

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021825Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FERRIPROX safely and effectively. See full prescribing information for FERRIPROX.

FERRIPROX® (deferiprone) tablets, for oral use
Initial U.S. Approval: 2011

WARNING: AGRANULOCYTOSIS/NEUTROPENIA

See full prescribing information for complete boxed warning.

- Ferriprox can cause agranulocytosis that can lead to serious infections and death. Neutropenia may precede the development of agranulocytosis. (5.1)
- Measure the absolute neutrophil count (ANC) before starting Ferriprox and monitor the ANC weekly on therapy. (5.1)
- Interrupt Ferriprox if infection develops and monitor the ANC more frequently. (5.1)
- Advise patients taking Ferriprox to report immediately any symptoms indicative of infection. (5.1)

INDICATIONS AND USAGE

FERRIPROX® (deferiprone) is an iron chelator indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. (1)

Approval is based on a reduction in serum ferritin levels. There are no controlled trials demonstrating a direct treatment benefit, such as improvement in disease-related symptoms, functioning, or increased survival.(1)

Limitation of Use

- Safety and effectiveness have not been established for the treatment of transfusional iron overload in patients with other chronic anemias. (1)

DOSAGE AND ADMINISTRATION

- 25 mg/kg to 33 mg/kg body weight, orally, three times per day, for a total daily dose of 75 mg/kg to 99mg/kg body weight. (2)

DOSAGE FORMS AND STRENGTHS

- 500 mg film-coated tablets with a functional score. (3)

CONTRAINDICATIONS

- Hypersensitivity to deferiprone or to any of the excipients in the formulation. (4)

WARNINGS AND PRECAUTIONS

- If infection occurs while on Ferriprox, interrupt therapy and monitor the ANC more frequently. (5.1)
- Ferriprox can cause fetal harm. Women should be advised of the potential hazard to the fetus and to avoid pregnancy while on this drug. (5.3)

ADVERSE REACTIONS

- The most common adverse reactions are (incidence \geq 5%) chromaturia, nausea, vomiting and abdominal pain, alanine aminotransferase increased, arthralgia and neutropenia. (5.1, 6)

To report SUSPECTED ADVERSE REACTIONS, contact ApoPharma Inc. at: Telephone: 1-866-949-0995

Email: medicalsafety@apopharma.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Avoid concomitant use with other drugs known to be associated with neutropenia or agranulocytosis; however, if this is not possible, closely monitor the absolute neutrophil count. (7.1)
- Allow at least a 4-hour interval between Ferriprox and mineral supplements, and antacids that contain polyvalent cations (e.g., iron, aluminum, and zinc). (7.3)

USE IN SPECIFIC POPULATIONS

- Special care must be taken with Ferriprox use in patients with renal or hepatic impairment since no specific studies have been conducted to evaluate its safety and efficacy in patients with these conditions. (8.6, 8.7)
- Nursing mothers: Discontinue the use of Ferriprox or discontinue nursing. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised: 10/2011

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FULL PRESCRIBING INFORMATION

WARNING: AGRANULOCYTOSIS/ NEUTROPENIA

- Ferriprox can cause agranulocytosis that can lead to serious infections and death. Neutropenia may precede the development of agranulocytosis. [see Warnings and Precautions (5.1)]
- Measure the absolute neutrophil count (ANC) before starting Ferriprox therapy and monitor the ANC weekly on therapy. Interrupt Ferriprox therapy if neutropenia develops. [see Warnings and Precautions (5.1)]
- Interrupt Ferriprox if infection develops, and monitor the ANC more frequently. [see Warnings and Precautions (5.1)]
- Advise patients taking Ferriprox to report immediately any symptoms indicative of infection. [see Warnings and Precautions (5.1)]

1 INDICATIONS AND USAGE

FERRIPROX® (deferiprone) is indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.

Approval is based on a reduction in serum ferritin levels. There are no controlled trials demonstrating a direct treatment benefit, such as improvement in disease-related symptoms, functioning, or increased survival [see Clinical Studies (14)].

Limitation of Use:

- Safety and effectiveness have not been established for the treatment of transfusional iron overload in patients with other chronic anemias.

2 DOSAGE AND ADMINISTRATION

The recommended initial dose of Ferriprox is 25 mg/kg, orally, three times per day for a total of 75 mg/kg/day. The maximum dose is 33 mg/kg, three times per day for a total of 99 mg/kg/day.

Dose adjustments up to 33 mg/kg, orally, three times per day should be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). The maximum recommended total daily dose is 99 mg/kg per day. The dose should be rounded by the prescriber to the nearest 250 mg (half-tablet).

Table 1a: Tablet requirement to achieve a 25 mg/kg (rounded to the nearest half-tablet) dose level for administration three times a day.

Body Weight (kg)	Dose (mg)	Number of tablets
20	500	1
30	750	1.5
40	1000	2
50	1250	2.5
60	1500	3
70	1750	3.5
80	2000	4
90	2250	4.5

Table 1b: Tablet requirement to achieve 33 mg/kg (rounded to the nearest half-tablet) dose level for administration three times a day.

Body Weight (kg)	Dose (mg)	Number of tablets
20	660	1.5
30	990	2
40	1320	2.5
50	1650	3.5
60	1980	4
70	2310	4.5
80	2640	5.5
90	2970	6

Monitor serum ferritin concentration every two to three months to assess the effects of Ferriprox on body iron stores. Dose adjustments should be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). If the serum ferritin falls consistently below 500 mcg/L, consider temporarily interrupting Ferriprox therapy.

2.1 Interactions with Foods, Vitamins and Antacids

Allow at least a 4-hour interval between Ferriprox and other medications or supplements containing polyvalent cations such as iron, aluminum, and zinc [see Drug Interactions (7.3)].

3 DOSAGE FORMS AND STRENGTHS

500 mg film-coated tablets with a functional score.

4 CONTRAINDICATIONS

- Ferriprox is contraindicated in patients with known hypersensitivity to deferiprone or to any of the excipients in the formulation. The following reactions have been reported in association with the administration of deferiprone: Henoch-Schönlein purpura; urticaria; and periorbital edema with skin rash [*see Post Marketing Experience (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Agranulocytosis/Neutropenia

Fatal agranulocytosis can occur with Ferriprox use. (Ferriprox can also cause neutropenia, which may foreshadow agranulocytosis. Measure the absolute neutrophil count (ANC) before starting Ferriprox therapy and monitor the ANC weekly on therapy [*see Boxed Warning*].

Interrupt Ferriprox therapy if neutropenia develops ($ANC < 1.5 \times 10^9/L$).

Interrupt Ferriprox if infection develops, and monitor the ANC more frequently.

Advise patients taking Ferriprox to immediately interrupt therapy and report to their physician if they experience any symptoms indicative of infection.

In pooled clinical trials, the incidence of agranulocytosis was 1.7% of patients. The mechanism of Ferriprox-associated agranulocytosis is unknown. Agranulocytosis and neutropenia usually resolve upon discontinuation of Ferriprox, but there have been reports of agranulocytosis leading to death.

Implement a plan to monitor for and to manage agranulocytosis/neutropenia prior to initiating Ferriprox treatment.

For neutropenia ($ANC < 1.5 \times 10^9/L$ and $> 0.5 \times 10^9/L$):

Instruct the patient to immediately discontinue Ferriprox and all other medications with a potential to cause neutropenia.

Obtain a complete blood cell (CBC) count, including a white blood cell (WBC) count corrected for the presence of nucleated red blood cells, an absolute neutrophil count (ANC), and a platelet count daily until recovery ($ANC \geq 1.5 \times 10^9/L$).

For agranulocytosis ($ANC < 0.5 \times 10^9/L$):

Consider hospitalization and other management as clinically appropriate.

Do not resume Ferriprox in patients who have developed agranulocytosis unless potential benefits outweigh potential risks. Do not rechallenge patients who develop neutropenia with Ferriprox unless potential benefits outweigh potential risks.

5.2 Cardiac QT Syndrome

A thorough QT study has not been conducted with Ferriprox. One patient with a history of QT prolongation experienced Torsades de Pointes during therapy with Ferriprox. Administer Ferriprox 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). Instruct any patient taking Ferriprox who experiences symptoms suggestive of an arrhythmia (such as palpitations, dizziness, lightheadedness, syncope, or seizures) to seek medical attention immediately.

5.3 Embryofetal toxicity

Based on evidence of genotoxicity and developmental toxicity in animal studies, Ferriprox can cause fetal harm when administered to a pregnant woman. In animal studies, administration of deferiprone during the period of organogenesis resulted in embryofetal death and malformations at doses lower than equivalent human clinical doses. If Ferriprox is used during pregnancy or if the patient becomes pregnant while taking Ferriprox, the patient should be apprised of the potential hazard to the fetus. Women of reproductive potential should be advised to avoid pregnancy when taking Ferriprox [*see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.1)*].

5.4 Laboratory Tests

Serum liver enzyme activities

In clinical studies, 7.5% of 642 subjects treated with Ferriprox developed increased ALT values. Four (0.62%) Ferriprox-treated subjects discontinued the drug due to increased serum ALT levels and 1 (0.16%) due to an increase in both ALT and AST.

Monitor serum ALT values monthly during therapy with Ferriprox, and consider interruption of therapy if there is a persistent increase in the serum transaminase levels.

Plasma Zinc concentration

Decreased plasma zinc concentrations have been observed on Ferriprox therapy. Monitor plasma zinc, and supplement in the event of a deficiency.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

The following adverse reactions are also discussed in other sections of the labeling: Agranulocytosis/Neutropenia [*see Warnings and Precautions (5.1)*]. Elevated ALT (5.4), Torsades de Pointes (5.2), Decreased plasma zinc concentrations (5.4).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reaction information for Ferriprox represents the pooled data collected from 642 patients who participated in single arm or active-controlled clinical studies.

The most serious adverse reaction reported in clinical trials with Ferriprox was agranulocytosis [see *Warnings and Precautions (5.1)*].

The most common adverse reactions reported during clinical trials were chromaturia, nausea, vomiting, abdominal pain, alanine aminotransferase increased, arthralgia and neutropenia.

The table below lists the adverse drug reactions that occurred in at least 1% of patients treated with Ferriprox in clinical trials.

Table 2: Adverse drug reactions occurring in \geq 1% of 642 Ferriprox-treated patients

Body System Preferred Term	% Subjects
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Neutropenia	6.2
Agranulocytosis	1.7
GASTROINTESTINAL DISORDERS	
Nausea	12.6
Abdominal pain/discomfort	10.4
Vomiting	9.8
Diarrhea	3.0
Dyspepsia	2.0
INVESTIGATIONS	
Alanine Aminotransferase increased	7.5
Neutrophil count decreased	7.3
Weight increased	1.9
Aspartate Aminotransferase increased	1.2
METABOLISM AND NUTRITION DISORDERS	
Increased appetite	4.0
Decreased appetite	1.1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Arthralgia	9.8
Back pain	2.0
Pain in extremity	1.9
Arthropathy	1.4
NERVOUS SYSTEM DISORDERS	
Headache	2.5
URINARY DISORDERS	
Chromaturia	14.6

Gastrointestinal symptoms such as nausea, vomiting, and abdominal pain were the most frequent adverse reactions reported by patients participating in clinical trials and led to the discontinuation of Ferriprox therapy in 1.6% of patients.

Chromaturia (reddish/brown discoloration of the urine) is a result of the excretion of the iron in the urine.

6.2 Postmarketing Experience

The following additional adverse reactions have been reported in patients receiving Ferriprox. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: thrombocytosis, pancytopenia.

Cardiac disorders: atrial fibrillation, cardiac failure.

Congenital, familial and genetic disorders: hypospadias.

Eye disorders: diplopia, papilledema, retinal toxicity.

Gastrointestinal disorders: enterocolitis, rectal hemorrhage, gastric ulcer, pancreatitis, parotid gland enlargement.

General disorders and administration site conditions: chills, pyrexia, edema peripheral, multi-organ failure.

Hepatobiliary disorders: jaundice, hepatomegaly.

Immune system disorders: anaphylactic shock, hypersensitivity.

Infections and infestations: cryptococcal cutaneous infection, enteroviral encephalitis, pharyngitis, pneumonia, sepsis, furuncle, infectious hepatitis, rash pustular, subcutaneous abscess.

Investigations: blood bilirubin increased, blood creatinine phosphokinase increased.

Metabolism and nutrition disorders: metabolic acidosis, dehydration.

Musculoskeletal and connective tissue disorders: myositis, chondropathy, trismus.

Nervous system disorders: cerebellar syndrome, cerebral hemorrhage, convulsion, gait disturbance, intracranial pressure increased, psychomotor skills impaired, pyramidal tract syndrome, somnolence.

Psychiatric disorders: bruxism, depression, obsessive-compulsive disorder.

Renal disorders: glycosuria, hemoglobinuria.

Respiratory, thoracic and mediastinal disorders: acute respiratory distress syndrome, epistaxis, hemoptysis, pulmonary embolism.

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