

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## **1. NAME OF THE MEDICINAL PRODUCT**

Ferriprox 100 mg/ml oral solution

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each ml of oral solution contains 100 mg deferiprone.

Excipient:

Each ml of oral solution contains 0.4 mg Sunset Yellow (E110).

For a full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Oral solution.

Clear, reddish orange coloured liquid.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

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

### **4.2 Posology and method of administration**

For oral use.

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

Deferiprone is usually given as 25 mg/kg body weight, orally, three times a day for a total daily dose of 75 mg/kg body weight. Dose per kilogram body weight should be calculated to the nearest 2.5 ml. See table below for recommended doses for body weights at 10 kg increments.

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

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

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

#### *Dose table*

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

Body weight	Total daily dose	Dose	ml of oral solution
20	1500	500	5.0
30	2250	750	7.5
40	3000	1000	10.0
50	3750	1250	12.5
60	4500	1500	15.0
70	5250	1750	17.5
80	6000	2000	20.0
90	6750	2250	22.5

### 4.3 Contraindications

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

History of recurrent episodes of neutropenia.

History of agranulocytosis.

Pregnancy or breast-feeding (see section 4.6).

Due to the unknown mechanism of deferiprone-induced neutropenia, patients must not take medicinal products known to be associated with neutropenia or those that can cause agranulocytosis (see section 4.5).

### 4.4 Special warnings and precautions for use

#### *Neutropenia/Agranulocytosis*

**Deferiprone has been shown to cause neutropenia, including agranulocytosis. The patient's neutrophil count should be monitored every week.**

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

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

Treatment with deferiprone should not be initiated if the patient is neutropenic. The risk of agranulocytosis and neutropenia is higher, if the baseline absolute neutrophil count (ANC) is less than  $1.5 \times 10^9/l$ .

#### *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, 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 data available on the use of deferiprone in patients with renal or hepatic impairment. Since deferiprone is eliminated mainly via the kidneys, there may be an increased risk of complications in patients with impaired renal function. Similarly, as deferiprone is metabolised in the liver, caution must be exercised in patients with hepatic dysfunction. Renal and hepatic function should be monitored in this patient population during deferiprone therapy. If there is a persistent increase in serum alanine aminotransferase (ALT), interruption of deferiprone therapy should be considered.

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

*Discoloration of urine*

Patients should be informed that their urine may show a reddish/brown discoloration due to the excretion of the iron-deferiprone complex.

*Chronic overdose and neurological disorders*

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

*Excipients*

Ferriprox oral solution contains the colouring agent Sunset Yellow (E110) which may cause allergic reactions.

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

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

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

Due to the unknown mechanism of deferiprone induced neutropenia, patients must not take medicinal products known to be associated with neutropenia or those that can cause agranulocytosis (see section 4.3).

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

##### *Pregnancy*

There are no adequate data from the use of deferiprone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Women of childbearing potential must be advised to avoid pregnancy due to the clastogenic and teratogenic properties of the medicinal product. These women should be counselled to take contraceptive measures and must be advised to immediately stop taking deferiprone if they become pregnant or plan to become pregnant (see section 4.3).

##### *Lactation*

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

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

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

#### **4.8 Undesirable effects**

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

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

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

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

Neurological disorders (such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, hand movements and axial hypotonia) have been observed in children who had been voluntarily prescribed more than 2.5 times the maximum recommended dose of 100 mg/kg/day for several years. The neurological disorders progressively regressed after deferiprone discontinuation (see sections 4.2, 4.4 and 4.9).

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

	<b>Adverse reaction</b>	<b>Rate of event (Per 100 patient years)</b>	<b>Percentage of patients affected</b>
<b><i>Investigations</i></b>			
Common	Increased liver enzymes	3.7	6.8
<b><i>Blood and lymphatic system disorders</i></b>			
Common	Neutropenia	2.5	5.9
Uncommon	Agranulocytosis	0.5	0.8
<b><i>Gastrointestinal disorders</i></b>			
Very common	Nausea	8.6	15.9
	Abdominal Pain	7.6	14.1
	Vomiting	7.2	13.3
Common	Diarrhoea	1.4	2.0
<b><i>Renal and urinary disorders</i></b>			
Very common	Reddish/Brown Urine	29.2	53.8
<b><i>Musculoskeletal and connective tissue disorders</i></b>			
Common	Arthralgia	5.1	9.4
<b><i>Metabolism and nutrition disorders</i></b>			
Common	Increased Appetite	2.9	5.4

## 4.9 Overdose

No cases of acute overdose have been reported. However, neurological disorders (such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, hand movements and axial hypotonia) have been observed in children who had been voluntarily prescribed more than 2.5 times the maximum recommended dose of 100 mg/kg/day for several years. The neurological disorders progressively regressed after deferiprone discontinuation.

In case of overdose, close clinical supervision of the patient is required.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Iron chelating agents, ATC code: V03AC02

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

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

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

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

## **5.2 Pharmacokinetic properties**

### *Absorption*

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

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

### *Biotransformation*

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

### *Elimination*

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

## **5.3 Preclinical safety data**

Non-clinical studies have been conducted in animal species including mice, rats, rabbits, dogs and monkeys.

The most common findings in non-iron-loaded animals at doses of 100 mg/kg/day and above were hematologic effects such as bone marrow hypocellularity, and decreased WBC, RBC and/or platelet counts in peripheral blood.

Atrophy of the thymus, lymphoid tissues, and testis, and hypertrophy of the adrenals, were reported at doses of 100 mg/kg/day or greater in non-iron-loaded animals.

No carcinogenicity studies in animals have been conducted with deferiprone. The genotoxic potential of deferiprone was evaluated in a set of *in vitro* and *in vivo* tests. Deferiprone did not show direct mutagenic properties; however, it did display clastogenic characteristics in *in vitro* assays and *in vivo* in animals.

Deferiprone was teratogenic and embryotoxic in reproductive studies in non-iron-loaded rats and rabbits at doses at least as low as 25 mg/kg/day. No prenatal and postnatal reproductive studies have been conducted in animals.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Purified water  
Hydroxyethylcellulose  
Glycerol  
Hydrochloric acid, concentrated  
Artificial cherry flavour  
Peppermint oil  
Sunset Yellow (E110)  
Sucralose (E955)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

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**

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

Date of first authorisation: 25/08/1999  
Date of latest renewal: 25/08/2004

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