

ANNEX 1

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

The tablets are white, capsule-shaped, film coated tablets imprinted “APO” bisect “500” on one side, plain on the other. The tablet is scored and breakable in half.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of iron overload in patients with thalassemia major for whom deferoxamine therapy is contra-indicated or who present serious toxicity with deferoxamine therapy.

4.2 Posology and method of administration

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

Deferiprone is given as 25 mg/kg body weight, oral use, 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 nature of the serious adverse events which can occur with the use of deferiprone, special monitoring is required for all patients. Caution must be used when baseline ANC count is low, as well as when treating patients with renal insufficiency or hepatic dysfunction. See section 4.4 “Special warnings and special precautions for use”.

Dosage Table

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 any of the excipients

History of recurrent episodes of neutropenia

History of agranulocytosis

Pregnancy or breast-feeding

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.

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 this has been effective in identifying cases of neutropenia and agranulocytosis. Neutropenia and agranulocytosis resolved once therapy was withdrawn. If the patient develops an infection, 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 for 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 medicinal product-associated neutropenia. The patient should be advised to limit contact with other individuals in order to reduce the risk of potential infection. Obtain a complete blood cell count, corrected white blood cell count, neutrophil count, and a platelet count immediately upon diagnosing the event and then repeat daily. It is recommended that following recovery of the neutrophil count, weekly Complete Blood Cell count (CBC), corrected White Blood Cell count (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 concurrent with the neutropenia, the appropriate cultures and diagnostic procedures should be performed and an appropriate antibiotic regimen instituted.

In the event of severe neutropenia or agranulocytosis:

Follow the guidelines above and administer appropriate therapy such as granulocyte growth factors, beginning the same day that the event is identified; administer daily until the neutrophil count recovers. Provide protective isolation and if clinically indicated admit patient to the hospital.

Limited data are available regarding rechallenge. Therefore in the event of neutropenia rechallenge is not recommended. In the event of agranulocytosis a rechallenge is contra-indicated.

Carcinogenic properties

No data on the carcinogenic properties are available. However, in view of the genotoxicity results in preclinical testing, a carcinogenic potential of deferiprone cannot be excluded (see section 5.3 Preclinical safety data.).

Serum ferritin concentrations/ plasma Zn²⁺

It is recommended that serum ferritin concentrations be monitored monthly or at least every two 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.

A monitoring of plasma Zn²⁺, as well as supplementation in case of a deficiency is recommended.

Additional data to be made available in the future

In the present state of scientific knowledge comprehensive information cannot be provided. The Marketing Authorisation Holder will perform a prospective study assessing the lymphocyte clastogenicity in patients switching from deferoxamine therapy to deferiprone. In addition efficacy and safety data following 4 years of therapy with deferiprone in approximately 100 thalassemia patients will be provided as soon as they are available.

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 is associated with neutropenia and agranulocytosis, therapy in immune compromised patients should not be initiated unless potential benefits outweigh potential risks.

Use in children

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

Renal or hepatic impairment and liver fibrosis

There are no available data in patients with renal or hepatic impairment. Since deferiprone is excreted by the kidney, 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. There is still doubt whether deferiprone may worsen hepatic fibrosis. In thalassemia patients there is an association between liver fibrosis and 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.

Renal and hepatic function should be monitored in this patient population during deferiprone therapy. If there is a persistent increase in serum ALT, interruption of deferiprone therapy should be considered.

Cardiac function

There are not sufficient data available on the effect of deferiprone on cardiac function.

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

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 concurrent deferiprone and vitamin C.

4.6 Pregnancy and lactation

Reproductive studies in non iron-loaded rats and rabbits have indicated that the active substance in deferiprone is teratogenic and embryotoxic at doses as low as 25 mg/kg body weight.

There are no relevant data in pregnant women, however, based on animal studies, deferiprone should not be used in pregnant or lactating women.

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

4.7 Effects on ability to drive and use machines

There is no evidence that deferiprone affects the ability of patients to drive or use machinery.

4.8 Undesirable effects

The most serious undesirable effect of therapy reported in clinical trials with deferiprone is agranulocytosis (neutrophils $<0.5 \times 10^9/l$) with an incidence of 1.2% (0.6 cases per 100 patient years of treatment). The observed incidence of the less severe form of neutropenia (neutrophils $<1.5 \times 10^9/l$) is 6.5% (3.5 cases per 100 patient years). This rate should be considered in context of the underlying elevated incidence of neutropenia in thalassemia patients, particularly in those with hypersplenism.

The most common undesirable effect reported with deferiprone was reddish/brown urine, reported to be due to the excretion of the iron-deferiprone complex.

Other common effects include: nausea, vomiting, abdominal pain and increased appetite. These effects are more frequent at the beginning of therapy with deferiprone and in most patients are resolved 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 total 75 mg/kg/day.

Arthropathies have also been reported in patients treated with deferiprone. These events ranged from mild pain in one or more joints to severe arthritis. Most patients recover despite continuing therapy.

Increased ALT values have been reported in patients taking deferiprone. In the majority of these patients this increase was asymptomatic and transient, and their ALT values returned to baseline without discontinuation or decreasing the dose of deferiprone (see also section 4.4. Special warnings and special precautions for use).

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.

Adverse Reaction	Rate of Event (Per 100 Patient Years)	Percentage of Patients Affected
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 ALT	3.7	6.8
Neutropenia	3.5	6.5
Increased Appetite	2.9	5.4
Agranulocytosis	0.6	1.2

4.9 Overdose

There have been no reports of acute overdose with deferiprone.

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 can prevent the progression of iron accumulation as assessed by serum ferritin, in transfusion-dependent thalassemia patients. However, chelation therapy may not 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 substance absorbed when given with food.

Metabolism

Deferiprone is metabolised predominantly to a glucuronide conjugate. This metabolite lacks iron binding capacity because of 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 with reports of 75% to 90% of the ingested dose being recovered in the urine in the first 24 hours, in the form of free deferiprone, the glucuronide metabolite and the iron-deferiprone complex.

A variable amount of elimination into 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 main toxicity observed was bone marrow depression and an associated drop in white blood cell counts. In non-iron loaded animals these effects appeared to be dose dependent and were observed at doses of 100 mg/kg/day and above. In these animals, there is an inverse correlation between toxicity and tissue iron load.

Atrophy of the thymus and testis was reported at doses of 100 to 400 mg/kg in non-iron loaded animals. Hypertrophy of the adrenals was seen at doses of 150 mg/kg in non-iron loaded animals.

Chronic carcinogenicity studies have not been undertaken 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 non-iron loaded systems.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet

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

Deferiprone is provided in HDPE tablet containers of 100 tablets with child resistant closures.

6.6 Instructions for use and handling, and disposal

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