ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT
Ferriprox 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 500 mg deferiprone.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.
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.

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
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 table for the body weight of the patient. Sample body weights at 10 kg increments are listed.

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

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).

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 measurements fall 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.
- History of recurrent episodes of neutropenia.
- History of agranulocytosis.
- Pregnancy (see section 4.6).
- Breastfeeding (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 1.5x10⁹/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 Zn\(^{2+}\) concentration
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 4.8 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).

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.

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).

Breastfeeding
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 animal studies to evaluate the potential effects of deferiprone on fertility have been reported.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

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 x 10⁹/l, which occurred in approximately 1% of patients. Less severe episodes of neutropenia were reported in approximately 5% of patients.

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

<table>
<thead>
<tr>
<th>SYSTEM ORGAN CLASS</th>
<th>VERY COMMON (≥1/10)</th>
<th>COMMON (≥1/100 to &lt;1/10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td>Increased Appetite</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Abdominal Pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td>Arthralgia</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Chromaturia</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td>Increased liver enzymes</td>
</tr>
</tbody>
</table>

The most serious adverse reaction reported in clinical trials with deferiprone is agranulocytosis (neutrophils <0.5x10⁹/l), with an incidence of 1.1% (0.6 cases per 100 patient-years of treatment) (see
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. The neurological disorders progressively regressed after deferiprone discontinuation (see sections 4.4 and 4.9).

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. 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 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 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 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 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.

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**

*Tablet core*
- Microcrystalline cellulose
- Magnesium stearate
- Colloidal silicon dioxide

*Coating*
- Hypromellose
- Macrogol
- Titanium dioxide

**6.2 Incompatibilities**
Not applicable.

**6.3 Shelf life**
5 years.
6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottles with child resistant closure (polypropylene). Each pack contains one bottle of 100 tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

EU/1/99/108/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25/08/1999
Date of latest renewal: 25/08/2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this 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:
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**

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.

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Total daily dose (mg)</th>
<th>Dose (mg, three times/day)</th>
<th>ml of oral solution (three times/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1500</td>
<td>500</td>
<td>5.0</td>
</tr>
<tr>
<td>30</td>
<td>2250</td>
<td>750</td>
<td>7.5</td>
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<tr>
<td>40</td>
<td>3000</td>
<td>1000</td>
<td>10.0</td>
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<td>50</td>
<td>3750</td>
<td>1250</td>
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<td>60</td>
<td>4500</td>
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</tr>
<tr>
<td>90</td>
<td>6750</td>
<td>2250</td>
<td>22.5</td>
</tr>
</tbody>
</table>

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).
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 measurements fall 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.
- History of recurrent episodes of neutropenia.
- History of agranulocytosis.
- Pregnancy (see section 4.6).
- Breastfeeding (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 Zn$^{2+}$ concentration
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 4.8 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
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).

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.

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).

Breastfeeding
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 animal studies to evaluate the potential effects of deferiprone on fertility have been reported.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

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 x 10^9/l, which occurred in approximately 1% of patients. Less severe episodes of neutropenia were reported in approximately 5% of patients.

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

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

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. 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 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 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 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 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 Apoptex studies, demonstrating less heart disease and/or increased survival in Ferriprox-treated patients than in those treated with deferoxamine.

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
2 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 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: 25/08/1999
Date of latest renewal: 25/08/2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu
1. NAME OF THE MEDICINAL PRODUCT
Ferriprox 1000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 1000 mg deferiprone.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.
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 with thalassaemia major when 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 table for the body weight of the patient. Sample body weights at 10 kg increments are listed.

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Total daily dose (mg)</th>
<th>Number of 1000 mg tablets*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Morning</td>
</tr>
<tr>
<td>20</td>
<td>1500</td>
<td>0.5</td>
</tr>
<tr>
<td>30</td>
<td>2250</td>
<td>1.0</td>
</tr>
<tr>
<td>40</td>
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<td>50</td>
<td>3750</td>
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<td>5250</td>
<td>2.0</td>
</tr>
<tr>
<td>80</td>
<td>6000</td>
<td>2.0</td>
</tr>
<tr>
<td>90</td>
<td>6750</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*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).
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 measurements fall 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.
- History of recurrent episodes of neutropenia.
- History of agranulocytosis.
- Pregnancy (see section 4.6).
- Breastfeeding (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, 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.

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 4.8 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).

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.

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).

Breastfeeding
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 animal studies to evaluate the potential effects of deferiprone on fertility have been reported.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

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 x 10^9/l, which occurred in approximately 1% of patients. Less severe episodes of neutropenia were reported in approximately 5% of patients.

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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.

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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

*Tablet core*
Methylcellulose USP A15LV
Crospovidone
Magnesium stearate

*Coating*
Hyromellose 2910 USP/EP
Hydroxypropyl cellulose
Macrogol
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.
For the bottle: After first opening use within 50 days.
6.4 Special precautions for storage

Do not store above 30ºC.
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

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

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25/08/1999
Date of latest renewal: 25/08/2009

10. DATE OF REVISION OF THE TEXT

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

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A. MANUFACTURING AUTHORITY 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 OF THE MARKETING AUTHORIZATION

- CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORIZATION HOLDER

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

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

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

- OTHER CONDITIONS

  _Pharmacovigilance system_
  The MAH must ensure that the system of pharmacovigilance, as described in version 02 presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

  _Risk Management plan_
  The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan as agreed in version 4 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

  As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

  In addition, an updated RMP should be submitted:
  - When new information is received that may impact on the current Safety specification, Pharmacovigilance Plan or risk minimisation activities
  - Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
  - At the request of the European Medicines Agency.

  _PSURs:_ the MAH will continue to provide Periodic Safety Update Reports every year.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
# PARTICULARES 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

Film-coated tablets
100 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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

<table>
<thead>
<tr>
<th>Apotex Europe B.V.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darwinweg 20</td>
</tr>
<tr>
<td>2333 CR Leiden</td>
</tr>
<tr>
<td>Netherlands</td>
</tr>
</tbody>
</table>

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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 AUTHOURISATION 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 tablets
100 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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)

bottle of 50 tablets
bottle of 100 tablets
blisters, package of 50 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
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLISTERS</strong></td>
</tr>
</tbody>
</table>

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
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 any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
- 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.

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. How to store Ferriprox
6. Further 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 deferoxamine therapy is contraindicated or inadequate.

2. BEFORE YOU TAKE FERRIPROX

Do not take Ferriprox
- if you are allergic (hypersensitive) to deferiprone or any of the other ingredients of Ferriprox.
- 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 “Taking other medicines”).
- if you are pregnant or breastfeeding.

Take special care with Ferriprox
- 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 about 1 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 and 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 also might ask you to undergo liver biopsies.

Taking other medicines
Do not take medicines known to cause neutropenia or agranulocytosis (see “Do not take Ferriprox”). Please inform your doctor or pharmacist if you are taking or have recently taken 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 breastfeeding
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 Ferriprox exactly as your doctor has told you. You should 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/day. The total daily dose should not exceed 100 mg/kg/day. 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, Ferriprox can have 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 fewer than 2 in 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 (affects more than 1 user in 10):
- abdominal pain
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** (affects 1 to 10 users in 100):
- low white blood cell count (agranulocytosis and neutropenia)
- headache
- diarrhoea
- increase in liver enzymes
- fatigue
- increase in appetite

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.

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 not listed in this leaflet, please tell your doctor or pharmacist.

5. **HOW TO STORE FERRIPROX**

Keep out of the reach and sight of children.
Do not use Ferriprox after the expiry date which is stated on the carton and the label after EXP.
Do not store above 30ºC.

6. **FURTHER 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**
Marketing Authorisation Holder: Apotex Europe B.V.
Darwinweg 20
2333 CR Leiden
Netherlands
Manufacturing Authorisation Holder: Apotex Nederland B.V.
Bio Science Park
Archimedesweg 2
2333 CN Leiden
Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
SWEDISH ORPHAN INTERNATIONAL SARL
Tél/Tel: + 33 1 41 92 18 01

България
ТП „Торекс Киези Фарма”
Тел.: +359 2 920 12 05

Česká republika
Apotex CR
Tel: +00420 234 705 700

Danmark
SWEDISH ORPHAN A/S
Tlf: + 45 32 96 68 69

Deutschland
SWEDISH ORPHAN INTERNATIONAL GmbH
Tel: +49 6103 20 26 90

Eesti
Oy SWEDISH ORPHAN Ab
Tel: +358 201 558 840

Ελλάδα
DEMO ABEE
Τηλ: + 30 210 8161802

España
Swedish Orphan International Spain S.L.
Tel: + 34 913 91 35 80

France
Swedish Orphan International SARL
Tél: + 33 1 41 92 18 01

Ireland
SWEDISH ORPHAN INTERNATIONAL LTD
Tel: + 44 1638 72 23 80

Ísland
SWEDISH ORPHAN A/S
Sími: + 45 32 96 68 69

Luxembourg/Luxemburg
SWEDISH ORPHAN INTERNATIONAL SARL
Tél/Tel: + 33 1 41 92 18 01

Magyarország
Torrex Chiesi Hungária Kereskedelmi Kft.
Tel.: + 36-1-429 1060

Malta
Swedish Orphan International s.r.l.
Tel: + 39 0521 19111

Nederland
SWEDISH ORPHAN INTERNATIONAL LTD
Tel: +44 1638 72 23 80

Norge
SWEDISH ORPHAN AS
Tlf: + 47 66 82 34 00

Österreich
SWEDISH ORPHAN INTERNATIONAL GmbH
Tel: +49 6103 20 26 90

Polska
Apotex Inc. Korporacja
Przedstawicielstwo w Polsce
Tel.: + 48 22 812 10 02

Portugal
SWEDISH ORPHAN INTERNATIONAL AB
Tel: + 351 21 383 08 91

România
Torrex Chiesi Pharma GmbH
Tel: + 40 729 995 020

Slovenija
Torrex Chiesi Slovenija, d.o.o.
Tel: + 386-1-43 00 901

Slovenská republika
Torrex Chiesi Slovákia, s.r.o.
Tel: + 421-2-59 30 00 60
This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.
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 any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
- 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.

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. How to store Ferriprox
6. Further 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 deferoxamine therapy is contraindicated or inadequate.

2. BEFORE YOU TAKE FERRIPROX

Do not take Ferriprox
- if you are allergic (hypersensitive) to deferiprone or any of the other ingredients of Ferriprox.
- 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 “Taking other medicines”).
- if you are pregnant or breastfeeding.

Take special care with Ferriprox
- the most serious side effects 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 about 1 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 and 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 also might ask you to undergo liver biopsies.

**Taking other medicines**
Do not take medicines known to cause neutropenia or agranulocytosis (see “Do not take Ferriprox”). Please inform your doctor or pharmacist if you are taking or have recently taken 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 breastfeeding**
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.

**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**
Always take Ferriprox exactly as your doctor has told you. You should 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/day. The total daily dose should not exceed 100 mg/kg/day. 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, Ferriprox can have 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 fewer than 2 in 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 (affects more than 1 user in 10):
- abdominal pain
- nausea
- vomiting
- reddish/brown discoloration 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 (affects 1 to 10 users in 100):
- low white blood cell count (agranulocytosis and neutropenia)
- headache
- diarrhoea
- increase in liver enzymes
- fatigue
- increase in appetite

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.

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 not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE FERRIPROX

Keep out of the reach and sight of children.
Do not use Ferriprox 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 30ºC.
Store in the original package in order to protect from light.

6. FURTHER 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.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: Apotex Europe B.V.
Darwinweg 20
2333 CR Leiden
Netherlands
Manufacturer: Apotex Nederland B.V.
Bio Science Park
Archimedesweg 2
2333 CN Leiden
Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**
SWEDISH ORPHAN INTERNATIONAL SARL
Tél/Tel: + 33 1 41 92 18 01

**Luxembourg/Luxemburg**
SWEDISH ORPHAN INTERNATIONAL SARL
Tél/Tel: + 33 1 41 92 18 01

**България**
ТП „Торекс Киези Фарма”
Тел.: +359 2 920 12 05

**Magyarország**
Torrex Chiesi Hungária Kereskedelmi Kft.
Tel.: + 36-1-429 1060

**Česká republika**
Apotex CR
Tel: +00420 234 705 700

**Malta**
Swedish Orphan International s.r.l.
Tel: + 39 0521 19111

**Danmark**
SWEDISH ORPHAN A/S
Tlf: + 45 32 96 68 69

**Nederland**
SWEDISH ORPHAN INTERNATIONAL LTD
Tel: +44 1638 72 23 80

**Deutschland**
SWEDISH ORPHAN INTERNATIONAL GmbH
Tel: +49 6103 20 26 90

**Österreich**
SWEDISH ORPHAN INTERNATIONAL GmbH
Tel: +49 6103 20 26 90

**Ελλάδα**
DEMO ABEE
Τηλ: + 30 210 8161802

**Polska**
Apotex Inc. Korporacja
Przedstawicielstwo w Polsce
Tel.: + 48 22 812 10 02

**España**
Swedish Orphan International Spain S.L.
Tel: + 34 913 91 35 80

**Portugal**
SWEDISH ORPHAN INTERNATIONAL AB
Tel: + 351 21 383 08 91

**France**
Swedish Orphan International SARL
Tél: + 33 1 41 92 18 01

**România**
Torrex Chiesi Pharma GmbH
Tel: + 40 729 995 020

**Ireland**
SWEDISH ORPHAN INTERNATIONAL LTD
Tel: + 44 1638 72 23 80

**Slovenija**
Torrex Chiesi Slovenija, d.o.o.
Tel: + 386-1-43 00 901

**Ísland**
SWEDISH ORPHAN A/S
Sími: + 45 32 96 68 69

**Slovenská republika**
Torrex Chiesi Slovacia, s.r.o.
Tel: + 421-2-59 30 00 60
This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.
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 any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
- 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.

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. How to store Ferriprox
6. Further 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 deferoxamine therapy is contraindicated or inadequate.

2. BEFORE YOU TAKE FERRIPROX

Do not take Ferriprox
- if you are allergic (hypersensitive) to deferiprone or any of the other ingredients of Ferriprox.
- 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 “Taking other medicines”).
- if you are pregnant or breastfeeding.

Take special care with Ferriprox
- 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 about 1 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 and 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 also might ask you to undergo liver biopsies.

**Taking other medicines**
Do not take medicines known to cause neutropenia or agranulocytosis (see “Do not take Ferriprox”). Please inform your doctor or pharmacist if you are taking or have recently taken 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 breastfeeding**
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 Ferriprox exactly as your doctor has told you. You should 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/day. The total daily dose should not exceed 100 mg/kg/day. 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, Ferriprox can have 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 fewer than 2 in 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** (affects more than 1 user in 10):
- 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** (affects 1 to 10 users in 100):
- low white blood cell count (agranulocytosis and neutropenia)
- headache
- diarrhoea
- increase in liver enzymes
- fatigue
- increase in appetite

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.

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 not listed in this leaflet, please tell your doctor or pharmacist.

5. **HOW TO STORE FERRIPROX**

Keep out of the reach and sight of children.
Do not use Ferriprox 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.

6. **FURTHER INFORMATION**

**What Ferriprox contains**
The active substance is deferiprone.

Each 1000 mg tablet contains 1000 mg deferiprone.
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.
Bio Science Park
Archimedesweg 2
2333 CN Leiden
Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

Belgïe/Belgique/Belgien
SWEDISH ORPHAN INTERNATIONAL SARL
Tél/Tel: + 33 1 41 92 18 01

Ελλάδα
DEMO ABEE
Τηλ: + 30 210 8161802

España
Swedish Orphan International Spain S.L.
Tel: + 34 913 91 35 80

France
Swedish Orphan International SARL
Tél: + 33 1 41 92 18 01

Ireland
SWEDISH ORPHAN INTERNATIONAL LTD
Tel: + 44 1638 72 23 80

Ísland
SWEDISH ORPHAN A/S
Sími: + 45 32 96 68 69

Magyarország
Torrex Chiesi Hungária Kereskedelmi Kft.
Tel.: + 36-1-429 1060

Malta
Swedish Orphan International s.r.l.
Tel: +39 0521 19111

Nederland
SWEDISH ORPHAN INTERNATIONAL LTD
Tel: +44 1638 72 23 80

Österreich
SWEDISH ORPHAN INTERNATIONAL GmbH
Tel: +49 6103 20 26 90

Polska
Apotex Inc. Korporacja
Przedstawicielstwo w Polsce
Tel.: + 48 22 812 10 02

Portugal
SWEDISH ORPHAN INTERNATIONAL AB
Tel: + 351 21 383 08 91

România
Torrex Chiesi Pharma GmbH
Tel: + 40 729 995 020

Slovenija
Torrex Chiesi Slovenija, d.o.o.
Tel: + 386-1-43 00 901

Slovenská republika
Torrex Chiesi Slovakia, s.r.o.
Tel: + 421-2-59 30 00 60
Italia
Chiesi Farmaceutici S.p.A
Tel: + 39 0521 2791

Suomi/Finland
Oy SWEDISH ORPHAN Ab
Puh/Tel: + 358 201 558 840

Κύπρος
The Star Medicines Importers Co. Ltd.
Τηλ: + 357 25 371056

Sverige
SWEDISH ORPHAN AB
Tel: + 46 8 412 98 00

Latvija
Oy SWEDISH ORPHAN Ab
Tel: + 358 201 558 840

United Kingdom
SWEDISH ORPHAN INTERNATIONAL LTD
Tel: + 44 1638 722380

Lietuva
Oy SWEDISH ORPHAN Ab
Tel: + 358 201 558 840

This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site:
### Important Safety Reminders for Patients taking Ferriprox (deferiprone)

**Prescribing doctor:** _______________________

**Phone No:** _______________________

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### FOR WOMEN OF CHILD BEARING AGE

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.

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.

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### MONITORING YOUR WHITE BLOOD CELL COUNT WITH FERRIPROX

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 10 users in 100, it is important to monitor your blood on a regular basis.

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### Make sure you do the following:

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.