

Ferriprox[®] (deferiprone)

Prescribing Information
and Medication Guide

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

WARNING: AGRANULOCYTOSIS/NEUTROPENIA

See full prescribing information for complete boxed warning.

- FERRIPROX can cause agranulocytosis that can lead to serious infections and death. Neutropenia may precede the development of agranulocytosis. (5.1)
- Measure the absolute neutrophil count (ANC) before starting FERRIPROX and monitor 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)

08/2019

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

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

- Embryofetal Toxicity: Advise women of the potential hazard to the fetus and to avoid pregnancy while on this drug. (5.2)
- Liver Enzyme Elevations: Monitor monthly and discontinue for persistent elevations. (5.3)
- Zinc Deficiency: Monitor during therapy and supplement for deficiency. (5.4)

ADVERSE REACTIONS

- The most common adverse reactions are (incidence \geq 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

- 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: 08/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: AGRANULOCYTOSIS/NEUTROPENIA

- **FERRIPROX can cause agranulocytosis that can lead to serious infections and death. Neutropenia may precede the development of agranulocytosis. [see Warnings and Precautions (5.1)]**
- **Measure the absolute neutrophil count (ANC) before starting FERRIPROX therapy and monitor 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. Round dose to the nearest 500 mg (half-tablet).

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, three times per day for a total of 99 mg/kg/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 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

1,000 mg film-coated tablets with functional scoring.

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 ($ANC < 1.5 \times 10^9/L$).

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

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

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

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

Consider hospitalization and other management as clinically appropriate.

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

5.2 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 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 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 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.

5.4 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 clinically significant 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 nausea, vomiting, abdominal pain, alanine aminotransferase increased, arthralgia and neutropenia.

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

Table 2: Adverse drug reactions occurring in \geq 1% of 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 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 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 (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.

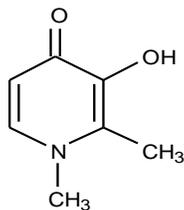
10 OVERDOSAGE

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) 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, and titanium dioxide.

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

The pharmacokinetics of deferiprone were not significantly influenced in subjects with mild renal impairment (eGFR 60 - 89 mL/min/1.73 m²), moderate renal impairment (eGFR 30 - 59 mL/min/1.73 m²), or severe renal impairment (eGFR 15 - 29 mL/min/1.73 m²), compared with healthy subjects (eGFR ≥ 90 mL/min/1.73 m²), given a single oral dose of FERRIPROX 33 mg/kg.

Patients with Hepatic Impairment

The pharmacokinetics of deferiprone and deferiprone 3-*O*-glucuronide were not influenced in subjects with mild hepatic impairment (Child Pugh Class A: 5-6 points) or moderate hepatic impairment (Child Pugh Class B: 7-9 points), compared with healthy subjects given a single oral dose of FERRIPROX 33 mg/kg. The pharmacokinetics of deferiprone and deferiprone 3-*O*-glucuronide have not been evaluated in subjects 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 $\geq 20\%$ 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.
- 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 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.

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