PACKAGE INSERT

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

For oral use.

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

Ferriprox® 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.

Doses above 100 mg/kg/day are not recommended because of the potentially increased risk of adverse reactions (see sections 4.4, 4.8 and 4.9).

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

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

Dose table

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

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- History of recurrent episodes of neutropenia.
- History of agranulocytosis.
- Pregnancy or breast-feeding (see section 4.6).
- Due to the unknown mechanism of deferiprone-induced neutropenia, patients must not take medicinal products known to be associated with neutropenia or those that can cause agranulocytosis (see section 4.5).

4.4 Special warnings and precautions for use

Neutropenia/Agranulocytosis

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

In clinical trials, weekly monitoring of the neutrophil count has been effective in identifying cases of neutropenia and agranulocytosis. Neutropenia and agranulocytosis resolved once therapy was withdrawn. If the patient develops an infection while on deferiprone, therapy

should be interrupted and the neutrophil count monitored more frequently. Patients should be advised to report immediately to their physician any symptoms indicative of infection such as fever, sore throat and flu-like symptoms.

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

Treatment with deferiprone should not be initiated if the patient is neutropenic. The risk of agranulocytosis and neutropenia is higher, if the baseline absolute neutrophil count (ANC) is less than $1.5x10^9$/l.

In the event of neutropenia:

Instruct the patient to immediately discontinue deferiprone and all other 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^{2+} concentration

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

Monitoring of plasma Zn^{2+} concentration, and supplementation in case of a deficiency, is recommended.

HIV positive or other immune compromised patients

No data are available on the use of deferiprone in HIV positive or in other immune compromised patients. Given that deferiprone can be associated with neutropenia and agranulocytosis, therapy in immune compromised patients should not be initiated unless potential benefits outweigh potential risks.

Renal or hepatic impairment and liver fibrosis

There are no 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.

Cardiac function

Studies on cardiac iron concentrations suggest that deferiprone protects the heart against the toxicity of iron overload.

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.

Neurological disorders

Neurological disorders have been observed in children treated with approximately 2.5-times the maximum recommended dose for several months but have also been observed with standard doses of deferiprone. Prescribers are reminded that the use of doses above 100 mg/kg/day are not recommended. Deferiprone use should be discontinued if neurological disorders are observed (see sections 4.8 and 4.9).

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 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 (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 1.1% (0.6 cases per 100 patient-years of treatment) (see section 4.4). The observed incidence of the less severe form of neutropenia (neutrophils $<1.5 \times 10^9$/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 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.

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 approximately 2.5-times the maximum recommended dose of 100 mg/kg/day for several months. Episodes of hypotonia, instability, inability to walk, and hypertonia with inability of limb movement, have been reported in children in the post-marketing setting with standard doses of deferiprone. The neurological disorders progressively regressed after deferiprone discontinuation (see sections 4.4 and 4.9).

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

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

4.9 Overdose

No cases of acute overdose have been reported. However, neurological disorders (such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, hand movements and axial hypotonia) have been observed in children who had been voluntarily prescribed

approximately 2.5-times the maximum recommended dose of 100 mg/kg/day for several months. 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 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

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 bottle contains 100 tablets.

6.6 Instructions for use and handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.

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Italy

8. DATE OF REVISION OF THE TEXT

07/2021