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 99 mg/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. (5.2)

----------ADVERSE REACTIONS----------

- The most common adverse reactions are (incidence ≥ 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----------

- Safety and efficacy of Ferriprox has not been evaluated in patients with severe hepatic impairment. (8.7)
- Nursing mothers: Discontinue the use of Ferriprox or discontinue nursing. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed.

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 Adverse Reactions (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.

Interrupt Ferriprox therapy if neutropenia develops (ANC < 1.5 x 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 x 10^9/L and > 0.5 x 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 ≥ 1.5 x 10^9/L).

For agranulocytosis (ANC < 0.5 x 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 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)]*.

5.3 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 (5.3), Decreased plasma zinc concentrations (5.3).

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 ≥ 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.

Skin, subcutaneous tissue disorders: hyperhidrosis, periorbital edema, photosensitivity reaction, pruritis, urticaria, rash, Henoch-Schönlein purpura.

Vascular disorders: hypotension, hypertension.

7 DRUG INTERACTIONS

7.1 Drugs Associated with Neutropenia or Agranulocytosis

Avoid concomitant use of Ferriprox with other drugs known to be associated with neutropenia or agranulocytosis; however, if this is not possible, closely monitor the absolute neutrophil count *[see Warnings and Precautions (5.1)]*.

7.2 UDP-Glucuronosyltransferases (UGTs)

Deferiprone is primarily eliminated via metabolism to the 3-*O*-glucuronide. *In vitro* studies suggest that UDP glucuronosyltransferase (UGT) 1A6 is primarily responsible for the glucuronidation of deferiprone which can be reduced up to 78% in the presence of the UGT1A6 inhibitor phenylbutazone. However, the clinical significance of coadministration of Ferriprox with a UGT1A6 inhibitor (e.g. diclofenac, probenecid, or silymarin (milk thistle)) on the systemic exposure of deferiprone has not been determined. Closely monitor patients for adverse reactions that may require downward dose titration or interruption when Ferriprox is concomitantly administered with a UGT1A6 inhibitor.

7.3 Polyvalent Cations

Concurrent use of Ferriprox with foods, mineral supplements, and antacids that contain polyvalent cations has not been studied. However, since deferiprone has the potential to bind polyvalent cations (e.g., iron, aluminum, and zinc), allow at least a 4-hour interval between Ferriprox and other medications (e.g., antacids), or supplements containing these polyvalent cations *[see Dosage and Administration (2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.2), Nonclinical Toxicology (13.1)]*

Risk Summary

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. There are no studies in pregnant women, and available human data are limited. 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.

Animal Data

Skeletal and soft tissue malformations occurred in offspring of rats and rabbits that received deferiprone orally during organogenesis at the lowest doses tested (25 mg/kg per day in rats; 10 mg/kg per day in rabbits). These doses were equivalent to 3% to 4% of the maximum recommended human dose (MRHD) based on body surface area. No maternal toxicity was evident at these doses.

Embryofetal lethality and maternal toxicity occurred in pregnant rabbits given 100 mg/kg/day deferiprone orally during the period of organogenesis. This dose is equivalent to 32% of the MRHD based on body surface area.

8.3 Nursing Mothers

It is not known whether deferiprone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from Ferriprox, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of Ferriprox tablets for oral use in pediatric patients have not been established.

8.5 Geriatric Use

Safety and effectiveness in elderly individuals have not been established. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

An open-label, non-randomized, parallel group clinical study was conducted to evaluate the effect of impaired renal function on the safety, tolerability, and pharmacokinetics of a single 33 mg/kg oral dose of Ferriprox. Subjects were categorized into 4 groups based on estimated glomerular filtration rate (eGFR): healthy volunteers (eGFR $\geq$ 90 mL/min/1.73m^2), mild renal impairment (eGFR 60–89 mL/min/1.73m^2), moderate renal impairment (eGFR 30–59 mL/min/1.73m^2), and severe renal impairment (eGFR 15–29 mL/min/1.73m^2). Systemic exposure to deferiprone and to its metabolite deferiprone 3-*O*-glucuronide was assessed by the PK parameters C_{max} and AUC.

Regardless of the degree of renal impairment, the majority of the dose of Ferriprox was excreted in the urine over the first 24 hours as deferiprone 3-*O*-glucuronide. No significant effect of renal impairment was seen on systemic exposure to deferiprone. Systemic exposure to the inactive 3-*O*-glucuronide increased with decreasing eGFR. Based on the results of this study, no adjustment of the Ferriprox dosage regimen is required in patients with impaired renal function.

8.7 Hepatic Impairment

The influence of severe hepatic impairment on the pharmacokinetics of deferiprone and deferiprone 3-*O*-glucuronide has not been evaluated. Safety and efficacy of Ferriprox have not been evaluated in patients with severe hepatic impairment.

An open-label, non-randomized, parallel group clinical study was conducted to evaluate the effect of impaired hepatic function on the safety, tolerability, and pharmacokinetics of a single 33 mg/kg oral dose of Ferriprox. Subjects were categorized into 3 groups based on the Child-Pugh classification score: healthy volunteers, mild hepatic impairment (Class A: 5– 6 points), and moderate hepatic impairment (Class B: 7– 9 points). Systemic exposure to deferiprone and to its metabolite deferiprone 3-*O*-glucuronide was assessed by the PK parameters C_{max} and AUC. The PK of both deferiprone and deferiprone 3-*O*-glucuronide was generally similar in all subjects, regardless of degree of liver impairment. A serious adverse event of acute liver and renal injury was seen in one subject with moderate hepatic impairment. Based on the results of this study, no adjustment of the Ferriprox dosage regimen is required in patients with mildly or moderately impaired hepatic function.

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