HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FERRIPROX Tablets safely and effectively. See full prescribing information for FERRIPROX Tablets.
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----------

Indications and Usage (1) 04/2021

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

FERRIPROX Tablets are an iron chelator indicated for the treatment of transfusional iron overload in adult and pediatric patients 8 years of age and older with thalassemia syndromes. (1.1)

FERRIPROX Tablets are an iron chelator indicated for the treatment of transfusional iron overload in adult and pediatric patients 8 years of age and older with sickle cell disease or other anemias. (1.2)

Limitations of Use

Safety and effectiveness have not been established for the treatment of transfusional iron overload in patients with myelodysplastic syndrome or in patients with Diamond Blackfan anemia. (1.3)

----------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 in patients with thalassemia (incidence ≥ 6%) are nausea, vomiting, abdominal pain, arthralgia, ALT increased and neutropenia. (5.1, 6)
- The most common adverse reactions in patients with sickle cell disease or other anemias (incidence ≥6%) are pyrexia, abdominal pain, bone pain, headache, vomiting, pain in extremity, sickle cell anemia with crisis, back pain, ALT increased, AST increased, arthralgia, oropharyngeal pain, nasopharyngitis, neutrophil count decreased, cough and nausea. (5.1, 6)

To report SUSPECTED ADVERSE REACTIONS, contact Chiesi USA, Inc. at 1-888-661-9260 or FDA at 1-800-FDA-1088 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: 04/2021

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

1.1 Transfusional Iron Overload in Patients with Thalassemia Syndromes

FERRIPROX Tablets are indicated for the treatment of transfusional iron overload in adult and pediatric patients 8 years of age and older with thalassemia syndromes.

1.2 Transfusional Iron Overload in Patients with Sickle Cell Disease or Other Anemias

FERRIPROX Tablets are indicated for the treatment of transfusional iron overload in adult and pediatric patients 8 years of age and older with sickle cell disease or other anemias.

1.3 Limitations of Use

- Safety and effectiveness have not been established for the treatment of transfusional iron overload in patients with myelodysplastic syndrome or in patients with Diamond Blackfan anemia.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for FERRIPROX Tablets for Adult and Pediatric Patients with Transfusional Iron Overload due to Thalassemia Syndromes, Sickle Cell Disease or Other Anemias

Starting Dosage

The recommended starting oral dosage of FERRIPROX Tablets is 25 mg/kg (actual body weight), 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

To minimize gastrointestinal upset when first starting therapy, dosing can start at 45 mg/kg/day and increase weekly by 15 mg/kg/day increments until the full prescribed dose is achieved.

Dosage Adjustments

Tailor dosage adjustments to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). The maximum oral dosagee 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

For patients who have trouble swallowing tablets, consider the use of FERRIPROX Oral Solution (see the prescribing information for FERRIPROX Oral Solution).

2.2 Monitoring Ferritin Levels to Assess Efficacy

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.

2.3 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.

The incidence of agranulocytosis was 1.7% of patients in pooled clinical trials of 642 patients with thalassemia syndromes and 1.5% of patients in pooled clinical trials of 196 patients with sickle cell disease or other anemias. 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 pooled clinical trials, 7.5% of 642 patients with thalassemia syndromes 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. In pooled clinical trials, 7.7% of 196 patients with sickle cell disease or other anemias treated with FERRIPROX developed increased ALT values.

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 embryo-fetal 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.

The following adverse reaction information represents the pooled data collected from single arm or active-controlled clinical trials with FERRIPROX Tablets (deferiprone) (three times a day) or FERRIPROX Oral Solution (deferiprone).

Thalassemia Syndromes

The safety of FERRIPROX was evaluated in the pooled clinical trial database *[see Clinical Studies (14.1)]*. Patients received FERRIPROX Tablets (three times a day) or FERRIPROX Oral Solution. FERRIPROX was administered orally three times a day (total daily dose either 50, 75, or 99 mg/kg), N=642. Among 642 patients receiving FERRIPROX , 492 (76.6%) were exposed for 6 months or longer and 365 (56.9%) were exposed for greater than one year.

The median age of patients who received FERRIPROX was 19 years (range 1, 77 years); 50.2% female; 71.2% White, 17.8% Asian, 9.2% Unknown, 1.2% Multi-racial and 0.6% Black.

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

The most common adverse reactions (≥6%) reported during clinical trials were nausea, vomiting, abdominal pain, arthralgia, alanine aminotransferase increased and neutropenia.

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

Table 2:Adverse reactions occurring in ≥ 1% of FERRIPROX-treated patients with thalassemia syndromes

Body System **Adverse Reaction**	**(N=642)** **% Patients**
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.

Sickle Cell Disease or Other Anemias

The safety of FERRIPROX compared to deferoxamine was evaluated in LA38-0411 *[see Clinical Studies (14.2)]*. Patients received FERRIPROX Tablets or FERRIPROX Oral Solution orally three times a day (total daily dose 75-99 mg/kg/day) n=152) or the control arm, deferoxamine, 20-40 mg/kg/day (children) or 40-50 mg/kg/day (adults), by subcutaneous infusion for 5 – 7 days per week, n=76. Among 152 patients receiving FERRIPROX, 120 (78.9%) were exposed for 6 months or longer and 17 (11.2%) were exposed for greater than one year.

The median age of patients who received FERRIPROX was 15 years (range 3, 59 years); 54.6% male; 78.9% White, 15.1% Black and 5.9% Multi-racial.

The most common adverse reactions (≥6%) reported during clinical trials in patients with SCD or other anemias were pyrexia, abdominal pain, bone pain, headache, vomiting, pain in extremity, sickle cell anemia with crisis, back pain, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, arthralgia, oropharyngeal pain, nasopharyngitis, neutrophil count decreased, cough and nausea.

The table below lists the adverse reactions (irrespective of a causal assessment; adverse events) of interest that occurred in patients treated with FERRIPROX in clinical trials in subjects with sickle cell disease or other anemias.

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