

**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 as active substance.

For excipients, see 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 tablets are scored and breakable in half.

## **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.

Deferiprone is most commonly given as 25 mg/kg body weight, orally, three times a day for a total daily dose of 75 mg/kg body weight. Dosage per kilogram body weight should be calculated to the nearest half tablet. See Dosage Table below.

Doses above 100 mg/kg/day are not recommended because of the potentially increased risk of adverse reactions.

There are limited data available on the use of deferiprone in children between 6 and 10 years of age, and no data on deferiprone use in children under 6 years of age. Due to the serious nature of agranulocytosis that can occur with the use of deferiprone, special monitoring is required for all patients. Caution must be used when the patient's absolute neutrophil count (ANC) is low, as well as when treating patients with renal insufficiency or hepatic dysfunction (see section 4.4).

## Dosage 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.

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

### 4.3 Contraindications

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

History of recurrent episodes of neutropenia.

History of agranulocytosis.

Pregnancy or breast-feeding (see section 4.6).

Due to the unknown mechanism of deferiprone-induced neutropenia, patients should 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 special precautions for use

#### Neutropenia/Agranulocytosis

**Deferiprone has been shown to cause neutropenia, including agranulocytosis. It is recommended that a patient's neutrophil count 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 ANC count is less than  $1.5 \times 10^9/l$ .

**In the event of neutropenia:**

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

**In the event of severe neutropenia or agranulocytosis:**

Follow the guidelines above and administer appropriate therapy such as granulocyte colony stimulating factor, beginning the same day that the event is identified; administer daily until the condition resolves. Provide protective isolation and if clinically indicated, admit patient to the hospital.

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

Carcinogenicity/mutagenicity/effects on fertility

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

Serum ferritin concentration/plasma Zn<sup>2+</sup> concentration

It is recommended that serum ferritin concentrations, or other indicators of body iron load, be monitored every two to three months to assess the long-term effectiveness of the chelation regimen in controlling the body iron load. Interruption of therapy with deferiprone should be considered if serum ferritin measurements fall below 500 µg/l.

Monitoring of plasma Zn<sup>2+</sup> 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 available data 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.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

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

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

#### **4.6 Pregnancy and lactation**

*Pregnancy:* there is no adequate information on the use of deferiprone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Women of childbearing potential must be advised to avoid pregnancy due to the clastogenic and teratogenic properties of the medicinal product. These women should be counselled to take contraceptive measures and must be advised to immediately stop taking deferiprone if they become pregnant or plan to become pregnant.

*Lactation:* it is not known whether deferiprone is excreted in human milk. No prenatal and postnatal reproductive studies have been conducted in animals. Deferiprone should not be used by nursing mothers. If treatment is unavoidable, breast feeding must be stopped.

#### **4.7 Effects on ability to drive and use machines**

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

#### **4.8 Undesirable effects**

The most serious adverse reaction reported in clinical trials with deferiprone is agranulocytosis (neutrophils  $<0.5 \times 10^9/l$ ), with an incidence of 0.8% (0.5 cases per 100 patient-years of treatment) (see section 4.4). The observed incidence of the less severe form of neutropenia (neutrophils  $<1.5 \times 10^9/l$ ) is 5.9% (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 in most patients resolve within a few weeks without the discontinuation of treatment. In some patients it may be beneficial to reduce the dose of deferiprone and then scale it back up to the former dose. Arthropathy events, which ranged from mild pain in one or more joints to severe arthritis with effusion and significant disability, have also been reported in patients treated with deferiprone. Mild arthropathies are generally transient.

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

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

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

<b>Adverse Reaction</b>	<b>Rate of Event (Per 100 Patient Years)</b>	<b>Percentage of Patients Affected</b>
Reddish/Brown Urine	29.2	53.8
Nausea	8.6	15.9
Abdominal Pain	7.6	14.1
Vomiting	7.2	13.3
Arthralgia	5.1	9.4
Increased liver enzymes	3.7	6.8
Neutropenia	2.5	5.9
Increased Appetite	2.9	5.4
Diarrhoea	1.4	2.0
Agranulocytosis	0.5	0.8

#### **4.9 Overdose**

No case of overdose has been reported. In case of overdose, close clinical supervision of the patient is required.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Iron Chelator, ATC code: V03AC02

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

Clinical studies have demonstrated that deferiprone is effective in promoting iron excretion and that a dose of 25 mg/kg three times per day can prevent the progression of iron accumulation as assessed by serum ferritin, in patients with transfusion-dependent thalassaemia. However, chelation therapy may not necessarily protect against iron-induced organ damage.

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

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

#### **5.2 Pharmacokinetic properties**

##### **Absorption**

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

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**

Preclinical 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**

3 years

### **6.4 Special precautions for storage**

Do not store above 30°C

### **6.5 Nature and contents of container**

Ferriprox is provided in HDPE bottles of 100 tablets with child resistant closures.

### **6.6 Instructions for use and handling**

No special requirements

## **7. MARKETING AUTHORISATION HOLDER**

Apotex Europe Ltd., Rowan House, 41 London Street, Reading, Berkshire, RG1 4PS, United Kingdom

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/99/108/001

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

25/08/99

## **10. DATE OF REVISION OF THE TEXT**

**ANNEX II**

- A. MANUFACTURING AUTHORISATION HOLDER  
RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

**A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer responsible for batch release

Chiesi Farmaceutici S.p.A  
26/A Via Palermo  
43100 Parma  
Italy

**B CONDITIONS OF THE MARKETING AUTHORISATION**

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

• **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

*PSURs*: the MAH will continue to provide Periodic Safety Update Reports every 6 months.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING**

Ferriprox 500 mg film-coated tablets  
deferiprone

One tablet contains 500 mg deferiprone

Film-coated tablets  
100 tablets

Oral use

Keep out of the reach and sight of children

EXP:

Do not store above 30°C

Apotex Europe Ltd., Rowan House, 41 London Street, Reading, Berkshire, RG1 4PS, United Kingdom

EU/1/99/108/001

Lot:

Medicinal product subject to medical prescription

For more details please refer to the package leaflet

## MINIMUM PARTICULARS ON SMALL IMMEDIATE PACKAGING UNITS

Ferriprox 500 mg film-coated tablets  
deferiprone

100 tablets  
Oral use

Read the package leaflet before use

Keep out of the reach and sight of children

EXP:

Do not store above 30°C

Apotex Europe Ltd., Rowan House, 41 London Street, Reading, Berkshire, RG1 4PS, United Kingdom

EU/1/99/108/001

Lot:

**B. PACKAGE LEAFLET**

## 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 further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

### **In this leaflet:**

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

**Ferriprox** 500 mg film-coated tablets  
Deferiprone

The active substance is deferiprone 500 mg/tablet

The other ingredients are:

### **Tablet core**

Microcrystalline cellulose  
Magnesium stearate  
Colloidal silicon dioxide

### **Coating**

Hypromellose  
Macrogol  
Titanium dioxide

Marketing Authorisation Holder:

Apotex Europe Ltd.  
Rowan House, 41 London Street,  
Reading, Berkshire, RG1 4PS  
United Kingdom

Manufacturing Authorisation Holder:

Chiesi Farmaceutici S.p.A.  
26/A Via Palermo  
43100 Parma  
Italy

## **1. WHAT FERRIPROX IS AND WHAT IT IS USED FOR**

Ferriprox is a medicine that removes iron from the body. Deferiprone is the active substance in Ferriprox.

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.

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

## 2. BEFORE YOU TAKE FERRIPROX

### **Do not take Ferriprox:**

- if you are hypersensitive (allergic) to deferiprone or any of the other ingredients of Ferriprox.
- if you have a history of repeated episodes of neutropenia (low neutrophil count).
- if you have a history of agranulocytosis (very low white blood cell count  $<0.5 \times 10^9/l$ ).
- if you are currently taking medication known to cause neutropenia.
- if you are pregnant or breast-feeding.

Therapy with Ferriprox may be associated with the occurrence of a very low white blood cell count in some patients. This condition is known as severe neutropenia or agranulocytosis and may place you at risk of developing a serious infection. The way Ferriprox causes neutropenia is not known. Patients should not take medicinal products known to be associated with neutropenia or those that can cause agranulocytosis.

### **Take special care with Ferriprox:**

- if you have a history of neutropenia, since one of the most serious side effects that may occur 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. Report immediately to your doctor any symptoms of infection such as fever, sore throat or flu-like symptoms.

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.

### **Pregnancy**

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

### **Breast-feeding**

Do not use Ferriprox if you are a nursing mother.

### **Driving and using machines:**

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

### **Taking other medicines:**

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed. Do not take aluminium-based antacids while taking Ferriprox.

## 3. HOW TO TAKE FERRIPROX

Always take Ferriprox exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. 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. It is not necessary to take Ferriprox with food. However, you may find it easier to remember to take your medication, if you take it with your meals.

### **If you take more Ferriprox than you should:**

There are no reports of overdose with Ferriprox. If you have taken more than the prescribed dose of Ferriprox, 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.

The most serious side effect of Ferriprox is the occurrence of 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. A low white blood cell count can also be associated with a serious and potentially life-threatening infection. Report immediately to your doctor any symptoms of infection such as: fever, sore throat or flu-like symptoms.

Some of the patients enrolled in clinical studies with Ferriprox developed joint pain and swelling. These events ranged from mild pain in one or more joints to severe disability. In most patients, the pain disappeared while still taking Ferriprox.

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

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

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

#### **5. STORING FERRIPROX**

Keep out of the reach and sight of children

Do not store above 30°C

Do not use after the expiry date stated on the label.

## 6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

### **België/Belgique/Belgien**

SWEDISH ORPHAN INTERNATIONAL AB  
Tél/Tel: 0800 70199 (numéro vert)

### **Česká republika**

Apotex CR  
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### **Danmark**

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### **Deutschland**

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### **Eesti**

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### **Italia**

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### **Κύπρος**

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**This leaflet was last approved on**