360 mm

90 mm

42 mm

400 mm

FERRIPROX™ 100 mg/ml

Deferiprone Oral Solution

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 FCF (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 1 year of age and older with thalassaemia major.

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 (see sections 4.4, 4.8, and 4.9).

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 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 (kg)	Total daily dose (mg)	Dose (mg, three times/day)	ml of oral solution (three times/day)
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

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.

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.

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
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.

QT prolongation
No significant inhibition of hERG K^+ channels was seen at deferiprone concentrations up to 3,000 μM, and no effect on QT interval or other cardiovascular and electrocardiographic parameters were noted in iron-loaded and non-iron-loaded monkeys that received deferiprone for up to 12 months. However, the tested concentrations and doses were low, limiting the predictive value of negative findings. One episode of *Torsade de pointes* during therapy with Ferriprox was observed in a patient with a history of QT prolongation. Ferriprox should be administered with caution to patients who may be at increased risk of prolongation of the cardiac QT interval (e.g., those with congestive heart failure, bradycardia, use of a diuretic, cardiac hypertrophy, hypokalemia or hypomagnesemia). Any patient taking Ferriprox who experiences symptoms suggestive of an arrhythmia (such as palpitations, dizziness, lightheadedness, syncope, or seizures) should seek medical attention immediately.

Use in the elderly
Currently, there are no available data in elderly patients.

Paediatric use
The safety and efficacy of Ferriprox for paediatric use was evaluated in 220 children aged 1 to 15 years with transfusion-dependent anaemias. The data show that Ferriprox was effective in decreasing body iron load as measured by serum ferritin concentrations and it was not associated with new health concerns in this patient population. The effects of Ferriprox on growth are unknown.

Effects on laboratory tests: Serum ferritin concentrations
It is recommended that serum ferritin concentrations be monitored regularly (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 Ferriprox should be considered if serum ferritin measurements fall below 500 μg/l.

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 up to 16 months. Prescribers are reminded that the use of doses above 100 mg/kg/day are not recommended (see sections 4.8 and 4.9).

Allergic reactions
Ferriprox oral solution contains the colouring agent sunset yellow FCF (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 effects on fertility or early embryonic development were noted in animals (see section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The most serious adverse reaction reported in clinical trials with deferiprone is agranulocytosis (neutrophils $<0.5x10^9$/l), with an incidence between 1% and 2% (see section 4.4). The observed incidence of the less severe form of neutropenia (neutrophils $<1.5x10^9$/l) is approximately 5%. 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.

000000

BACK

FERRIPROX™ 100 mg/ml
Deferiprone Oral Solution

visual code centered on spine do not remove

FRONT

FERRIPROX™ 100 mg/ml
Deferiprone Oral Solution

000000

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 up to 16 months. 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 (≥1/1000 to 1/100).

System Organ Class	Very Common (≥1/10)	Common (≥1/100 to 1/10)	Uncommon (≥1/1000 to 1/100)
Blood and Lymphatic System Disorders	None	Agranulocytosis, Neutropenia	Blood Disorder, Hypersplenism, Leukopenia, Thrombocytopenia
Cardiac Disorders	None	None	Arrhythmia, *Torsade de Pointes*
Ear and Labyrinth Disorders	None	None	Deafness, Ear Pain, Tinnitus, Vertigo
Gastrointestinal Disorders	Nausea, Vomiting	Abdominal Discomfort, Abdominal Pain, Abdominal Pain Upper, Diarrhoea, Dyspepsia	Abdominal Distension, Abdominal Pain Lower, Aphthous Stomatitis, Constipation, Epigastric Discomfort, Eructation, Gastritis, Reflux Oesophagitis, Stomach Discomfort
General Disorders and Administration Site Conditions	None	Oedema Peripheral	Asthenia, Chest Pain, Discomfort, Fatigue, Influenza Like Illness, Malaise, Pyrexia, Thirst
Hepatobiliary Disorders	None	None	Hepatic Pain, Hepatitis, Hepatomegaly, Jaundice, Liver Tenderness
Immune System Disorders	None	None	Hypersensitivity
Infections and Infestations	None	None	Cytomegalovirus Hepatitis, Diabetic Foot Infection, Gastroenteritis, Gastroenteritis Viral, Influenza, Nasopharyngitis, Sepsis, Upper Respiratory Tract Infection, *Yersinia* Infection
Injury, Poisoning and Procedural Complications	None	None	Epicondylitis, Transfusion Reaction
Investigations	None	Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Neutrophil Count Decreased, Weight Increased, White Blood Cell Count Decreased	Blood Bilirubin Increased, Blood Creatinine Increased, Blood Lactate Dehydrogenase Increased, Blood Phosphorus Increased, Blood Zinc Decreased, Electrocardiogram T Wave Inversion, Gamma-Glutamyltransferase Increased, Hepatic Enzyme Increased, Platelet Count Decreased, Platelet Count Increased, Weight Decreased
Metabolism and Nutrition Disorders	None	Anorexia, Increased Appetite	Decreased Appetite, Fluid Retention
Musculoskeletal and Connective Tissue Disorders	Arthralgia	Arthropathy, Back Pain, Joint Swelling, Pain In Extremity	Arthritis, Bone Pain, Joint Crepitation, Joint Effusion, Joint Range Of Motion Decreased, Joint Stiffness, Metatarsalgia, Muscle Spasms, Muscular Weakness, Musculoskeletal Chest Pain, Musculoskeletal Pain, Myalgia, Polyarthritis, Synovial Cyst
Nervous System Disorders	None	Headache	Dizziness, Hypogeusia, Migraine, Somnolence
Renal and Urinary Disorders	Chromaturia (red/brown)	None	Pollakiuria
Reproductive System and Breast Disorders	None	None	Amenorrhoea, Menstruation Irregular
Respiratory, Thoracic and Mediastinal Disorders	None	None	Asthma, Dry Throat, Oropharyngeal Pain
Skin and Subcutaneous Tissue Disorders	None	None	Alopecia, Hyperhidrosis, Pruritus, Rash, Rash Generalised, Rash Pruritic, Skin Hypopigmentation, Urticaria, Xeroderma

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 up to 16 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 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 thalassaemia 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 thalassaemia 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 thalassaemia 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 pregnant rats and rabbits at doses at least as low as 25 mg/kg/day. No effects on fertility or early embryonic development were noted in non-iron-loaded male and female rats that received deferiprone orally at doses of up to 75 mg/kg twice daily for 28 days (males) or 2 weeks (females) prior to mating and until termination (males) or through early gestation (females). In females, an effect on the oestrous cycle delayed time to confirmed mating at all doses tested.

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 FCF (E110)
Sucralose (E955)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date can be found on the packaging
After first opening use within 35 days.

6.4 Special precautions for storage

Do not store above 30ºC. 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

Keep all medicine out of the reach of children

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Reg. No: DKI1019200635A1

Manufactured by: Apotex Inc. – Richmond Hill Site, Ontario, Canada for Chiesi Farmaceutici S.p.A., Parma, Italy

Imported by: PT. Sydna Farma, Jakarta, Indonesia

Marketed by: PT. Quamed, Jakarta, Indonesia

Chiesi