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) oral solution, 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 weekly while 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)**

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Dosing (2.1) 04/2018

----------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).

Limitations 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. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Oral Solution: 80 mg/mL (40 g/500 mL and 20 g/250 mL) (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. Advise women 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%) 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 or FDA at 1-800-FDA-1088
Email: medicalsafety@apopharma.com or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Avoid 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)
- Avoid use of UGT1A6 inhibitors with FERRIPROX. (7.2)
- Allow at least a 4-hour interval between FERRIPROX and mineral supplements or antacids that contain polyvalent cations (e.g., iron, aluminum, or zinc). (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2018

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 weekly while 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)]*.

Limitations 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

2.1 Dosing

Starting Dose

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

Table 1a: Volume of 80 mg/mL oral solution (rounded to the nearest 2.5 mL) required to achieve a 25 mg/kg dose for administration three times a day.

Body Weight (kg)	Dose (mg)	mL of oral solution
24	600	7.5
32	800	10
40	1,000	12.5
48	1,200	15
56	1,400	17.5
64	1,600	20
72	1,800	22.5
80	2,000	25
88	2,200	27.5
96	2,400	30

Dose Adjustments

Dose adjustments should be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). The maximum dose is 33 mg/kg, three times per day for a total of 99 mg/kg/day. The dose should be rounded by the prescriber to the nearest 2.5 mL.

Table 1b: Volume of 80 mg/mL oral solution (rounded to the nearest 2.5 mL) required to achieve a 33 mg/kg dose for administration three times a day.		
Body Weight (kg)	**Dose (mg)**	**mL of oral solution**
18	600	7.5
24	800	10
30	1,000	12.5
36	1,200	15
42	1,400	17.5
48	1,600	20
54	1,800	22.5
60	2,000	25
66	2,200	27.5
72	2,400	30

Monitor serum ferritin concentration every two to three months to assess the effects of FERRIPROX on body iron stores. If the serum ferritin is consistently below 500 mcg/L, consider temporarily interrupting FERRIPROX therapy until serum ferritin rises above 500 mcg/L.

2.2 Interactions with Foods, Vitamins and Drugs

Allow at least a 4-hour interval between FERRIPROX and other medications or supplements containing polyvalent cations such as iron, aluminum, or zinc. Avoid use of UGT1A6 inhibitors (e.g. diclofenac, probenecid, or silymarin (milk thistle)) with FERRIPROX *[see Drug Interactions (7.2 and 7.3), Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Oral Solution: 80 mg/mL (40 g/500 mL and 20 g/250 mL)

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 it weekly while on therapy.

Interrupt FERRIPROX therapy if neutropenia develops (ANC < 1.5 x 10^9/L).

Interrupt FERRIPROX if infection develops, and monitor the ANC 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. The limited available data on the use of FERRIPROX in pregnant women are insufficient to inform a risk. In animal studies, administration of deferiprone during the period of organogenesis resulted in adverse developmental outcomes including embryofetal death and malformations at doses lower than equivalent human clinical doses.

Advise pregnant women of the potential risk to the fetus [*see Use in Specific Populations (8.1, 8.3)*]. Advise females of reproductive potential to use highly effective contraception during treatment with FERRIPROX. Six months of contraception is recommended after cessation of therapy. Advise males of reproductive potential to use effective contraception during treatment with FERRIPROX. Three months of contraception is recommended after cessation of therapy *[see Use in Specific Populations (8.1)]*.

5.3 Liver Enzyme Elevations

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.

5.4 Zinc Deficiency

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

6 ADVERSE REACTIONS

The following adverse reactions are described below and elsewhere in the labeling:

- Agranulocytosis/Neutropenia *[see Warnings and Precautions (5.1)]*
- Liver Enzyme Elevations *[see Warnings and Precautions (5.3)]*
- Zinc Deficiency *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trial Experience

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 trials.

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 FERRIPROX-treated patients

Body System **Adverse Reaction**	(N=642) **% Subjects**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Neutropenia	6
Agranulocytosis	2
GASTROINTESTINAL DISORDERS	
Nausea	13
Abdominal pain/discomfort	10
Vomiting	10
Diarrhea	3
Dyspepsia	2
INVESTIGATIONS	
Alanine Aminotransferase increased	7
Weight increased	2
Aspartate Aminotransferase increased	1
METABOLISM AND NUTRITION DISORDERS	
Increased appetite	4
Decreased appetite	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Arthralgia	10
Back pain	2
Pain in extremity	2
Arthropathy	1
NERVOUS SYSTEM DISORDERS	
Headache	2

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 iron in the urine and is not harmful.

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

7.2 UDP-Glucuronosyltransferases (UGTs)

Avoid use of UGT1A6 inhibitors (e.g., diclofenac, probenecid, or silymarin (milk thistle)) with FERRIPROX *[see Dosage and Administration (2.2), Adverse Reactions (6.1), Clinical Pharmacology (12.3)]*.

7.3 Polyvalent Cations

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 (2.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data with FERRIPROX use in pregnant women are insufficient to inform a drug-associated risk of major birth defects and miscarriage. FERRIPROX can cause fetal harm when administered to a pregnant woman based on genotoxicity and developmental toxicity in animal studies *(see Data)*.

In animal reproduction studies, administration of deferiprone to pregnant animals during the period of organogenesis resulted in adverse developmental outcomes including embryofetal death and malformations in rats and rabbits at doses much lower than the MRHD (maximum recommended human dose) based on body surface area *(see Data)*. Advise women of the risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and of miscarriage is 2-4% and 15-20%, respectively.

Data

Human Data

Post-marketing data available from 39 pregnancies of Ferriprox-treated patients and 10 pregnancies of partners of Ferriprox-treated patients are as follows:

Of the 39 pregnancies in Ferriprox-treated patients, 23 resulted in healthy newborns, 6 ended in spontaneous abortion, 9 had unknown outcomes, and 1 infant was born with anal atresia, nephroptosis, ventricular septal defect, hemivertebra and urethral fistula.

Of the 10 pregnancies in partners of Ferriprox-treated patients, 5 resulted in healthy newborns, 1 resulted in a healthy newborn with slight hypospadias, 1 was electively terminated, 1 resulted in the intrauterine death of twins, and 2 had unknown outcomes.

Animal Data

During organogenesis, pregnant rats and rabbits received deferiprone at oral doses of 0, 30, 80 or 200 mg/kg/day, and 0, 10, 50, or 150 mg/kg/day, respectively. The daily dose was administered as two equal divided doses approximately 7 hours apart. Doses of 200 mg/kg/day in rats and 150 mg/kg/day in rabbits, approximately 33% and 49% of the MRHD, respectively, resulted in increased post-implantation loss and reduced fetal weights in the presence of maternal toxicity (reduced maternal body weight and body weight

gain in both rats and rabbits; abnormal large placenta at low incidence in rats). The 200 mg/kg/day dose in rats resulted in external, visceral and skeletal fetal malformations (absent eye bulge, cranial meningocele, domed head, limb malrotation, protruding tongue, anal atresia, cleft palate, internal hydrocephaly, anophthalmia, misshapen bones of the face and naso-pharyngeal tract, and fused bones in the axial skeleton). The dose of 150 mg/kg/day in rabbits resulted in external fetal malformations (partially opened eyes) and minor blood vessel and skeletal variations.

In rats, malformations including micrognathia and persistent ductus arteriosus could be observed in the absence of maternal toxicity at doses equal to or greater than 30 and 80 mg/kg/day, approximately 5% and 13% of the MHRD, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of deferiprone in human milk, the effects on the breastfed child, or the effects on milk production.

Because of the potential for serious adverse reactions, including the potential for tumorigenicity shown for deferiprone in animal studies, advise patients not to breastfeed during FERRIPROX treatment and for 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

FERRIPROX can cause fetal harm when administered to a pregnant female.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating FERRIPROX therapy.

Contraception

Females

Advise females of reproductive potential to avoid pregnancy during treatment with FERRIPROX and 6 months of contraception is recommended after cessation of therapy. Advise females to immediately report pregnancy *[see Use in Specific Populations (8.1)]*.

Males

Advise males with female sexual partners of reproductive potential to use effective contraception during treatment with FERRIPROX and 3 months of contraception is recommended after cessation of therapy [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and effectiveness of FERRIPROX in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of FERRIPROX did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

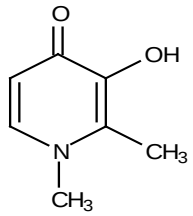
10 OVERDOSAGE

No cases of acute overdose have been reported. There is no specific antidote to FERRIPROX overdose.

Neurological disorders such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, hand movements and axial hypotonia have been observed in children treated with 2.5 to 3 times the recommended dose for more than one year. The neurological disorders progressively regressed after deferiprone discontinuation.

11 DESCRIPTION

FERRIPROX (deferiprone) oral solution contains 80 mg/mL deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one), a synthetic, orally active, iron-chelating agent. The molecular formula for deferiprone is $C_7H_9NO_2$ and its molecular weight is 139.15 g/mol. Deferiprone has the following structural formula:



Deferiprone is a white to pinkish-white powder. It is sparingly soluble in deionized water and has a melting point range of 272°C - 278°C.

FERRIPROX 80 mg/mL oral solution is a clear, reddish pink colored solution. Each mL of oral solution contains 80 mg deferiprone and the following inactive ingredients: purified water, hydroxyethylcellulose, glycerin, hydrochloric acid, sucralose, potassium sorbate, bubble gum flavor and cyanocobalamin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Deferiprone is a chelating agent with an affinity for ferric ion (iron III). Deferiprone binds with ferric ions to form neutral 3:1 (deferiprone:iron) complexes that are stable over a wide range of pH values. Deferiprone has a lower binding affinity for other metals such as copper, aluminum and zinc than for iron.

12.2 Pharmacodynamics

No clinical studies were performed to assess the relationship between the dose of FERRIPROX and the amount of iron eliminated from the body.

Cardiac Electrophysiology

At a dose 1.5 times the maximum recommended dose, FERRIPROX does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Deferiprone is rapidly absorbed from the upper part of the gastrointestinal tract, appearing in the blood within 5 to 10 minutes of oral administration. Peak serum concentrations occur approximately 1 hour after a single dose in fasted healthy subjects and patients, and up to 2 hours after a single dose in the fed state. Administration with food decreased the maximum concentration (C_{max}) of deferiprone by 38% and the area under the concentration-time curve (AUC) by 10%. The magnitude of the exposure change does not warrant dose adjustment.

In healthy subjects, the mean C_{max} of deferiprone in serum was about 20 mcg/mL, and the mean AUC was about 50 mcg·h/mL following oral administration of a 1,500 mg dose of FERRIPROX tablets or oral solution in the fasting state. Dose proportionality over the labeled dosage range of 25 to 33 mg/kg three times per day (75 to 99 mg/kg per day) has not been studied.

The elimination half-life of deferiprone is approximately 2 hours. Following oral administration, 75% to 90% of the administered dose is recovered in the urine in the first 24 hours, primarily as metabolite. In humans, the majority of the deferiprone is metabolized, primarily by UGT1A6. The contribution of extrahepatic (e.g., renal) UGT1A6 is unknown. The major metabolite of deferiprone is the 3-*O*-glucuronide, which lacks iron binding capability.

Specific Populations

The pharmacokinetics of deferiprone has not been studied in geriatric or pediatric populations, and the influence of race, gender, or obesity has not been established.

Patients with Renal Impairment

Following a single oral dose of FERRIPROX 33 mg/kg to healthy subjects (eGFR $\geq$ 90 mL/min/1.73 m^2) and subjects with mild renal impairment (eGFR 60 - 89 mL/min/1.73 m^2), moderate renal impairment (eGFR 30 - 59 mL/min/1.73 m^2), and severe renal impairment (eGFR 15 - 29 mL/min/1.73 m^2), renal impairment did not significantly influence the pharmacokinetics of deferiprone.

Patients with Hepatic Impairment

Following a single oral dose of FERRIPROX 33 mg/kg to healthy volunteers, and volunteers with mild hepatic impairment (Child Pugh Class A: 5-6 points) and moderate hepatic impairment (Child Pugh Class B: 7-9 points), mild and moderate hepatic impairment was determined to not influence the pharmacokinetics of deferiprone and deferiprone 3-*O*-glucuronide. The pharmacokinetics of deferiprone and deferiprone 3-*O*-glucuronide have not been evaluated in patients with severe hepatic impairment (Child Pugh Class C: 10-15 points).

Drug Interactions

Deferiprone is primarily eliminated via metabolism to the 3-*O*-glucuronide. *In vitro* UGT1A6 is primarily responsible for the glucuronidation of deferiprone which can be reduced up to 78% in the presence of the UGT1A6 inhibitor phenylbutazone.

Deferiprone has the potential to bind polyvalent cations (e.g., iron, aluminum, and zinc).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with deferiprone. However, in view of the genotoxicity results, and the findings of mammary gland hyperplasia and mammary gland tumors in rats treated with deferiprone in the 52-week toxicology study, tumor formation in carcinogenicity studies must be regarded as likely.

Deferiprone was positive in a mouse lymphoma cell assay *in vitro*. Deferiprone was clastogenic in an *in vitro* chromosomal aberration test in mice and in a chromosomal aberration test in Chinese Hamster Ovary cells. Deferiprone given orally or intraperitoneally was clastogenic in a bone marrow micronucleus assay in non-iron-loaded mice. A micronucleus test was also positive when mice predosed with iron dextran were treated with deferiprone. Deferiprone was not mutagenic in the Ames bacterial reverse mutation test.

A fertility and early embryonic development study of deferiprone was conducted in rats. Sperm counts, motility and morphology were unaffected by treatment with deferiprone. There were no effects observed on male or female fertility or reproductive function at the highest dose which was 25% of the MRHD based on body surface area.

14 CLINICAL STUDIES

In a prospective, planned, pooled analysis of patients from several studies, the efficacy of FERRIPROX was assessed in transfusion-dependent iron overload patients in whom previous iron chelation therapy had failed or was considered inadequate due to poor tolerance. The main criterion for chelation failure was serum ferritin > 2,500 mcg/L before treatment with FERRIPROX. FERRIPROX therapy (35-99 mg/kg/day) was considered successful in individual patients who experienced a ≥ 20% decline in serum ferritin within one year of starting therapy.

Data from a total of 236 patients were analyzed. Of the 224 patients with thalassemia who received deferiprone monotherapy and were eligible for serum ferritin analysis, 105 (47%) were male and 119 (53%) were female. The mean age of these patients was 18.2 years.

For the patients in the analysis, the endpoint of at least a 20% reduction in serum ferritin was met in 50% (of 236 subjects), with a 95% confidence interval of 43% to 57%.

A small number of patients with thalassemia and iron overload were assessed by measuring the change in the number of milliseconds (ms) in the cardiac MRI T2* value before and after treatment with deferiprone for one year. There was an increase in cardiac MRI T2* from a mean at baseline of 11.8 ± 4.9 ms to a mean of 15.1 ± 7.0 ms after approximately one year of treatment. The clinical significance of this observation is not known.

16 HOW SUPPLIED/STORAGE AND HANDLING

FERRIPROX® (deferiprone) oral solution is provided in amber polyethylene terephthalate (PET) bottles with child resistant closures (polypropylene). Each pack contains one bottle of 500 mL or 250 mL oral solution and a graduated measuring cup (polypropylene).

Oral solution, 80 mg/mL (40 g/500 mL), NDC 52609-4503-7

Oral solution, 80 mg/mL (20 g/250 mL), NDC 52609-4503-4

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Store in the original bottle and carton to protect from light.

After first opening of the bottle, discard any unused portion after 8 weeks.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use)

- Instruct patients and their caregivers that FERRIPROX oral solution is light sensitive and to store FERRIPROX oral solution in the originally supplied bottle and carton. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Instruct patients and their caregivers to store FERRIPROX out of the sight and reach of children.
- Inform patients of the risks of developing agranulocytosis and instruct them to immediately interrupt therapy and report to their physician if they experience any symptoms of infection such as fever, sore throat or flu-like symptoms.
- Advise patients that the amount of FERRIPROX prescribed is based on body weight and on the therapeutic goal (reduction or stabilization of the body iron load). Advise patients to use the measuring cup provided with FERRIPROX to measure the volume prescribed. Instruct patients to add about 10-15 mL of water to the measuring cup and swirl it around to mix the water with any remaining medicine in the cup and drink the mixture. The measuring cup should be hand-washed with water after use.
- Advise patients to take the first dose of FERRIPROX in the morning, the second dose at midday, and the third dose in the evening. Clinical experience suggests that taking FERRIPROX with meals may reduce nausea. If a dose of this medicine has been missed, take it as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not catch-up or double doses.
- Advise patients to contact their physician in the event of overdose.
- Inform patients that their urine might show a reddish/brown discoloration due to the excretion of the iron-deferiprone complex. This is a very common sign of the desired effect of FERRIPROX, and it is not harmful.
- Advise females of reproductive potential to use effective contraception during treatment with FERRIPROX and to immediately notify their physician if they become pregnant.
- Six months of contraception is recommended after cessation of therapy for females of reproductive potential. Three months of contraception is recommended after cessation of therapy for males of reproductive potential.
- Inform patients that they should not breastfeed while taking FERRIPROX.

Distributed by ApoPharma USA, Inc., Weston, FL, United States of America, 33326. Manufactured by Apotex Inc., Toronto, Ontario, Canada, M9L 1T9.

Medication Guide
FERRIPROX® (Feh' ri prox)
(deferiprone)
oral solution, 80 mg/mL

What is the most important information I should know about FERRIPROX?

FERRIPROX can cause serious side effects, including a very low white blood cell count. One type of white blood cell that is important for fighting infections is called a neutrophil. If your neutrophil count is low (neutropenia), you may be at risk of developing a serious infection that can lead to death. Neutropenia is common with FERRIPROX and can become severe in some people. Severe neutropenia is known as agranulocytosis. If you develop agranulocytosis, you will be at risk of developing serious infections that can lead to death.

Your healthcare provider should do a blood test before you start FERRIPROX and weekly during treatment to check your neutrophil count. If you develop neutropenia, your healthcare provider should check your blood counts every day until your white blood cell count improves. Your healthcare provider may temporarily stop treatment with FERRIPROX if you develop neutropenia or infection.

Stop taking FERRIPROX and get medical help right away if you develop any of these symptoms of infection:

- fever
- sore throat or mouth sores
- flu-like symptoms
- chills and severe shaking

See **"What are the possible side effects of FERRIPROX?"** for more information about side effects.

What is FERRIPROX?

FERRIPROX is a prescription medicine used to treat people with thalassemia syndromes who have iron overload from blood transfusions, when current iron removal (chelation) therapy does not work well enough.

It is not known if FERRIPROX is safe and effective:

- to treat iron overload due to blood transfusions in people with any other type of anemia that is long lasting (chronic)
- in children

Do not take FERRIPROX if you are allergic to deferiprone or any of the ingredients in FERRIPROX.

See the end of this Medication Guide for a complete list of ingredients in FERRIPROX.

Before you take FERRIPROX, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems
- are pregnant or plan to become pregnant. FERRIPROX can harm your unborn baby. You should avoid becoming pregnant during treatment with FERRIPROX. Tell your healthcare provider right away if you become pregnant during treatment with FERRIPROX.

  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test before you start treatment with FERRIPROX.
  - You should use effective birth control during treatment with FERRIPROX and for at least 6 months after the last dose.

  Males with female partners who are able to become pregnant:
  - You should use effective birth control during treatment with FERRIPROX and for at least 3 months after the last dose.
- are breastfeeding or plan to breastfeed. It is not known if FERRIPROX passes into your breast milk. Do not breastfeed during treatment with FERRIPROX and for 2 weeks after the last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

How should I take FERRIPROX?

Read the Instructions for Use for detailed instructions about how to measure and take a dose of FERRIPROX oral solution.

- Take FERRIPROX exactly as your healthcare provider tells you.
- Your healthcare provider will prescribe FERRIPROX based on your body weight.
- Your healthcare provider will check your body iron level during treatment with FERRIPROX and may change your dose if needed. Your healthcare provider may also change your dose of FERRIPROX if you have certain side effects. Do not change your dose of FERRIPROX unless your healthcare provider tells you to.
- Use the measuring cup that comes with FERRIPROX to measure your prescribed dose.
- Take FERRIPROX 3 times each day. Take your first dose in the morning, the second dose at mid-day, and the third

dose in the evening.

- Taking FERRIPROX with meals may help reduce nausea.
- **If you must take a medicine to treat indigestion (antacid), or mineral supplements that contain iron, aluminum, or zinc during treatment with FERRIPROX, allow at least 4 hours between taking FERRIPROX and these products.**
- If you take too much FERRIPROX, call your healthcare provider.
- If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and then continue with your regular schedule. Do not try to catch-up or take 2 doses at the same time to make up for a missed dose.

What are the possible side effects of FERRIPROX?

FERRIPROX can cause serious side effects, including:

- **See "What is the most important information I should know about FERRIPROX?"**
- **Increased liver enzyme levels in your blood.** Your healthcare provider should do monthly blood tests to check your liver function during treatment with FERRIPROX.
- **Decreased levels of zinc in your blood.** Your healthcare provider will do blood tests to check your zinc levels during treatment with FERRIPROX and may prescribe a zinc supplement for you if your zinc levels are low.

The most common side effects of FERRIPROX include:

- nausea
- vomiting
- stomach-area (abdominal) pain
- joint pain

FERRIPROX may cause a change in urine color to reddish-brown. This is not harmful and is expected during treatment with FERRIPROX.

These are not all the possible side effects of FERRIPROX.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store FERRIPROX?

- Store FERRIPROX oral solution at room temperature, 68°F to 77°F (20°C to 25°C).
- Store FERRIPROX oral solution in the original bottle and carton to protect from light.
- After first opening, write the date on the bottle and the carton. Use the bottle of FERRIPROX oral solution within 8 weeks from this date. After 8 weeks, discard the bottle and any unused FERRIPROX oral solution.

Keep FERRIPROX and all medicines out of the reach of children.

General information about the safe and effective use of FERRIPROX.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use FERRIPROX for a condition for which it was not prescribed. Do not give FERRIPROX to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about FERRIPROX that is written for health professionals.

What are the ingredients in FERRIPROX?

Active ingredient: deferiprone

Inactive ingredients: purified water, hydroxyethylcellulose, glycerin, hydrochloric acid, sucralose, potassium sorbate, bubble gum flavor and cyanocobalamin.

Distributed by: ApoPharma USA, Inc., Weston, FL, United States of America, 33326.
Manufactured by: Apotex Inc., Toronto, Ontario, Canada, M9L 1T9.
For more information, call 1-866-949-0995.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 04/2018

Instructions for Use
FERRIPROX® (Feh' ri prox)
(deferiprone)
oral solution, 80 mg/mL

Read this Instructions for Use before taking FERRIPROX oral solution and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Important information:

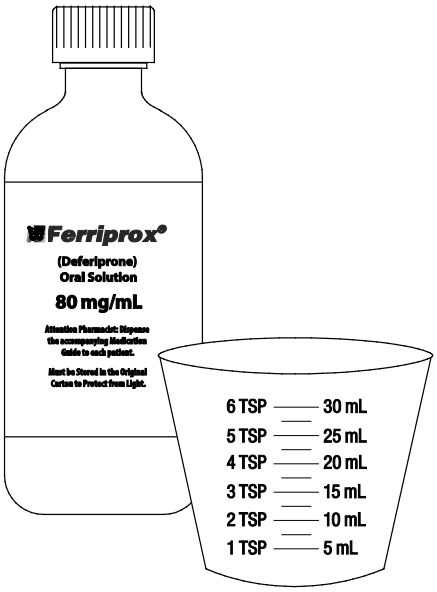
- Store FERRIPROX oral solution at room temperature, 68°F to 77°F (20°C to 25°C).
- Store FERRIPROX oral solution in the original bottle and carton to protect from light.
- After first opening the bottle, write the date on the bottle and the carton. Use the bottle of FERRIPROX oral solution within 8 weeks from this date. After 8 weeks, discard the bottle and any unused FERRIPROX oral solution.

Keep FERRIPROX oral solution and all medicines out of the reach of children.

Supplies needed to measure and take a dose of FERRIPROX oral solution **(See Figure A)**:

- 1 bottle of FERRIPROX oral solution
- 1 measuring cup (supplied with each bottle of FERRIPROX oral solution). The measuring cup has markings for teaspoons (TSP) and milliliters (mL). **Note:** 1 TSP is equal to 5 mL.

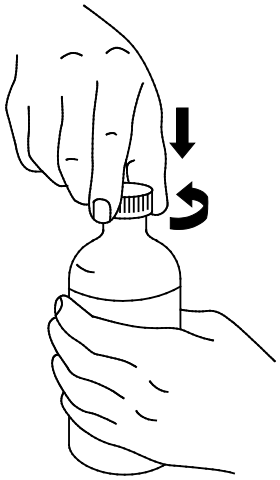
Figure A



If you do not receive a measuring cup with your FERRIPROX oral solution, ask your pharmacist. Only use the measuring cup that comes with FERRIPROX oral solution to make sure that you measure the right amount of medicine.

Step 1: To open the bottle of FERRIPROX oral solution, remove the outer plastic wrapper from the child-resistant cap. Push down on the child-resistant cap and turn the cap in the direction of the arrow **(See Figure B)**.

Figure B

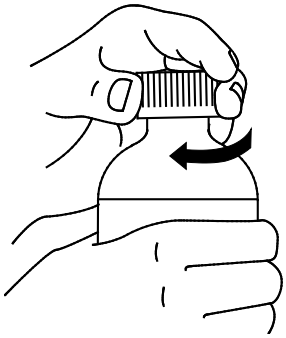


Step 2: Pour the prescribed dose of FERRIPROX oral solution into the measuring cup **(See Figure C)**.

Figure C

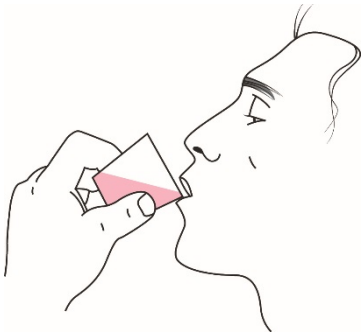
Step 3: Put the child-resistant cap back on the FERRIPROX oral solution bottle and turn it in the direction of the arrow. (**See Figure D**)

Figure D



Step 4: Swallow the prescribed dose of FERRIPROX oral solution (**See Figure E**).

Figure E



Step 5: Add about 10 to 15 mL of water to the measuring cup (**See Figure F**). Gently swirl the measuring cup to mix the water and any FERRIPROX oral solution left in the measuring cup (**See Figure G**). Drink all the mixture in the measuring cup (**See Figure H**).

Figure F

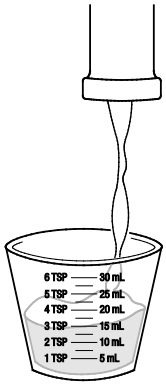


Figure G

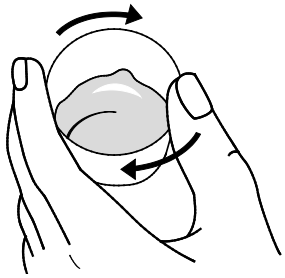
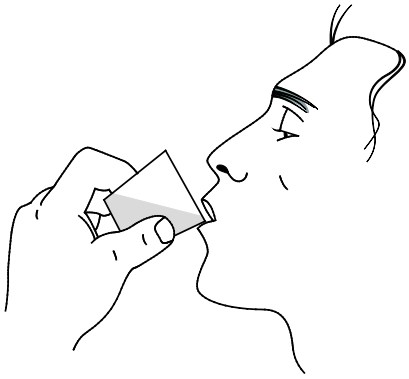


Figure H



Step 6: Hand-wash the measuring cup with water.

Step 7: Keep the measuring cup with the bottle of FERRIPROX oral solution.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Distributed by:
ApoPharma USA, Inc., Weston, FL, United States of America, 33326.

Manufactured by:
Apotex Inc., Toronto, Ontario, Canada, M9L 1T9.

Issued: 04/2018.