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 AND 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)**

----------INDICATIONS AND USAGE----------

FERRIPROX® 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 actual 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----------

Tablets: 500 mg film-coated, with functional scoring. (3)

----------CONTRAINDICATIONS----------

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

----------WARNINGS AND PRECAUTIONS----------

- Liver Enzyme Elevations: Monitor monthly and discontinue for persistent elevations. (5.2)
- Zinc Deficiency: Monitor during therapy and supplement for deficiency. (5.3)
- Embryo-Fetal Toxicity: Can cause fetal harm. (5.4)

----------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 at: Telephone: 1-866-949-0995 or FDA at 1-800-FDA-1088
Email: medicalsafety@apopharma.com or www.fda.gov/medwatch

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

- Drugs Associated with Neutropenia or Agranulocytosis: Avoid co-administration. If co-administration is unavoidable, closely monitor the absolute neutrophil count. (7.1)
- UGT1A6 inhibitors: Avoid co-administration. (7.2)
- Polyvalent Cations: Allow at least a 4-hour interval between administration of FERRIPROX and drugs or supplements containing polyvalent cations (e.g., iron, aluminum, or zinc). (2.2, 7.2)

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

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: MM/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: AGRANULOCYTOSIS AND 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® 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 Recommended Dosage

Starting Dose

The recommended initial dose of FERRIPROX is 25 mg/kg actual body weight, orally, three times per day for a total of 75 mg/kg/day. Round dose to the nearest 250 mg (half-tablet).

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

Body Weight (kg)	Dose (mg)	Number of 500 mg tablets
20	500	1
30	750	1.5
40	1,000	2
50	1,250	2.5
60	1,500	3
70	1,750	3.5
80	2,000	4
90	2,250	4.5

Dose Adjustments

Tailor dose adjustments to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). The maximum dose is 33 mg/kg actual body weight, three times per day for a total of 99 mg/kg/day.

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

Body Weight (kg)	Dose (mg)	Number of 500 mg tablets
20	660	1.5
30	990	2
40	1,320	2.5
50	1,650	3.5
60	1,980	4
70	2,310	4.5
80	2,640	5.5
90	2,970	6

Monitor serum ferritin concentration every two to three months to assess the effect 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 Dosage Modification for Drug Interactions

Allow at least a 4-hour interval between administration of FERRIPROX and other drugs or supplements containing polyvalent cations such as iron, aluminum, or zinc *[see Drug Interactions (7.2), Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 500 mg film-coated, capsule-shaped, white to off-white tablets with functional scoring, and imprinted with "APO" score "500" on one side and plain on the other.

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 and 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 and neutropenia prior to initiating FERRIPROX treatment.

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 have developed neutropenia with FERRIPROX unless potential benefits outweigh potential risks.

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).

5.2 Liver Enzyme Elevations

In clinical studies, 7.5% of 642 patients 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.

5.3 Zinc Deficiency

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

5.4 Embryo-Fetal Toxicity

Based on findings from animal reproduction studies and evidence of genotoxicity, FERRIPROX can cause fetal harm when administered to a pregnant woman. The available data on the use of FERRIPROX in pregnant women are insufficient to inform risk. 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. Advise pregnant women and females of reproductive potential of the potential risk to the fetus *[see Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use an effective method of contraception during treatment with FERRIPROX and for at least six months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with FERRIPROX and for at least three months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

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

- Agranulocytosis and Neutropenia *[see Warnings and Precautions (5.1)]*
- Liver Enzyme Elevations *[see Warnings and Precautions (5.2)]*
- Zinc Deficiency *[see Warnings and Precautions (5.3)]*

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 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.

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 co-administration of FERRIPROX with other drugs known to be associated with neutropenia or agranulocytosis. If co-administration is unavoidable, closely monitor the absolute neutrophil count *[see Warnings and Precautions (5.1)]*.

7.2 Effect of Other Drugs on FERRIPROX

UDP-Glucuronosyltransferases (UGTs)

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

Polyvalent Cations

Deferiprone has the potential to bind polyvalent cations (e.g., iron, aluminum, and zinc); allow at least a 4-hour interval between administration of 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

In animal reproduction studies, oral administration of deferiprone to pregnant rats and rabbits during organogenesis at doses 33% and 49%, respectively, of the maximum recommended human dose (MRHD) resulted in structural abnormalities, embryo-fetal mortality and alterations to growth *(see Data).* The limited data from FERRIPROX use in pregnant women are insufficient to inform a drug-associated risk of major birth defects and miscarriage. Based on evidence of genotoxicity and developmental toxicity in animal studies, FERRIPROX can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background 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, such as cranial malformations, cleft palate, limb malrotation, anal atresia, internal hydrocephaly, anophthalmia, and fused bones. 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 in the breastfed child, including the potential for tumorigenicity shown for deferiprone in animal studies, advise patients that breastfeeding is not recommended during treatment with FERRIPROX, and for at least 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating FERRIPROX.

Contraception

Females

FERRIPROX can cause embryo-fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraception during treatment with FERRIPROX and for at least 6 months after the last dose.

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with FERRIPROX and for at least 3 months after the last dose *[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.

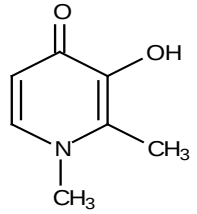
10 OVERDOSAGE

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) tablets contain 500 mg 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 tablets are white to off-white, capsule-shaped tablets, and imprinted with “APO” score “500” on one side and plain on the other. The tablets can be broken in half along the score line. Each tablet contains 500 mg deferiprone and the following inactive ingredients: Tablet core - microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide; Coating - hypromellose, polyethylene glycol, titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Deferiprone is a chelating agent that binds with ferric ions (iron III) 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 (e.g., copper, aluminum and zinc) than for iron.

12.2 Pharmacodynamics

Deferiprone exposure-response relationships and the time course of pharmacodynamics response are unknown.

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

The mean C_{max} and AUC of deferiprone was 20 mcg/mL and 50 mcg·h/mL, respectively, in healthy subjects. The dose proportionality of deferiprone over the approved recommended dosage range is unknown.

Absorption

Deferiprone appeared in the blood within 5 to 10 minutes after oral administration. Peak serum concentration of deferiprone was reached approximately 1 to 2 hours after a single dose.

Effect of Food

No clinically significant differences in the pharmacokinetics of deferiprone were observed following administration with food.

Elimination

The elimination half-life of deferiprone is approximately 2 hours.

Metabolism

Deferiprone is metabolized primarily by UGT1A6. The major metabolite of deferiprone is the 3-*O*-glucuronide, which lacks iron binding capability.

Excretion

Following oral administration, 75% to 90% of the administered dose was recovered in urine (primarily as metabolite) in the first 24 hours.

Specific Populations

No clinically significant differences in the pharmacokinetics of deferiprone were observed based on sex, race/ethnicity, body weight, mild to severe (eGFR 15 to 89 mL/min/1.73 m^2) renal impairment, or mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. The effect of age, including geriatric or pediatric populations, end stage renal disease, or severe (Child Pugh Class C) hepatic impairment on the pharmacokinetics of deferiprone is unknown.

Drug Interaction Studies

In Vitro Studies

UGT1A6 Inhibitors: Co-administration of deferiprone with phenylbutazone (UGT1A6 inhibitor) decreased glucuronidation of deferiprone by up to 78%.

Polyvalent Cations: 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.

14 CLINICAL STUDIES

Transfusional Iron Overload

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) tablets are white to off-white capsule-shaped tablets, film-coated, and have a functional score imprinted with “APO” score “500” on one side and are plain on the other. They are provided in HDPE bottles.

500 mg film-coated tablets, 100 tablets NDC 52609-0006-1

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide)

- Instruct patients and their caregivers to store FERRIPROX at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted to 15 °C to 30 °C (59 °F to 86 °F) [see USP Controlled Room Temperature]. Instruct patients and their caregivers to store FERRIPROX out of the reach and sight 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.
- Inform patients that their blood will be checked to monitor liver function and zinc levels. A zinc supplement may be prescribed if zinc levels are low.
- 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 iron. This is a very common sign of the desired effect of FERRIPROX, and it is not harmful.

Embryo-Fetal toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraception during treatment with FERRIPROX and for at least six months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*. Advise males with female partners of reproductive potential to

use effective contraception during treatment with FERRIPROX and for at least three months after the last dose *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)]*.

Lactation

Advise females not to breastfeed during treatment with FERRIPROX and for at least 2 weeks after the last dose *[see Use in Specific Populations (8.2)]*.

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

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 AND 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, Recommended Dosage (2.1) 08/2019

----------INDICATIONS AND USAGE----------

FERRIPROX® 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 actual 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----------

Tablets: 1,000 mg film-coated, with functional scoring. (3)

----------CONTRAINDICATIONS----------

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

----------WARNINGS AND PRECAUTIONS----------

- Liver Enzyme Elevations: Monitor monthly and discontinue for persistent elevations. (5.2)
- Zinc Deficiency: Monitor during therapy and supplement for deficiency. (5.3)
- Embryo-Fetal Toxicity: Can cause fetal harm. (5.4)

----------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 at: Telephone: 1-866-949-0995 or FDA at 1-800-FDA-1088
Email: medicalsafety@apopharma.com or www.fda.gov/medwatch

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

- Drugs Associated with Neutropenia or Agranulocytosis: Avoid co-administration. If co-administration is unavoidable, closely monitor the absolute neutrophil count. (7.1)
- UGT1A6 inhibitors: Avoid co-administration. (7.2)
- Polyvalent Cations: Allow at least a 4-hour interval between administration of FERRIPROX and drugs or supplements containing polyvalent cations (e.g., iron, aluminum, or zinc). (2.2, 7.2)

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

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: MM/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: AGRANULOCYTOSIS AND 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® 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 Recommended Dosage

Starting Dose

The recommended initial dose of FERRIPROX is 25 mg/kg actual body weight, orally, three times per day for a total of 75 mg/kg/day. Round dose to the nearest 500 mg (half-tablet).

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

Body Weight (kg)	Number of 1,000 mg tablets		
	Morning	Midday	Evening
20	0.5	0.5	0.5
30	1	0.5	1
40	1	1	1
50	1.5	1	1.5
60	1.5	1.5	1.5
70	2	1.5	2
80	2	2	2
90	2.5	2	2.5

Dose Adjustments

Tailor dose adjustments to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). The maximum dose is 33 mg/kg actual body weight, three times per day for a total of 99 mg/kg/day.

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

Body Weight (kg)	Number of 1,000 mg tablets		
	Morning	Midday	Evening
20	0.5	0.5	1
30	1	1	1
40	1.5	1	1.5
50	1.5	1.5	2
60	2	2	2
70	2.5	2	2.5
80	2.5	2.5	3
90	3	3	3

Monitor serum ferritin concentration every two to three months to assess the effect 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 Dosage Modification for Drug Interactions

Allow at least a 4-hour interval between administration of FERRIPROX and other drugs or supplements containing polyvalent cations such as iron, aluminum, or zinc *[see Drug Interactions (7.2), Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 1,000 mg film-coated, capsule-shaped, white to off-white tablets with functional scoring, and imprinted with "APO" score "1000" on one side and plain on the other.

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 and 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 and neutropenia prior to initiating FERRIPROX treatment.

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 have developed neutropenia with FERRIPROX unless potential benefits outweigh potential risks.

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).

5.2 Liver Enzyme Elevations

In clinical studies, 7.5% of 642 patients 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.

5.3 Zinc Deficiency

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

5.4 Embryo-Fetal Toxicity

Based on findings from animal reproduction studies and evidence of genotoxicity, FERRIPROX can cause fetal harm when administered to a pregnant woman. The available data on the use of FERRIPROX in pregnant women are insufficient to inform risk. 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. Advise pregnant women and females of reproductive potential of the potential risk to the fetus *[see Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use an effective method of contraception during treatment with FERRIPROX and for at least six months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with FERRIPROX and for at least three months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

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

- Agranulocytosis and Neutropenia *[see Warnings and Precautions (5.1)]*
- Liver Enzyme Elevations *[see Warnings and Precautions (5.2)]*
- Zinc Deficiency *[see Warnings and Precautions (5.3)]*

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 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.

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 co-administration of FERRIPROX with other drugs known to be associated with neutropenia or agranulocytosis. If co-administration is unavoidable, closely monitor the absolute neutrophil count *[see Warnings and Precautions (5.1)]*.

7.2 Effect of Other Drugs on FERRIPROX

UDP-Glucuronosyltransferases (UGTs)

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

Polyvalent Cations

Deferiprone has the potential to bind polyvalent cations (e.g., iron, aluminum, and zinc); allow at least a 4-hour interval between administration of 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

In animal reproduction studies, oral administration of deferiprone to pregnant rats and rabbits during organogenesis at doses 33% and 49%, respectively, of the maximum recommended human dose (MRHD) resulted in structural abnormalities, embryo-fetal mortality and alterations to growth *(see Data).* The limited data from FERRIPROX use in pregnant women are insufficient to inform a drug-associated risk of major birth defects and miscarriage. Based on evidence of genotoxicity and developmental toxicity in animal studies, FERRIPROX can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background 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, such as cranial malformations, cleft palate, limb malrotation, anal atresia, internal hydrocephaly, anophthalmia, and fused bones. 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 in the breastfed child, including the potential for tumorigenicity shown for deferiprone in animal studies, advise patients that breastfeeding is not recommended during treatment with FERRIPROX, and for at least 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating FERRIPROX.

Contraception

Females

FERRIPROX can cause embryo-fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraception during treatment with FERRIPROX and for at least 6 months after the last dose.

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with FERRIPROX and for at least 3 months after the last dose *[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.

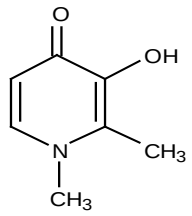
10 OVERDOSAGE

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) tablets contain 1,000 mg 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 tablets are white to off-white, capsule-shaped tablets, and imprinted with “APO” score “1000” on one side and plain on the other. The tablets can be broken in half along the score line. Each tablet contains 1,000 mg deferiprone and the following inactive ingredients: Tablet core - methylcellulose, crospovidone, and magnesium stearate; Coating - hypromellose, hydroxypropyl cellulose, macrogol, titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Deferiprone is a chelating agent that binds with ferric ions (iron III) 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 (e.g., copper, aluminum and zinc) than for iron.

12.2 Pharmacodynamics

Deferiprone exposure-response relationships and the time course of pharmacodynamics response are unknown.

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

The mean C_{max} and AUC of deferiprone was 20 mcg/mL and 50 mcg·h/mL, respectively, in healthy subjects. The dose proportionality of deferiprone over the approved recommended dosage range is unknown.

Absorption

Deferiprone appeared in the blood within 5 to 10 minutes after oral administration. Peak serum concentration of deferiprone was reached approximately 1 to 2 hours after a single dose.

Effect of Food

No clinically significant differences in the pharmacokinetics of deferiprone were observed following administration with food.

Elimination

The elimination half-life of deferiprone is approximately 2 hours.

Metabolism

Deferiprone is metabolized primarily by UGT1A6. The major metabolite of deferiprone is the 3-*O*-glucuronide, which lacks iron binding capability.

Excretion

Following oral administration, 75% to 90% of the administered dose was recovered in urine (primarily as metabolite) in the first 24 hours.

Specific Populations

No clinically significant differences in the pharmacokinetics of deferiprone were observed based on sex, race/ethnicity, body weight, mild to severe (eGFR 15 to 89 mL/min/1.73 m^2) renal impairment, or mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. The effect of age, including geriatric or pediatric populations, end stage renal disease, or severe (Child Pugh Class C) hepatic impairment on the pharmacokinetics of deferiprone is unknown.

Drug Interaction Studies

In Vitro Studies

UGT1A6 Inhibitors: Co-administration of deferiprone with phenylbutazone (UGT1A6 inhibitor) decreased glucuronidation of deferiprone by up to 78%.

Polyvalent Cations: 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.

14 CLINICAL STUDIES

Transfusional Iron Overload

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) tablets are white to off-white capsule-shaped tablets, film-coated, and have a functional score imprinted with “APO” score “1000” on one side and are plain on the other. They are provided in HDPE bottles.

1,000 mg film-coated tablets, 50 tablets NDC 52609-0007-5

Store at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted to 15 °C to 30 °C (59 °F to 86 °F) [see USP Controlled Room Temperature]. Keep the bottle tightly closed to protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide)

- Instruct patients and their caregivers to store FERRIPROX in the originally supplied bottle, closed tightly to protect from moisture. Store at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted to 15 °C to 30 °C (59 °F to 86 °F) [see USP Controlled Room Temperature]. Instruct patients and their caregivers to store FERRIPROX out of the reach and sight 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.
- Inform patients that their blood will be checked to monitor liver function and zinc levels. A zinc supplement may be prescribed if zinc levels are low.
- 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 iron. This is a very common sign of the desired effect of FERRIPROX, and it is not harmful.

Embryo-Fetal toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraception during treatment with FERRIPROX and for at least six months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*. Advise males with female partners of reproductive potential to use effective contraception during treatment with FERRIPROX and for at least three months after the last dose *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)]*.

Lactation

Advise females not to breastfeed during treatment with FERRIPROX and for at least 2 weeks after the last dose *[see Use in Specific Populations (8.2)]*.

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)
tablets

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?
- 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.
- 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 tablets at room temperature, 68°F to 77°F (20°C to 25°C).

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:
Tablet core: microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide.
Coating: hypromellose, polyethylene glycol, and titanium dioxide.

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: MM/YYYY