes are marketed.

Ferriprox is indicated for the treatment of iron overload in patients with thalassemia major when deferoxamine therapy is contra-indicated or inadequate.

Pharmacotherapeutic group: Iron Chelator, ATC code: V03AC02

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. 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 transfusion-dependent thalassemia patients.

Deferiprone is rapidly absorbed from the upper part of the gastro-intestinal tract. Peak serum concentration is reported to occur 45 to 60 minutes following a single dose in fasted patients. This may be extended to 2 hours in fed patients. Deferiprone is metabolised predominantly to a glucuronide conjugate. This metabolite lacks iron-binding capacity due to inactivation of the 3-hydroxy group of deferiprone. In humans, deferiprone is eliminated mainly via the kidneys with reports of 75% to 90% of the ingested dose being recovered in the urine in the first 24 hours, in the form of free deferiprone, the glucuronide metabolite and the iron-deferiprone complex.

2. BEFORE YOU TAKE FERRIPROX

Ferriprox is unable to be taken if:
- you have a history of hypersensitivity (an allergy) to the active substance or any of the other ingredients (see above)
- you have a history of repeated episodes of neutropenia (low white blood cell count)

- you have a history of agranulocytosis (very low white blood cell count < 0.5 x 10^9/L)
- you are currently taking medication known to cause neutropenia
- you are pregnant or breast-feeding

The way deferiprone causes neutropenia is not known. Patients should not take medicinal products known to be associated with neutropenia or those which can cause agranulocytosis.

Special warnings for taking Ferriprox:
The most serious undesirable effect of deferiprone is the occurrence of a very low white blood cell count. This condition, known as severe neutropenia or agranulocytosis, has occurred in about 1 out of 100 patients who have taken deferiprone in clinical studies. Because white blood cells help to fight infection, a low white blood cell count may place you at risk to develop a serious infection. If an infection of this nature is not discovered and treated early, it could cause death. Your doctor will ask you to have a blood test (to check your white blood cell count) performed regularly, as frequently as every week. It is very important for you to keep all of these appointments. Report immediately to your doctor any symptoms of infection such as: fever, sore throat or flu-like symptoms.

Your doctor may monitor your serum ALT level at regular intervals during therapy with Ferriprox, and interruption of therapy may be considered if a persistent increase in serum ALT levels occurs.

Ferriprox should be prescribed by a Hematologist, Pediatrician or other Medical Physician.

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

Patients with iron overload are at increased risk of cancer. In these circumstances, the impact of deferiprone is not known.

The positive and negative effects of iron chelation can only be demonstrated after many years. Therefore, further studies are ongoing. In addition, cancer-predicting studies are underway.

Use during pregnancy and breast-feeding:
Do not take this medication if you are breast-feeding, if you are pregnant, or if you are trying to become pregnant. This medication 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.

Driving and using machines:
There is no evidence that Ferriprox affects your ability to drive or use machinery.

Taking Ferriprox with other products:
Tell your doctor about all other medications that you are taking, even ones that you can buy without a prescription. Your doctor can tell you which medications you can safely take with Ferriprox.

Since this compound binds to metallic cations, the potential exists for interactions between deferiprone and trivalent cation-dependent medicinal products such as aluminium-based antacids.

Based on the reported adverse interaction that can occur between deferoxamine and vitamin C, caution should be used when administering concurrent deferiprone and vitamin C.

Do not take medications known to cause neutropenia (see above).

Important information about some of the ingredients of Ferriprox:
Ferriprox oral solution contains Sunset Yellow (E110) which may cause allergic reactions.

3. HOW TO TAKE FERRIPROX

It is important to follow the directions that your doctor has given to you. The amount of deferiprone that you take will depend on your weight. Ferriprox is usually prescribed as 25 mg/kg body weight, calculated to the nearest 2.5 mL, to be taken three (3) times per day for a total daily dose of 75 mg/kg body weight. Take your first dose in the morning. Take your second dose midday. Take your third dose in the evening. It is not necessary to take Ferriprox with food. However, you may find it easier to remember to take your medication, if you take it with your meals. 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 the missed dose, just continue with your normal schedule. Do not change your daily dose without first consulting with your doctor.

Very limited data are available on Ferriprox use in children under 6 years of age; therefore, the use of Ferriprox in this group should not be recommended unless the potential benefits outweigh the potential risks.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, deferiprone can have side effects.

The most serious undesirable effect of deferiprone is the occurrence of a very low white blood cell count. This condition, known as severe neutropenia or agranulocytosis, has occurred in about 1 out of 100 patients who have taken deferiprone in clinical studies. A low white blood cell count can also 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.

Some of the patients enrolled in clinical studies with deferiprone developed joint pain and swelling. In most patients, the pain disappeared while still taking Ferriprox.

Some patients treated with Ferriprox have experienced some or all of the following symptoms: increase in liver enzymes, abdominal pain, nausea, vomiting, diarrhea, increase in appetite, headache and fatigue. Most patients find that these undesirable effects disappear after a few days to a few weeks of continued treatment. If you experience nausea or vomiting, it may help to take your Ferriprox with some food.

Your urine may become reddish/brown in colour. This is the most common undesirable effect of deferiprone and it is not harmful.

In post-marketing experience with 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. They recovered from these symptoms after Ferriprox discontinuation.

If you notice any side effects, please inform your doctor, pharmacist or the local distributing company immediately, who will in turn communicate it to the Medical Information Division at Apotex (Canada) by calling: +1 (416) 401-7780.

5. STORING FERRIPROX

Do not store above 30°C.
Do not use Ferriprox after the expiry date stated on the container.
Store in the original package in order to protect from light.
After first opening use within 35 days.
Keep out of the reach and sight of children.

Thai Reg. No. 1C 116/52 (NC)

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