FERRIPROX®

Deferiprone 500mg film-coated tablets
Iron chelating agent

PHARMACOLOGY

Deferiprone is a bidentate ligand, which binds to iron in a 3:1 molar ratio and removes iron from the body. Clinical studies have demonstrated that deferiprone is effective in promoting iron excretion and can lower serum ferritin levels and tissue iron stores in patients with transfusion-dependent thalassemia. The precise mechanism by which deferiprone is effective in promoting iron excretion and preventing the progress of iron accumulation is unknown.

Pharmacokinetics

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

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 into the feces has been reported. The elimination half-life in most patients is 2 to 3 hours.

INDICATION

Ferriprox® is indicated for the treatment of iron overload in patients with thalassemia major when deferoxamine therapy is contra-indicated or inadequate.

ADVERSE REACTIONS

The following side effects were reported in patients taking Ferriprox® in clinical trials:

Very Common (≥1/10): Nausea, vomiting, abdominal pain. Joint disease.

Common (≥1/100 to <1/10): Low white blood cell count (agranulocytosis and neutropenia). Stomach upset, increased appetite, diarrhea. Pain, headache, back pain, fatigue, flu syndrome, swelling. Elevated liver enzyme (ALT), low number of blood platelets, decline in other blood cell counts.

Uncommon (≥1/1,000 to <1/100): Fever, bacterial infections, malaise, cyst. Elevated liver enzymes (AST, GGT), depletion of minerals. Dizziness, sleepiness, decreased muscle activity. Taste loss, deafness, ear pain. Sore throat. Liver tenderness, jaundice, hepatitis. Anorexia (loss of appetite), excess gas, gastritis. Skin reactions (rash,

itchiness, redness). Bone pain, muscle pain, leg cramps, epicondylitis. Loss of menstruation, frequent urination.

If the patient notices any side effects not mentioned in this leaflet, they should inform their doctor, pharmacist, or the local distributor immediately who will, in turn, communicate it to the Medical Safety division of ApoPharma (Canada) by calling +1-416-401-7650.

The most serious adverse reaction with deferiprone is agranulocytosis, which occurred in 1.1% of people participating in clinical trials (0.6 cases per 100 patient-years of treatment). The incidence of the less severe form of neutropenia 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 thalassemia patients, particularly in those with hypersplenism.

Episodes of diarrhea, mostly mild and transient, have been reported in patients treated with Ferriprox®. Gastrointestinal effects are more frequent at the beginning of therapy and in most patients, resolve within a few weeks without the discontinuation of treatment. Arthropathy events, which ranged from mild pain in one or more joints to severe arthritis with effusion and significant disability, have also been reported. Mild arthropathies are generally transient.

PRECAUTIONS/WARNINGS

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, and in allowing early interruption of deferiprone therapy. Under those circumstances, 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.

It is recommended that a management protocol as outlined below 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 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.

Renal or hepatic impairment and liver fibrosis
Currently there is no available information on patients with renal impairment and limited information on patients with 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 metabolized 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 persistent increase in serum ALT, interruption of deferiprone therapy should be considered.

In thalassemia 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
A comparative study indicates that deferiprone has a cardio-protective effect at least as good as, if not better than, the standard treatment with subcutaneous deferoxamine.

Carcinogenicity/mutagenicity/effects on fertility
Deferiprone displayed clastogenic characteristics in *in vitro* and *in vivo* non-iron-loaded and iron-loaded systems. Deferiprone was non-mutagenic in the bacterial reverse mutation assay. A comparative study of clastogenicity in the lymphocytes of patients with thalassemia treated with deferiprone or with deferoxamine indicated that deferiprone is not associated with a greater frequency of chromosomal aberrations than that observed during therapy with deferoxamine. No carcinogenicity studies have been conducted with deferiprone. In view of the genotoxicity results, a carcinogenic potential of deferiprone cannot be excluded.

Use in pregnancy
There is no adequate information on the use of deferiprone in pregnant women. Studies in animals have shown reproductive toxicity. Reproductive studies in non-iron-loaded rats and rabbits have indicated that deferiprone is teratogenic and embryotoxic at doses at least as low as 25 mg/kg body weight. 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 counseled to take contraceptive measures and must be advised to immediately stop taking deferiprone if they become pregnant or plan to become pregnant.

Use in lactation
It is not known whether deferiprone is excreted in human milk. Deferiprone should not be used by nursing mothers.

Laboratory tests
It is recommended that serum ferritin concentrations or other assessments of body iron load be monitored regularly 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+}, and supplementation in case of 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 is associated with neutropenia and agranulocytosis, therapy in immune compromised patients should not be initiated unless potential benefits outweigh potential risks.

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

CONTRAINDICATIONS
Ferriprox® is contraindicated in patients who:

- Have demonstrated hypersensitivity to the active substance or any of the excipients.
- Have a history of recurrent episodes of neutropenia.
- Have a history of agranulocytosis.
- Are pregnant or breast-feeding.

DRUG INTERACTIONS
Interaction 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. Therefore, it is not recommended to concomitantly ingest aluminium-based antacids.

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.

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.

RECOMMENDED DOSAGE

Ferriprox® 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.

Dosage Table

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

Doses above 100 mg/kg/day are not recommended because of the potentially increased risk of adverse reactions. Limited information is available on the use of deferiprone in children between 6 and 10 years of age, and very limited information is available on deferiprone use in children under 6 years of age.

It is not necessary to take deferiprone with food. However, it may be easier to remember to take doses with meals, and clinical experience suggests nausea may be minimized if deferiprone is taken with food.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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.

STRENGTH AND DOSAGE FORMS AVAILABLE

Ferriprox® contains 500 mg deferiprone in film-coated tablets. The tablets are white to off-white, capsule-shaped, and imprinted “APO” bisect “500” on one side. The tablets are scored and breakable in half. Ferriprox® is available in HDPE bottles of 100 or 30 tablets with child-resistant closures. Not all pack sizes may be marketed.

STORAGE CONDITIONS

Do not store above 30°C.
Keep out of the reach and sight of children.

SHELF-LIFE
Do not use after the expiry date stated on the label.

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