PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

FERRIPROX

Deferiprone Tablets
500 mg and 1000 mg

Deferiprone Oral Solution
100 mg/mL

Iron Chelating Agent

ATC Code: V03AC02

ApoPharma Inc.
200 Barmac Drive
Toronto, ON M9L 2Z7

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FERRIPROX

Deferiprone Tablets
Deferiprone Oral Solution

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	tablets, 500 mg, 1000 mg	None
Oral	oral solution, 100 mg/mL	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

FERRIPROX (deferiprone) is indicated for:

- the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.

FERRIPROX should only be prescribed by a qualified physician experienced in the treatment of patients with transfusional iron overload due to thalassemia syndromes.

FERRIPROX is available only through a controlled distribution program called **FERRIPROX Assist**. Under this program, only physicians and pharmacists registered with the program are able to prescribe and dispense the product. In addition, FERRIPROX can be dispensed only to patients who are registered with and meet the conditions of the **FERRIPROX Assist** program. Please call 1-844-347-7200 or log onto ferriproxassist.ca.

Geriatrics (> 65 years of age):
There are limited data on the use of FERRIPROX in this population.

Pediatrics (1 - 15 years of age):
Two hundred and twenty two (222) children 1 – 15 years of age, with iron overload, have been studied in clinical trials of FERRIPROX (see WARNINGS AND PRECAUTIONS, Special Populations – Pediatrics (1 - 15 years of age)). In clinical trials, pediatric patients experienced a higher frequency of decreased neutrophil counts than older patients (see WARNINGS AND PRECAUTIONS, Special Populations).

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- Women who are pregnant and/or breastfeeding.
- Patients who have baseline severe neutropenia (absolute neutrophil count < 0.5×10^9/L).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- FERRIPROX can cause agranulocytosis/severe neutropenia that may lead to serious and life-threatening infections. Neutropenia may precede the development of agranulocytosis (see ADVERSE REACTIONS).
  - Measure the absolute neutrophil count (ANC) before starting FERRIPROX and monitor the ANC weekly on therapy (see Hematologic and ADVERSE REACTIONS sections below). Interrupt FERRIPROX therapy if neutropenia develops.
  - Interrupt FERRIPROX therapy if infection develops and monitor the ANC more frequently.
  - Advise patients taking FERRIPROX to immediately seek medical help and present their wallet card if experiencing any symptoms indicative of infection.

Carcinogenesis and Mutagenesis

Non-clinical carcinogenicity studies have not been conducted with deferiprone. However, in view of positive genotoxicity results and the findings of mammary gland hyperplasia and mammary gland tumors in rats treated with deferiprone for 52 weeks, tumor formation in rodent carcinogenicity studies must be regarded as likely. Deferiprone was clastogenic in an *in vitro* mouse lymphoma cell assay and in a Chinese hamster ovary cell chromosomal aberration test. 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 (see TOXICOLOGY).

Hematologic

Agranulocytosis/Severe Neutropenia

FERRIPROX can cause agranulocytosis/severe neutropenia that may lead to serious and life-threatening infections. Agranulocytosis may be preceded by neutropenia (see ADVERSE REACTIONS). The mechanism of FERRIPROX-associated agranulocytosis is unknown.

In the pooled safety database, agranulocytosis/severe neutropenia was reported in 1.7% of patients. Agranulocytosis and neutropenia usually resolve upon discontinuation of FERRIPROX, but there have been post-marketing reports of agranulocytosis leading to death. Suggested management of cases of neutropenia and agranulocytosis is outlined below. It is recommended that such a management protocol be in place prior to initiating any patient on FERRIPROX treatment.

Patients should avoid other medicinal products known to be associated with neutropenia or agranulocytosis. Measure the absolute neutrophil count (ANC) before starting FERRIPROX therapy and monitor the ANC weekly on therapy.

Advise the patient to present the wallet card when seeing any healthcare professional for any reason as patients should avoid other medicinal products known to be associated with neutropenia or agranulocytosis.

For infection

Interrupt FERRIPROX therapy if infection develops and monitor the ANC more frequently.

If patients taking FERRIPROX experience any symptoms indicative of infection, advise them to immediately interrupt therapy, seek medical help and present the wallet card to the healthcare professional.

For neutropenia (ANC < 1.5×10^9/L and ≥ 0.5×10^9/L):

Interrupt FERRIPROX therapy if neutropenia develops.

Instruct the patient to immediately discontinue FERRIPROX and all other medications with a potential to cause neutropenia. The patient should be advised to limit contact with other individuals in order to reduce the risk of infection.

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 ≥ 1.5×10^9/L). Should any evidence of infection develop concurrently with the neutropenia, the appropriate cultures and diagnostic procedures should be performed and an appropriate therapeutic regimen instituted.

For agranulocytosis/severe neutropenia (ANC < 0.5×10^9/L):

Follow the above guidelines for neutropenia and if clinically indicated, admit patient to the hospital and institute other management as clinically appropriate.

Limited information is available regarding rechallenge in patients who experienced FERRIPROX-induced neutropenia or agranulocytosis. FERRIPROX therapy has been resumed in 31 patients (3 from clinical trials and 28 in post-marketing surveillance) who previously experienced FERRIPROX-induced agranulocytosis, and agranulocytosis recurred in 14 (45%) of these patients. In clinical trials, rechallenge in patients with moderate or severe neutropenia was not permitted by protocol. Resumption of FERRIPROX in patients who develop agranulocytosis is not recommended.

Patients with Diamond-Blackfan anemia, an unauthorized indication, may be at greater risk of FERRIPROX-induced agranulocytosis/severe neutropenia. FERRIPROX therapy is not recommended in patients with Diamond-Blackfan anemia.

Hepatic/Biliary/Pancreatic
In the pooled safety database, 7.5% of 642 patients treated with FERRIPROX developed increased serum alanine aminotransferase (ALT) values. The majority of these events were transient. Four (0.6%) FERRIPROX-treated patients discontinued the drug due to increased serum ALT levels and 1 (0.2%) due to an increase in both ALT and aspartate aminotransferase (AST) values.

Serum ALT values should be monitored periodically during therapy with FERRIPROX and interruption of therapy should be considered if there is a persistent increase in ALT levels.

Immune
Given that FERRIPROX can be associated with neutropenia and agranulocytosis, therapy in immune-compromised patients should not be initiated unless potential benefits outweigh potential risks.

Interrupt FERRIPROX therapy if infection develops and monitor the ANC more frequently.

Advise patients taking FERRIPROX to immediately interrupt therapy and report to their physician if they experience any symptoms indicative of infection.

Neurologic
Neurological disorders such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, abnormal hand movements and axial hypotonia, have been observed in two children treated for several months with approximately 2.5 times the maximum recommended dose. The neurological disorders regressed after FERRIPROX discontinuation.

Special Populations

Pregnant Women: No studies in pregnant women have been conducted, and relevant data from clinical use are limited. 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 (see TOXICOLOGY).

Deferiprone is contraindicated in pregnancy. Women of childbearing potential must be advised to avoid pregnancy. These women should be advised to take highly effective contraceptive measures and to immediately stop taking FERRIPROX if they become pregnant or plan to become pregnant.

Nursing Women: No studies have been conducted to determine the extent of deferiprone excretion in human milk. No prenatal and postnatal reproductive studies have been conducted in animals. Deferiprone is contraindicated in nursing women. If treatment is unavoidable, breast-feeding must be stopped.

Pediatrics (1 - 15 years of age): FERRIPROX has been studied in 222 pediatric patients participating in clinical trials, including 61 children less than 6 years old. Decreased neutrophil count ($p = 0.001$), neutropenia ($p = 0.17$), increased alanine aminotransferase ($p = 0.05$), and

agranulocytosis ($p = 0.28$) were reported more frequently in children less than 6 years old than in older patients.

Hepatic Impairment
There are no data available on the use of FERRIPROX in patients with hepatic impairment. As deferiprone is metabolized in the liver, caution must be exercised in patients with hepatic dysfunction. Liver enzymes should be carefully monitored in this patient population during FERRIPROX therapy. If there is evidence of deterioration in hepatic function, discontinuation of FERRIPROX therapy should be considered.

Renal Impairment
A study of the pharmacokinetic profile of deferiprone in subjects with mild, moderate, or severe renal impairment demonstrated that systemic exposure to deferiprone, as indicated by C_{max} and AUC, is not significantly altered by the presence or severity of renal impairment (see ACTION AND CLINICAL PHARMACOLOGY).

Monitoring and Laboratory Tests
The long-term effectiveness of FERRIPROX in controlling body iron load should be evaluated on a regular basis. It is recommended to monitor serum ferritin concentrations every two to three months and to monitor liver and cardiac iron concentrations annually, or as clinically indicated (see DOSAGE AND ADMINISTRATION).

<u>Absolute Neutrophil Counts</u>
The absolute neutrophil count (ANC) should be measured before starting FERRIPROX therapy and monitored weekly on therapy (see CONTRAINDICATIONS and Hematologic section above).

<u>Hepatic function</u>
Hepatic status should be evaluated prior to initiating FERRIPROX treatment. Serum ALT values should be monitored periodically during therapy with FERRIPROX. In patients with hepatic impairment, hepatic enzymes should be monitored periodically. Special care must be taken to ensure that iron chelation in patients with hepatitis C is optimal. In these patients careful monitoring of liver enzymes and of liver histology is recommended.

<u>Plasma Zinc concentration</u>
Monitoring of plasma Zn^{2+} concentration, and supplementation in case of a deficiency, is recommended.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse reactions reported during therapy with FERRIPROX in clinical trials were chromaturia, nausea, abdominal pain, vomiting, arthralgia, alanine aminotransferase increased, and neutropenia. The most serious adverse reaction reported in clinical trials with

FERRIPROX was agranulocytosis/severe neutropenia, defined as an absolute neutrophil count of less than 0.5×10^9/L, which occurred in approximately 2% of patients. Less severe episodes of neutropenia were reported in approximately 6% of patients (see **WARNINGS AND PRECAUTIONS**).

Arthropathies (including arthralgia, arthritis, and arthropathy) led to FERRIPROX discontinuation in 1.9% of patients. Gastrointestinal symptoms led to the discontinuation of FERRIPROX therapy in 1.6% of patients. Chromaturia (reddish/brown discolouration of the urine) is a result of the excretion of deferiprone-iron complex in the urine; it is an expected effect of FERRIPROX therapy and it is not harmful.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Study LA16-0102

Adverse events described in Table 1 below reflect the safety data from Study LA16-0102, a randomized, controlled trial in which 29 patients who were treated with FERRIPROX for a median duration of 359 days were compared to 32 patients treated with deferoxamine for a median duration of treatment of 365 days. Therapy with FERRIPROX was initiated at 75 mg/kg/d and was gradually increased to 100 mg/kg/d over an approximately 8-week period. The mean dose of FERRIPROX during the study was 92 mg/kg/d. Adverse events occurring at ≥10% incidence in either the FERRIPROX or deferoxamine arms are presented.

Table 1: Adverse events reported in ≥10% in either the FERRIPROX or deferoxamine arms in Study LA16-0102

System Organ Class Preferred Term	FERRIPROX n subjects exposed=29 N subjects (%)	Deferoxamine n subjects exposed=32 N subjects (%)
Eye disorders	**3 (10)**	**4 (13)**
Conjunctivitis	3 (10)	4 (13)
Gastrointestinal disorders	**20 (69)**	**14 (44)**
Nausea	11 (38)	0 (0)
Abdominal pain upper	9 (31)	3 (9)
Vomiting	9 (31)	5 (16)
Diarrhea	7 (24)	2 (6)
Abdominal discomfort	4 (14)	1 (3)

System Organ Class Preferred Term	FERRIPROX n subjects exposed=29 N subjects (%)	Deferoxamine n subjects exposed=32 N subjects (%)
Abdominal pain	4 (14)	4 (13)
Epigastric discomfort	4 (14)	3 (9)
Eructation	4 (14)	0 (0)
Toothache	3 (10)	4 (13)
General disorders and administration site conditions	**5 (17)**	**4 (13)**
Asthenia	3 (10)	4 (13)
Chest pain	3 (10)	0 (0)
Infections and infestations	**19 (66)**	**22 (69)**
Pharyngitis	7 (24)	12 (38)
Rhinitis	6 (21)	5 (16)
Viral infection	6 (21)	9 (28)
Gastroenteritis	3 (10)	5 (16)
Tooth abscess	3 (10)	2 (6)
Vaginal infection	3 (10)	2 (6)
Nasopharyngitis	2 (7)	7 (22)
Injury, poisoning and procedural complications	**4 (14)**	**7 (22)**
Transfusion reaction	4 (14)	4 (13)
Allergic transfusion reaction	0 (0)	4 (13)
Investigations	**21 (72)**	**16 (50)**
Weight increased	12 (41)	6 (19)
Alanine aminotransferase increased	11 (38)	5 (16)
Aspartate aminotransferase increased	6 (21)	1 (3)
Electrocardiogram t wave inversion	6 (21)	0 (0)
White blood cell count decreased	5 (17)	6 (19)
Gamma-glutamyltransferase increased	4 (14)	2 (6)
Electrocardiogram repolarisation abnormality	3 (10)	0 (0)

System Organ Class Preferred Term	FERRIPROX n subjects exposed=29 N subjects (%)	Deferoxamine n subjects exposed=32 N subjects (%)
Neutrophil count decreased	1 (3)	4 (13)
Weight decreased	1 (3)	9 (28)
Metabolism and nutrition disorders	**9 (31)**	**0 (0)**
Increased appetite	9 (31)	0 (0)
Musculoskeletal and connective tissue disorders	**16 (55)**	**17 (53)**
Back pain	12 (41)	15 (47)
Arthralgia	8 (28)	4 (13)
Myalgia	3 (10)	2 (6)
Nervous system disorders	**15 (52)**	**16 (50)**
Headache	14 (48)	16 (50)
Dizziness	2 (7)	4 (13)
Reproductive system and breast disorders	**3 (10)**	**3 (9)**
Dysmenorrhoea	3 (10)	3 (9)
Respiratory, thoracic and mediastinal disorders	**0 (0)**	**6 (19)**
Cough	0 (0)	6 (19)
Skin and subcutaneous tissue disorders	**5 (17)**	**3 (9)**
Dermatitis contact	3 (10)	1 (3)
Urticaria	3 (10)	2 (6)

- Treatment Emergent Adverse Events are coded with MedDRA Dictionary Version 13.0.

Study LA36-0310

LA36-0310 was prospectively designed as a pooled analysis of pre-existing data from studies that evaluated the efficacy of FERRIPROX. A safety evaluation was not included in the LA36-0310 analysis.

Pooled Safety Database

The safety of FERRIPROX has been evaluated from a pooled safety population of 642 FERRIPROX-treated patients who participated in 11 single arm or active-controlled clinical studies for which safety data was collected.

Table 2 below lists the adverse drug reactions that occurred in at least 1% of patients in the FERRIPROX pooled safety database.

Table 2: Adverse drug reactions occurring in ≥ 1% of 642 FERRIPROX-treated patients from pooled safety database

Body System Preferred Term	% Patients
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Neutropenia	6.2
Agranulocytosis/severe neutropenia	1.7
GASTROINTESTINAL DISORDERS	
Nausea	12.6
Abdominal pain/discomfort	10.4
Vomiting	9.8
Diarrhea	3.0
Dyspepsia	2.0
INVESTIGATIONS	
Alanine aminotransferase increased	7.5
Neutrophil count decreased	7.3
Weight increased	1.9
Aspartate aminotransferase increased	1.2
METABOLISM AND NUTRITION DISORDERS	
Increased appetite	4.0
Decreased appetite	1.1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Arthralgia	9.8
Back pain	2.0
Pain in extremity	1.9
Arthropathy	1.4
NERVOUS SYSTEM DISORDERS	
Headache	2.5
URINARY DISORDERS	
Chromaturia	14.6

Abnormal Hematologic and Clinical Chemistry Findings

In clinical studies, 7.5% of 642 subjects treated with FERRIPROX developed increased serum alanine aminotransferase (ALT) values. The majority of these events were transient. Four (0.6%) FERRIPROX-treated subjects discontinued the drug due to increased serum ALT levels and 1 (0.2%) due to an increase in both ALT and AST values.

Post-Market Adverse Drug Reactions

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 possible to reliably estimate their frequency or to establish a causal relationship to

drug exposure.

Blood and lymphatic system disorders: agranulocytosis, including some fatal cases, thrombocytosis, pancytopenia.

Cardiac disorders: atrial fibrillation, cardiac failure.

Congenital, familial and genetic disorders: hypospadias, congenital anomaly.

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.

DRUG INTERACTIONS

Drug-Drug Interactions

Drugs associated with neutropenia or agranulocytosis
Avoid concomitant use of FERRIPROX with other drugs known to be associated with neutropenia or agranulocytosis (see WARNINGS AND PRECAUTIONS).

UDP-glucuronosyltransferases (UGTs) inhibitors and inducers
Deferiprone is primarily eliminated via metabolism to the 3-*O*-glucuronide. *In vitro* studies suggest that glucuronidation is catalyzed primarily by UDP glucuronosyltransferase 1A6. Deferiprone exposure may be increased in the presence of a UGT1A6 inhibitor (see ACTION AND CLINICAL PHARMACOLOGY/Pharmacokinetics). However, the clinical significance of coadministration of FERRIPROX with a UGT1A6 inhibitor (e.g., acetaminophen, probenecid, and valproic acid) or an inducer (e.g., omeprazole, phenobarbital, and carbamazepine) has not been determined. Closely monitor patients for adverse reactions that may require downward dose titration or interruption when FERRIPROX is concomitantly administered with a UGT1A6 inhibitor.

Polyvalent cations
Concurrent use of FERRIPROX with mineral supplements and antacids that contain polyvalent cations has not been studied. Since deferiprone has the potential to bind polyvalent cations (e.g., iron, aluminum, and zinc), the concurrent use may result in reduced absorption of deferiprone and mineral supplements. It is recommended to allow at least a 4-hour interval between taking FERRIPROX and other medications (e.g., antacids), or supplements containing these polyvalent cations (see DOSAGE AND ADMINISTRATION).

Drug-Food Interactions

Administration of FERRIPROX with food in healthy volunteers decreased the C_{max} of deferiprone by 38% and the AUC by 10% (see ACTION AND CLINICAL PHARMACOLOGY/Pharmacokinetics). FERRIPROX can be taken with or without food.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- The effect of FERRIPROX in decreasing the body iron load is directly influenced by the dose and the degree of iron overload (pre-existing iron load and amount of iron input (transfusional iron and gastrointestinal iron absorption)).
- The long-term effectiveness of FERRIPROX in controlling body iron load should be evaluated on a regular basis. It is recommended to monitor serum ferritin concentrations every two to three months and to monitor liver and cardiac iron concentrations annually, or as clinically indicated.

- Dose adjustments should be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden). Reduction in dose of FERRIPROX should be considered if serum ferritin measurements approach normal.

Recommended Dose and Dosage Adjustment

The recommended dose of FERRIPROX is 25 to 33 mg/kg body weight, orally, three times a day for a total daily dose of 75 to 100 mg/kg body weight.

FERRIPROX can be taken with or without food. Taking FERRIPROX with meals may reduce nausea. In patients who develop gastrointestinal upset, such as nausea, vomiting and abdominal pain, the dose of FERRIPROX should be decreased for one to two weeks.

Allow at least a 4-hour interval between FERRIPROX and other medications or supplements containing polyvalent cations such as iron, aluminum or zinc (see **DRUG INTERACTIONS**).

Adjustment of FERRIPROX dosage on the basis of impaired renal function is unnecessary. There are no data in patients with end-stage renal disease on dialysis.

For FERRIPROX tablets, dose per kilogram body weight should be calculated to the nearest half tablet. To obtain a dose of about 75 mg/kg/day, use the number of tablets suggested in the following tables for the body weight of the patient.

Table 3: Dosage table for FERRIPROX 500 mg tablets

Body weight (kg)	Total daily dose (mg)	Dose (mg, three times/day)	Number of 500 mg tablets* (three times/day)
20	1500	500	1.0
30	2250	750	1.5
40	3000	1000	2.0
50	3750	1250	2.5
60	4500	1500	3.0
70	5250	1750	3.5
80	6000	2000	4.0
90	6750	2250	4.5

*rounded to nearest half tablet

Table 4: Dosage table for FERRIPROX 1000 mg tablets

Body weight (kg)	Total daily dose (mg)	Number of 1000 mg tablets*		
		Morning	Midday	Evening
20	1500	0.5	0.5	0.5
30	2250	1.0	0.5	1.0
40	3000	1.0	1.0	1.0
50	3750	1.5	1.0	1.5
60	4500	1.5	1.5	1.5
70	5250	2.0	1.5	2.0
80	6000	2.0	2.0	2.0
90	6750	2.5	2.0	2.5

*rounded to nearest half tablet

For FERRIPROX oral solution, dose per kilogram body weight should be calculated to the nearest 2.5 mL. To obtain a dose of about 75 mg/kg/day, use the number of millilitres suggested in the following table for the body weight of the patient.

Table 5: Dosage table for FERRIPROX 100 mg/mL oral solution

Body weight (kg)	Total daily dose (mg)	Dose (mg, three times/day)	mL of oral solution* (three times/day)
20	1500	500	5.0
30	2250	750	7.5
40	3000	1000	10.0
50	3750	1250	12.5
60	4500	1500	15.0
70	5250	1750	17.5
80	6000	2000	20.0
90	6750	2250	22.5

*rounded to the nearest 2.5 mL

Missed Dose

If a dose of this medicine has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped, and the regular dosing schedule resumed. Patients should not catch up or double doses.

OVERDOSAGE

There is no specific antidote to FERRIPROX overdose.

Prolonged overdosing (at approximately 2.5 times the maximum recommended dose) has been reported to be associated with adverse neurological effects, such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, abnormal hand movements and axial hypotonia (see WARNINGS AND PRECAUTIONS). The neurological disorders regressed after FERRIPROX discontinuation.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Deferiprone is a chelating agent with an affinity for ferric ions (iron III), binding them in neutral 3:1 (deferiprone:iron) complexes. Deferiprone has a lower binding affinity for metal ions such as copper, aluminum, zinc and ferrous ions (iron II) than for ferric ions.

Pharmacodynamics

The amount of deferiprone-induced iron excretion from the body is related to the dose of deferiprone, and is also influenced by the pre-existing iron load.

Pharmacokinetics

Absorption: Deferiprone is rapidly absorbed from the upper part of the gastrointestinal tract, appearing in the blood within 5 to 10 minutes of oral administration. Following a single 1500 mg (~21.6 mg/kg) oral dose of deferiprone under fasting conditions in healthy subjects, the mean maximum concentration (C_{max}) of deferiprone in serum was 20 µg/mL, and the mean area under the concentration-time curve (AUC) was 53 µg·h/mL. Peak serum concentrations occurred approximately 1 hour after a single dose in fasted subjects, and up to 2 hours after a single dose in the fed state. Administration with food decreased the C_{max} of deferiprone by 38% and the AUC by 10%. Following a single dose of 33 mg/kg in healthy subjects under fasting conditions, the mean C_{max} was 35 µg/mL and $AUC_{0\text{-}t}$ 93 µg·h/mL. Mean maximum serum deferiprone concentrations were reached at approximately 0.8 hours and then declined in a multi-exponential manner. Exposures to deferiprone are dose proportional over the dose range of 22-50 mg/kg (see DETAILED PHARMACOLOGY).

Pharmacokinetic data in patients with iron overload are limited. In four adult patients with iron overload and biopsy-proven liver cirrhosis, the mean C_{max} was 11 µg/mL and AUCτ 33 µg·h/mL after a 25 mg/kg dose at steady state (25 mg/kg three times per day) following a standard breakfast. After an initial delay in absorption, deferiprone serum levels rose steadily to attain their maximum concentration at approximately 2 hours post-dose. In patients with iron overload, serum deferiprone levels are lower than in healthy subjects.

Metabolism: The majority of an oral dose of deferiprone is metabolized to deferiprone 3-*O*-glucuronide, which lacks iron binding capacity; *in vitro* evidence indicates that the conjugation is catalyzed primarily by UGT1A6. Peak serum concentration of the 3-*O*-glucuronide occurs approximately 3 to 4 hours after administration of deferiprone in healthy subjects and in patients with iron overload. Systemic exposure to deferiprone 3-*O*-glucuronide was 1.4- to 2-fold (on a molar basis) that of the parent drug in patients with iron overload.

Distribution: The volume of distribution of deferiprone is approximately 1 L/kg in healthy subjects and 1.6 L/kg in patients with iron overload. The *in vitro* plasma protein binding of deferiprone is approximately 14% (see DETAILED PHARMACOLOGY).

Excretion: More than 90% of deferiprone is eliminated from plasma within 8 hours of ingestion. Following oral administration, 75% to 90% is recovered in the urine in the first 24 hours, primarily as the glucuronide, while approximately 5% of the administered dose is excreted as deferiprone. The elimination half-life is approximately 1.8 hours for deferiprone and 2.5 hours for the glucuronide metabolite in fasting healthy volunteers (see Detailed Pharmacology/Pharmacokinetics).

Drug-drug interactions: *In vivo* drug-drug interactions with an inducer or inhibitor of UGT1A6 have not been studied. An *in vitro* study showed a dose-dependent inhibition of deferiprone glucuronide formation by acetaminophen (up to 33%) in human UGT1A6 Supersome incubations. Deferiprone glucuronide formation was increased by omeprazole (up to 43%) in human hepatocyte cultures.

In vitro, deferiprone up to 400 µM (56 µg/mL) did not inhibit any of the CYP450 enzymes tested, i.e., CYP3A4, 2D6, 2C9, 1A2, 2E1 and 1A1. Drug-drug interactions between deferiprone and medications metabolized by cytochrome P450 enzymes are unlikely to occur.

The influence of age, race, gender, or obesity on deferiprone pharmacokinetics has not been established.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of deferiprone in children was assessed in 7 patients with thalassemia and iron overload aged 11 to 18 years (mean age=15 ± 2.7 years; median=16 years). These patients were on long term therapy with deferiprone and were thus considered to be at steady state. Drug concentrations were measured following administration of a dose of deferiprone, 25 mg/kg, after a standard breakfast. The exposures to deferiprone of the pediatric patients were consistent with those determined in adult patients when the drug was administered under fed conditions. Serum levels of deferiprone were maximal approximately 2 hours after dosing and declined with a half-life of 1.8 hours; levels of deferiprone glucuronide peaked at approximately 3 hours and fell with a half-life of 2.0 hours. No pharmacokinetic study has been conducted in patients <11 years of age.

Hepatic Insufficiency: The pharmacokinetics of deferiprone have not been studied in subjects with hepatic impairment.

Renal Insufficiency: The pharmacokinetics of deferiprone and its 3-*O*-glucuronide metabolite following a single oral 33 mg/kg dose of FERRIPROX were compared in subjects with renal impairment and in healthy volunteers. Systemic exposure to deferiprone, as indicated by C_{max} and AUC, was not significantly altered by renal impairment. Conversely, systemic exposure to the 3-*O*-glucuronide metabolite increased 1.3-, 2.7- and 5.6-fold (AUC_{∞}) in subjects with mild, moderate and severe renal impairment, respectively, as compared to that in subjects with normal renal function. Renal clearances of both deferiprone and the 3-*O*-glucuronide metabolite were significantly reduced by renal impairment. Most of the dose of FERRIPROX was excreted in urine over the first 24 hours as the 3-*O*-glucuronide metabolite, irrespective of the severity of renal impairment. The pharmacokinetic profile of deferiprone in patients with end-stage renal disease on dialysis has not been studied.

Thorough QT/QT_C Study
A study was conducted to evaluate the effect of single therapeutic (33 mg/kg) and supratherapeutic (50 mg/kg) oral doses of deferiprone on the cardiac QT and QTc interval duration in healthy subjects. The upper bound of the 95% one-sided confidence interval for the least-squares mean difference in QTcF between placebo and either dose was < 10 milliseconds

(ms) at all post-dose time points. The largest mean differences in QTcF from placebo were recorded at the 2 h time point and were 3.0 ms (95% one-sided UCL: 5.0 ms) for the 33 mg/kg dose and 5.2 ms (95% one-sided UCL: 7.2 ms) for the 50 mg/kg dose. Deferiprone was concluded to produce no significant prolongation of the QTc interval.

The 33 mg/kg dose of deferiprone was associated with statistically significant positive mean differences from placebo in heart rate, with a maximum mean difference of 4.9 (beats per minute) bpm (90% CI 3.2, 6.6) at 3 h. The 50 mg/kg dose of deferiprone was associated with statistically significant increases in heart rate from 2-10 h post-dosing, inclusive, with a maximum mean difference from placebo of 12.9 bpm (90% CI 10.8, 15.0) at 4 h.

The 33 mg/kg dose of deferiprone was associated with statistically significant decreases in systolic blood pressure at 0.6 h and 2 h, with a maximal mean difference from placebo of -3.0 mmHg (90% CI -5.1, -0.9). The 50 mg/kg dose of deferiprone was associated with statistically significant decreases in systolic blood pressure from 1 to 6 h, inclusive, with a maximum mean difference from placebo of -4.4 mmHg (90% CI -6.6, -2.1) at 1 h post-dosing.

The 33 mg/kg dose of deferiprone was associated with statistically significant decreases in diastolic blood pressure at 1h, 2 h, and 6 h post-dosing, with a maximum mean difference from placebo of -3.2 mmHg (90% CI -5.0, -1.4) at 6 h. The 50 mg/kg dose of deferiprone was associated with statistically significant decreases in diastolic blood pressure at 1 h, 2 h, and 4 h post-dosing, with a maximum mean difference from placebo of -4.5 mmHg (90% CI -6.4, -2.7) at 4 h.

STORAGE AND STABILITY

Store at room temperature (15 to 30ºC).

Keep in a safe place out of the reach and sight of children.

For the oral solution: After first opening, use within 35 days.

DOSAGE FORMS, COMPOSITION AND PACKAGING

FERRIPROX 500 mg tablets

White to off-white, capsule-shaped tablets, scored and engraved with “APO” score “500” on one side and plain on the other. The tablets can be broken in half along the score. Each 500 mg tablet contains 500 mg deferiprone and the following inactive ingredients: “Tablet core” – colloidal silicon dioxide, magnesium stearate, and microcrystalline cellulose (M102), “Coating” – hydroxypropyl methyl cellulose (2910), polyethylene glycol (3350), and titanium dioxide. Supplied in bottles of 100 tablets.

FERRIPROX 1000 mg tablets

White to off-white, capsule-shaped tablets, scored and engraved with “APO” score “1000” on

one side and plain on the other. The tablets can be broken in half along the score. Each 1000 mg tablet contains 1000 mg deferiprone and the following inactive ingredients: “Tablet core” – crospovidone, magnesium stearate, and methyl cellulose (A15LV), “Coating” – hydroxypropyl cellulose (LF), hydroxypropyl methylcellulose (2910 E5), polyethylene glycol (8000), and titanium dioxide. Supplied in bottles of 50 tablets.

FERRIPROX 100 mg/mL oral solution

A clear, reddish orange-coloured liquid available in 500 mL bottles. Each mL of oral solution contains 100 mg deferiprone and the following inactive ingredients: artificial cherry flavour, glycerol, Sunset Yellow FCF, hydrochloric acid, hydroxyethyl cellulose (Type H Pharm), peppermint oil, purified water, and sucralose.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

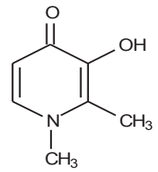
Drug Substance

Proper name: deferiprone

Chemical name: 3-hydroxy-1,2-dimethylpyridin-4-one

Molecular formula and molecular mass: $C_7H_9NO_2$; 139.15

Structural formula:



Physicochemical properties:

Solubility: deferiprone is slightly soluble in methanol and ethanol and very slightly soluble in acetone

The aqueous solubility of deferiprone throughout the pH range of 1 to 7.5 is provided in Table 6.

Table 6: Deferiprone - Aqueous pH Solubility Profile

Medium	Final pH Value	Solubility [mg/mL]
Water	5.7	14.3
0.01N HCl	2.0	16.0
0.1N HCl	1.1	32.7
Simulated Gastric Fluid (without enzymes)	1.2	28.9
0.05M Phosphate Buffer	2.5	17.1
0.05M Phosphate Buffer	4.5	14.6
0.05M Phosphate Buffer	6.0	13.9
0.05M Phosphate Buffer	6.8	13.4
0.05M Phosphate Buffer	7.2	13.8
0.05M Phosphate Buffer	7.5	13.3

CLINICAL TRIALS

The efficacy of FERRIPROX has been evaluated in twelve clinical studies: eight clinical trials, one of which (LA16-0102) is considered pivotal, three compassionate use studies, and an investigator sponsored study. LA36-0310, a prospectively planned, pooled analysis of pre-existing data from these twelve studies, evaluated the efficacy of FERRIPROX in transfusion-dependent iron-overloaded patients (nearly all with thalassemia) in whom previous iron chelation therapy (deferoxamine or deferasirox; mostly deferoxamine) had failed, due to an inadequate response or poor tolerance.

Demographic characteristics for LA16-0102 and for LA36-0310 are shown in Table 7.

Table 7: Summary of patient demographics for LA16-0102 and for LA36-0310

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range) (years)	Gender M/F
LA16-0102	Open-label, randomized, active comparator controlled clinical trial	FERRIPROX: Initiated at a dose of 25 mg/kg *tid* for a total daily dose of 75 mg/kg. Treatment was increased to 28.3 mg/kg *tid* approximately 4 weeks after therapy initiation and further increased to the maintenance dose of 33.3 mg/kg *tid* for a total daily dose of 100 mg/kg approximately 8 weeks after therapy initiation. Deferoxamine: 50 mg/kg/day, subcutaneous infusion on 5-7 days per week. Duration: 12 months	FERRIPROX = 29 Deferoxamine = 32	FERRIPROX = 25.1 (18-32) Deferoxamine = 26.2 (18-35)	FERRIPROX = 15 (52%)/14 (48%) Deferoxamine = 16 (50%)/16 (50%)
LA36-0310	Prospectively planned, pooled analysis of pre-existing data	FERRIPROX: 35 to 100 mg/kg/day, administered orally in either tablet or solution form. Duration: Up to 12 months	747	(monotherapy patients) For serum ferritin = 20 (2, 76) For LIC = 19 (6, 52) For MRI T2* = 25 (15, 32)	(monotherapy patients) For serum ferritin (236 patients) Female: 128 (54%) Male: 108 (46%) For LIC (87patients) Female: 45 (52%) Male: 42 (48%) For MRI T2* (31 patients[+]) Female: 16 (52%) Male: 15 (48%)

[+] 29 of 31 (93.5%) of the patients were from LA16-0102

LA16-0102

Study LA16-0102 was a 12-month, multi-centre, open-label, randomized, active controlled study conducted in transfusion-dependent β-thalassemia major patients between 18 and 36 years of age. Subjects had been receiving ongoing chelation therapy with deferoxamine for at least the past 5 years and had an abnormal (<20 milliseconds (ms)) but not severely abnormal (>8 ms) cardiac Magnetic Resonance Imaging T2-star (MRI T2*) value, a left ventricular ejection fraction (LVEF) greater than 56% (measured by Cardiovascular Magnetic Resonance), and a left ventricular shortening fraction greater than 30% (measured by echocardiogram). Patients were stratified into moderate (≥8 ms to <14 ms) or mild (≥14 ms to <20 ms) cardiac iron overload according to their baseline cardiac MRI T2* assessment and were randomized in a 1:1 ratio to receive either FERRIPROX administered three times a day (*tid*) orally in doses of 25 mg/kg for the first 4 weeks, increased to 28.3 mg/kg for the subsequent 4 weeks and maintained at 33.3 mg/kg for the remainder of the trial, or to continue with deferoxamine at a dose of 50 mg/kg/day administered by subcutaneous infusion on 5-7 days per week. A total of 61 patients were randomized and treated with FERRIPROX (N = 29) at an average dose of 92 mg/kg/day or with deferoxamine (N = 32) at an average dose of 43 mg/kg/day for 5.7 days per week.

The baseline demographics for age, sex, cardiac MRI T2* and liver iron concentration (LIC) were similar between the groups, although serum ferritin concentrations at baseline were higher in deferoxamine-treated patients (serum ferritin = 2,795 µg/L) compared to FERRIPROX-treated patients (serum ferritin = 1,790 µg/L). FERRIPROX-treated patients had a mean baseline cardiac MRI T2* value of 13.6 ms and LIC of 6.16 mg Fe/g dry weight (mg/g dw); corresponding values in deferoxamine-treated patients were similar at 13.9 ms and 6.32 mg Fe/g dry weight, respectively.

The primary efficacy measure was the subjects' cardiac iron status as determined by cardiac MRI T2*. An increase in cardiac iron concentration will decrease the cardiac MRI T2* value. A cardiac T2* value below 20 ms demonstrates cardiac iron overload, and lower cardiac T2* values are observed with increased severity of overload. Secondary efficacy measures were the assessment of serum ferritin concentration and LIC. LIC was assessed by the Superconducting Quantum-Interference Device (SQUID) BioSusceptometer. A tertiary efficacy measure was the LVEF measured by Cardiovascular Magnetic Resonance.

At the 12-month assessment, there was an improvement in cardiac MRI T2* of 3.5 ms (from 13.0 ms to 16.5 ms) in patients treated with FERRIPROX compared with a change of 1.7 ms (from 13.3 ms to 15.0 ms) in patients treated with deferoxamine, which corresponds to 27% increase and 13% increase for FERRIPROX and deferoxamine, respectively. The improvement in cardiac MRI T2* was significantly greater for FERRIPROX than deferoxamine (p = 0.02).

No significant difference (p = 0.16) in mean change of serum ferritin from baseline to 12 months between the two treatment groups was detected. In addition, the difference in mean decrease in LIC at 12 months (0.61 mg/g dw) between the 2 groups was statistically non-significant (p = 0.40). Over the same 12 months, LVEF increased from baseline by 3.1 ± 3.6 absolute units

(%) in the FERRIPROX group and by 0.3 ± 3.4 absolute units (%) in the deferoxamine group (difference between groups; nominal p = 0.003). Results for the efficacy endpoint MRI T2* are presented in Table 8. Results for efficacy endpoints serum ferritin, LIC and LVEF are presented in Table 9.

Table 8: LA16-0102: Relative Change in MRI T2* from baseline to 12 months for FERRIPROX and deferoxamine treatment groups – Intent-To-Treat Population

MRI T2*	Baseline		12 Months	
	FERRIPROX [n=29]	Deferoxamine [n=32]	FERRIPROX [n=29]	Deferoxamine [n=31]
Geometric Mean (milliseconds)†	13.0	13.3	16.5	15.0
Coefficient of Variation (%)§	32	30	38	39
Percentage of Baseline			127	113
Ratio of Means (%)‖	98		112	
p-value¶	0.77		0.02	

† Geometric mean is defined as antilog of the mean of the log data

§ Coefficient of variation is defined as $\sqrt{[e^{variance}-1]}$, where variance is the variance of the mean in log scale.

‖ The ratio is defined as FERRIPROX mean/deferoxamine mean. At 12 months, the ratio is corrected for the difference in baseline mean between the two treatment groups by dividing it by 0.98.

¶ The Log (MRI T2*) between the FERRIPROX and deferoxamine treatment groups was compared by the two-sample t-test.

Table 9: LA16-0102: Change in other efficacy endpoints from baseline to 12 months for FERRIPROX and deferoxamine treatment groups – Intent-To-Treat Population

Parameter	Change from baseline to 12 months		Difference between two treatment groups (95% Confidence Interval)	P-value for the difference
	FERRIPROX	Deferoxamine		
Mean (±SD) serum ferritin (µg/L) [N=number of study subjects]	-181 ± 826 (N=29)	-466 ± 739 (N=32)	285 (-116, 686)	0.16
Mean (±SD) LIC (mg/g dw) [N=number of study subjects]	-0.93 ± 2.93 (N=27)	-1.54 ± 2.49 (N=30)	0.61 (-0.83, 2.05)	0.40
Mean (±SD) LVEF (%) [N=number of study subjects]	3.07 ± 3.58 (N=29)	0.32 ± 3.38 (N=31)	2.75 (0.95, 4.55)	0.003

LA36-0310

In LA36-0310, data from 747 patients who had received FERRIPROX therapy were analyzed for study eligibility. Criteria for chelation failure were defined by one or more measures of iron accumulation above a boundary level associated with an increased risk of organ damage, as follows: serum ferritin > 2,500 µg/L before treatment with FERRIPROX (main criterion); or liver iron concentration (LIC) of > 7 mg/g dw; or excess cardiac iron stores as demonstrated by a cardiac MRI T2* < 20 ms. Results from patients who received FERRIPROX in combination with other chelation therapy are excluded from the presented analysis. Analysis criteria were met for serum ferritin, LIC, and cardiac MRI T2* for 236 patients, and 87 patients, and 31 patients, respectively. Most (29/31 (93.5%)) of the patients evaluated for the cardiac MRI T2* criterion were from LA16-0102.

FERRIPROX therapy was considered successful in individual patients who experienced a reduction in serum ferritin of ≥20% from baseline within one year of starting therapy (primary efficacy endpoint). Other success criteria (secondary efficacy endpoints) were a decline in LIC of ≥20% from baseline within one year of starting therapy or a decline in cardiac iron overload, defined as an increase in cardiac MRI T2* ≥20% from baseline within one year of starting therapy. Overall success rates were calculated as the proportion of patients with a successful outcome. In order to consider FERRIPROX therapy as successful for a particular measure, the lower limit of the 95% confidence interval (CI) for that efficacy measure had to be greater than 20%.

The dose of FERRIPROX ranged from 35-100 mg/kg/day, administered orally in either tablet or solution form. The majority (77%) of patients eligible for assessment for the primary efficacy

endpoint were administered a dose of 75 mg/kg/day; 18% received a dose of 100 mg/kg/day and 5% received a dose of ≤ 50 mg/kg/day.

The success rate for serum ferritin for patients on FERRIPROX monotherapy was 50% (95% CI: 43% to 57%). Mean serum ferritin decreased by 940 µg/L within one year of therapy (p=0.0001), i.e., from 4,444 µg/L at baseline to 3,503 µg/L at the last observation. The overall success rate for LIC was 38% (95% CI: 28% to 49%). For LIC, the mean decreased by 1.4 mg/g dw within one year of therapy (p=0.09), from 16.4 mg/g dw at baseline to 15.0 mg/g dw at the last observation. The overall success rate for cardiac MRI T2* was 65% (95% CI: 45% to 81%). For cardiac MRI T2* the mean increased by 3.9 ms within one year of therapy (p=0.0001), from 13.3 ms at baseline to 17.2 ms at the last observation.

Subgroup analyses were consistent with the primary analysis in that the lower limit of the 95% CI was greater than 20% for all subsets involved in analyses examining the impact of age, gender, and region.

Natural History Studies

Data from two natural history studies (Piga A, 2003; Borgna-Pignatti C, 2006) are supportive of the clinical effectiveness of FERRIPROX in the treatment of transfusional iron overload due to thalassemia syndromes.

DETAILED PHARMACOLOGY

Pharmacology

Deferiprone is an orally active, bidentate iron(III) chelating agent.

Pharmacodynamics

Primary pharmacodynamics

Deferiprone has a high affinity for iron(III) (pFe^{+3} = 19.4) and preferentially binds trivalent cations over divalent in the order of affinity: Fe(III) > Al(III) > Cu(II) > Zn(II) > Fe(II). Its small molecular size, lack of charge at physiological pH, and octanol:water distribution coefficient ($D_{7.4}$ = 0.19) support both rapid absorption from the gut and cell permeability. The uncharged ferric chelate is less cell membrane permeable ($D_{7.4}$ = 0.001), and increased iron uptake from the gut as the deferiprone:iron complex has been shown not to occur to any significant extent in humans and in various animal species.

Deferiprone prevents uptake by and mobilizes iron from primary cultures of cells, including rat cardiomyocytes, rat and human hepatocytes and mouse macrophages. Iron chelation reduces iron-mediated free radical damage measured by oxidative degradation of deoxyribose and lipid peroxyl activity, and protects against iron-induced loss of activities of mitochondrial respiratory enzyme complexes I-III.

Deferiprone increases iron excretion in multiple species, including the mouse, rat, gerbil, guinea pig and monkey, and removes iron from the kidney, pancreas and liver of iron-loaded animals. Some studies have shown reduction of excess cardiac iron levels.

A clinical study in thalassemia patients with iron overload demonstrated a dose-response relationship for deferiprone and 24-h urinary iron excretion at daily doses of between 25 and 100 mg/kg. Iron balance studies in thalassemia patients with iron overload demonstrated a dose-response relationship for deferiprone and iron excretion at doses of between 17 and 33 mg/kg three times daily. Deferiprone at doses of 25 mg/kg given three times daily promoted iron excretion sufficient to achieve negative iron balance or to neutralize the continued transfusional iron loading in the majority of transfusion-dependent patients.

Secondary Pharmacodynamics

Secondary pharmacodynamic effects of deferiprone may occur due to its binding of labile iron or other biologically important cations (e.g., Zn^{2+}, Cu^{2+}), which could result in depletion of cation pools required for metalloenzyme function. *In vivo* or *in vitro* studies revealed that deferiprone can inhibit the activity of the following enzymes at doses relevant to clinical exposures: tyrosine hydroxylase, tryptophan hydroxylase, hypoxia-inducible factor prolyl hydroxylase, ribonucleotide reductase, deoxyhypusine hydroxylase, catechol-*O*-methyltransferase, soybean LOX-1 (as a model for human 5-lipoxygenase) and heme iron-dependent cyclooxygenase. Inhibition of the non-heme iron-containing metalloenzyme ribonucleotide reductase is consistent with findings of clastogenicity, teratogenicity, and atrophy of proliferating tissues. Deferiprone was shown to reduce zinc levels and induce apoptosis in murine thymocytes.

Safety Pharmacology

Single oral doses of deferiprone of up to 100 mg/kg to mice and rats produced transient hypersalivation, whereas higher doses (300-600 mg/kg) affected behaviour, decreased rotarod performance and body temperature, and affected passive avoidance and motility. At doses lower than those used clinically, deferiprone has been shown to penetrate the blood brain barrier in rats, and to interfere with dopamine and serotonin metabolism through inhibitory effects on catechol-*O*-methyltransferase and tyrosine and tryptophan hydroxylases.

Single oral doses of up to 100 mg/kg deferiprone to rats increased urine volume and the excretion of sodium, potassium and chloride. Serum electrolyte levels and renal function were not investigated.

Deferiprone had no effect on hERG-mediated potassium currents in human cells, or on heart rate, blood pressure or ECG waveform at supratherapeutic doses in a 3-month oral toxicity study or in a single dose intravenous safety pharmacology study in cynomolgus monkeys.

Single oral doses of 30 mg/kg and higher stimulated dose dependent increases in plasma corticosterone and aldosterone in rats. Increases in ACTH release were detectable at 300 mg/kg. Studies of varying duration found that chronic administration of deferiprone in rats increased adrenal and pituitary gland weights.

Pharmacokinetics

Following administration of FERRIPROX 500 mg tablets at doses of 33 mg/kg and 50 mg/kg in healthy volunteers, mean maximum serum deferiprone concentrations were reached at approximately 0.8 hours and then declined in a multi-exponential manner. Mean apparent terminal elimination half-life was approximately 1.8 hours, and the AUC_{0-t} values were 93 and 148 µg·h/mL for the 33 mg/kg and 50 mg/kg doses, respectively (see Table 10 below).

Exposures to deferiprone and deferiprone 3-*O*-glucuronide were proportional to dose, i.e., approximately 60% higher following the 50 mg/kg deferiprone dose than after the 33 mg/kg dose. The PK parameter values of T_{max}, half-life, CL/F, and Vz/F were similar between the 2 treatments and doses.

Table 10: Mean (SD) Deferiprone and Glucuronide Serum Pharmacokinetic Parameters in Healthy Volunteers following a Single Dose under Fasting Conditions

Pharmacokinetic Parameters	33 mg/kg (N=46)	50 mg/kg (N=48)
Deferiprone		
C_{max} (µg/mL)	34 (8.85)	54 (16.4)
T_{max} (h)[a]	0.82 (0.32, 2.13)	0.82 (0.57, 4.07)
AUC_{0-t} (µg·h/mL)	93 (17.4)	148 (22.1)
$t_{1/2}$ (h)	1.85 (0.31)	1.84 (0.25)
CL/F (L/h)	25 (5.58)	23 (4.57)
V_Z/F (L)	66 (15.4)	62 (14.9)
Deferiprone glucuronide		
C_{max} (µg/mL)	35 (8.54)	51 (13.4)
T_{max} (h)[a]	3.07 (1.39, 4.07)	3.07 (2.07, 6.07)
AUC_{0-t} (µg·h/mL)	203 (44)	330 (75.2)
$t_{1/2}$ (h)	2.51 (0.52)	2.59 (0.24)

a. T_{max} is presented as Median (Minimum, Maximum)

Deferiprone is rapidly (T_{max} = 0.5-1.0 h) and extensively (F > 60%) absorbed in the upper gastrointestinal tract after oral dosing, and is cleared with serum half-life values of *ca.* 2.5 to 3 h in rats and 0.6 to 1.2 h in monkeys. *In vitro* binding to plasma proteins from human, rat and mouse is similar at 14.6 ± 2.6% over the concentration range of 10 - 400 µM (1.4 - 56 µg/mL) deferiprone.

A mass balance study in rats using oral administration of radiolabelled deferiprone 50 mg/kg showed wide and rapid distribution into tissues, with accumulation in the urine, liver, kidney, cecum, thyroid and nasal turbinates. Exposures were generally higher in females than in males. Tissue clearance was practically complete 72 h later, although radioactivity remained detectable in the thyroid, urine, nasal turbinates, liver, epididymis (in males), preputial gland (in females and hereafter), intra-orbital lacrimal gland, adrenal gland and spleen 168 h after dosing. Elimination of radioactivity was almost complete within 72 hours, primarily through urinary excretion (> 60%), with minor amounts present in bile and feces (≤ 10%). Most of the radioactivity was excreted as the pharmacologically inactive deferiprone-3-*O*-glucuronide, the

most abundant metabolite of deferiprone. Excretion of the parent compound and of the deferiprone-iron complex occurred to a lesser extent, and other minor metabolites accounted for < 1-2% of the administered dose.

No consistent or significant sex-related differences in exposure, accumulation of deferiprone or deferiprone-3-*O*-glucuronide, or reduction of exposure were noted following prolonged daily oral dosing of rats or cynomolgus monkeys. However, systemic exposures were lower in iron-loaded as compared to non-iron-loaded rats and monkeys.

TOXICOLOGY

Acute Toxicity

The median lethal dose (LD_{50}) of deferiprone in non-iron-loaded mice and rats given a single i.p. injection was 983 and 650 mg/kg, respectively. Convulsions preceded death in mice. The oral LD_{50} in rats was 2,000 to 3,000 mg/kg.

Subchronic and Long-Term Toxicity

In a 3-month rodent toxicology study, a minority of iron-supplemented rats given 125 mg/kg deferiprone *bid* orally were subject to unscheduled euthanasia during the latter two-thirds of the study, as a result of declining clinical condition, and decreased circulating RBC, platelet, and WBC counts. Microscopic examination revealed bone marrow hypocellularity, hepatic centrilobular degeneration and necrosis, and lymphocytic depletion in the thymic cortex. Bone marrow depression and non-regenerative anemia were considered to be the cause of death. Less severe effects were evident at 75 mg/kg *bid*, but no toxicologically relevant effects occurred at 37.5 mg/kg *bid*.

In a 3-month primate toxicology study, non-iron-loaded monkeys were terminated because of declining physical condition after 42-50 days' oral administration of deferiprone, 125 mg/kg *bid* and later 150 mg/kg *bid*; animals given 50 or 100 mg/kg *bid* (100 or 200 mg/kg/day) survived treatment as scheduled. Moderate to severe reductions in circulating platelet, reticulocyte and white cell (all types) counts were observed. Serum levels of iron were also decreased. Intestinal degeneration and necrosis were identified as the cause of morbidity, but bone marrow hypocellularity, depletion and necrosis of thymus, spleen and lymph nodes, and liver pathology were also significant. No toxicologically relevant effects were noted at 50 mg/kg *bid*.

In a 12-month rodent toxicology study, following administration of deferiprone at doses of 150 or 200 mg/kg/day in 2 divided doses (75 or 100 mg/kg bid), to non-iron-loaded or iron-loaded rats, respectively, 7 of 50 non-iron-loaded and 3 of 50 iron-loaded animals were either found dead or sacrificed moribund with severe anemia and slight to moderate centrilobular degeneration and necrosis. Animals from which blood samples could be collected prior to their unscheduled termination had elevated levels of total bilirubin, aspartate aminotransferase, and/or alanine aminotransferase of up to ca. 8, 4, and 14 times their respective group mean control value. These findings could be ascribed to hypoxia due to severe anemia (hemoglobin

concentration <2.5 g/dL). No findings of severe anemia with or without centrilobular degeneration and necrosis, or isolated findings of centrilobular degeneration and necrosis, were noted in non-iron-loaded or iron-loaded survivors. Relatively mild decreases in RBC and WBC counts in surviving rats partially reversed during a 4-week off-dose period following 12 months' treatment; recovery of bone marrow hypocellularity was complete in iron-loaded, but partial in non-iron-loaded, animals. The mean relative weight of the adrenal and pituitary gland was significantly greater in non-iron-loaded rats given 75 mg/kg deferiprone *bid* as compared to non-iron-loaded untreated rats.

In a 12-month primate toxicology study, no treatment-related changes were detected in non-iron-loaded monkeys dosed orally with 75 mg/kg deferiprone *bid*. Iron loading produced increases in serum ALT activity, which may have been exacerbated by deferiprone.

Fertility and Reproduction

Deferiprone had no significant effects on fertility and reproductive performance in non-iron-loaded male and female rats dosed orally at ≤ 75 mg/kg *bid* prior to and through mating (males) or through early gestation (females). In females, estrous cycle prolongation (manifested as time to confirmed mating) was noted at all doses tested.

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

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

Genotoxicity

Deferiprone was not mutagenic in a bacterial reverse mutation assay. It was positive in an *in vitro* L5178Y/TK+/- mouse lymphoma mutagenesis assay in the absence or presence of metabolic activation. Evidence of clastogenic effect was observed in a bone marrow micronucleus test in non-iron-loaded mice and after iron loading. There was no difference in the frequencies of lymphocyte chromosomal aberrations in thalassemia patients treated with deferiprone and deferoxamine in a clinical trial conducted to a crossover design.

Carcinogenicity

No rodent carcinogenicity studies have been conducted with deferiprone. In a 12 month rat toxicology study, reversible mammary gland hyperplasia occurred in female animals of all deferiprone-treated groups, irrespective of iron loading. The incidence of mammary tumors (1 of 65 males, 1 of 65 females) in deferiprone-treated animals was not statistically significantly different from that in controls.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

FERRIPROX

Deferiprone Tablets
Deferiprone Oral Solution

Read this carefully before you start taking FERRIPROX and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about FERRIPROX.

Serious Warnings and Precautions

FERRIPROX can cause a sudden severe drop in the neutrophil count. Some patients taking FERRIPROX developed a very low count of their neutrophils, a type of white blood cell that helps fight infections. This low count is called severe neutropenia or agranulocytosis. It can lead to a serious infection that can be deadly, if not treated.

Before you start FERRIPROX your doctor will order a blood test to check your neutrophil count. You will do this test every week while you are on FERRIPROX. If your count is too low, this testing may need to be done every day until you recover.

If you develop signs of infection such as fever, chills, sore throat, mouth sores, or flu-like symptoms, stop taking FERRIPROX and get medical help right away. Present your wallet card to the healthcare professional providing you with medical help. The card has important information about the drug you take.

What is FERRIPROX used for?

- FERRIPROX is used to treat patients with thalassemia syndromes who have too much iron in their body from blood transfusions. It is used when other iron removal drugs (chelators) do not work well enough.

How does FERRIPROX work?

FERRIPROX removes excess iron from the body. By doing this, it protects your body against toxic effects of iron.

What are the ingredients in FERRIPROX?

Medicinal ingredient: deferiprone
Non-medicinal ingredients:
FERRIPROX 500 mg tablets: colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide.

FERRIPROX 1000 mg tablets: crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methylcellulose, polyethylene glycol, titanium dioxide.

FERRIPROX 100 mg/mL oral solution: artificial cherry flavour, Sunset Yellow FCF, glycerol, hydrochloric acid, hydroxyethyl cellulose, peppermint oil, purified water, sucralose.

FERRIPROX comes in the following dosage forms:
Tablets: 500 mg or 1000 mg
Oral solution: 100 mg/mL

Do not use FERRIPROX if:
- you are allergic to deferiprone or any of the ingredients
- you are pregnant or breast-feeding
- you have a very low neutrophil count. Your doctor will only start you on FERRIPROX if you have enough neutrophils.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take FERRIPROX. Talk about any health conditions or problems you may have, including if you have:
- liver problems
- hepatitis C
- a weak immune system
- low zinc in your blood.

Other warnings you should know about:
- If you get neutropenia, avoid contact with other people. This may help to decrease the risk of infection.
- If you get a very low neutrophil count you may need to be treated in a hospital.
- If you have Diamond-Blackfan anemia you may be at greater risk if treated with FERRIPROX. FERRIPROX use is not recommended in these patients.
- FERRIPROX is likely to cause cancer in rodents. Talk with your doctor to learn more about this.

Warnings about Pregnancy, Birth Control and Breastfeeding
- If you want to get pregnant, discuss with your doctor the best way to do this.
- FERRIPROX can harm an unborn baby. If you become pregnant while taking FERRIPROX, tell your doctor right away.

Women on FERRIPROX who can bear children:
- should use highly effective birth control
- should avoid pregnancy
- should talk with their doctor about how to avoid pregnancy.

Breastfeeding:
- It is possible that FERRIPROX passes into breast milk. Decide with your doctor if you will take FERRIPROX or breastfeed. You must not do both.

Tell your healthcare professional about all the medicines you take, including any drugs,

vitamins, minerals, natural supplements, over-the-counter drugs or alternative medicines.

The following may interact with FERRIPROX:
- other medicines that can decrease your neutrophil count
- antacids or mineral supplements that contain iron, aluminum, or zinc. Wait at least 4 hours between taking these and FERRIPROX.

FERRIPROX is prescribed by a doctor experienced in the treatment of thalassemia patients with too much iron in their body. Take FERRIPROX under the care of a qualified doctor.

How to take FERRIPROX:
- exactly as prescribed by your doctor
- do not change your dose unless your doctor tells you to
- by mouth
- with or without food.

Taking FERRIPROX with meals may help reduce nausea. If you have nausea, vomiting or abdominal pain, the doctor may decrease your dose for one to two weeks.

Tablets: The dose of FERRIPROX is calculated to the nearest half-tablet. Cut or break tablets along the scoring line.

Oral Solution: The dose of FERRIPROX is calculated to the nearest 2.5 mL. Use the enclosed measuring cup to measure the volume required. Wash the measuring cup after each use.

Recommended dose: 25 to 33 mg/kg body weight three times a day.
Total Daily Dose: 75 to 100 mg/kg body weight.

Overdose:

If you think you have taken too much FERRIPROX, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget 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 possible side effects from using FERRIPROX?

These are not all the possible side effects you may feel when taking FERRIPROX. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

The most common side effects of FERRIPROX include:

- nausea, abdominal pain, vomiting, upset stomach
- increased or decreased appetite, weight gain
- headache
- joint, arm, leg, or back pain.

FERRIPROX can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret these results.

Your urine may become reddish-brown coloured. This is due to iron leaving the body, and is not harmful.

Tell your doctor if you have any side effect that bothers you and does not go away.

Wallet Card
Every time you receive a shipment of FERRIPROX, you will get a wallet card. This card has important safety information about FERRIPROX.

- carry this card with you

If you become ill or consult a healthcare professional:

- show the card to the healthcare professional providing you with medical help
- explain that the card has important information about the drug you take.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON **Low Neutrophil Count, Signs of Infection:** Fever, chills, sore throat, mouth sores, flu-like symptoms			✓
Neurological Side Effects: Tremors, walking disorders, double vision, involuntary muscle contractions, problems with movement coordination.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at room temperature (15 to 30°C).

Do not use FERRIPROX after the expiry date, which is stated on the label after EXP.

Keep out of reach and sight of children.

For the oral solution: After first opening, use within 35 days. Keep the measuring cup with the bottle of oral solution.

FERRIPROX Assist
FERRIPROX is only available through the **FERRIPROX Assist** program. The program will help manage the risk of low white blood cell counts in patients taking FERRIPROX.

DOCTOR
Only doctors registered in the program can prescribe FERRIPROX.

PHARMACIST
Only pharmacists registered in the program can dispense FERRIPROX.
They do this by shipping the medication to you. In each shipment, you will receive:

- wallet card
- a month supply of FERRIPROX. The tablets/oral solution may be sent to you:
  - in the bottle produced by the manufacturer
  - in a bottle prepared by the pharmacist
  - you may get a combination of these.
- Patient Medication Information
  - may come on loose printed papers

- may be attached to the manufacturer's bottle
- if there are changes to this information, you will receive information on a separate sheet. The sheet will be in a different colour.

If you need to talk to the pharmacist call 1-844-347-7200 or log onto ferriproxassist.ca. You can only receive drug counselling by phone.

PATIENT
FERRIPROX can only be dispensed to patients enrolled in **FERRIPROX Assist.** If you need more FERRIPROX for any reason such as travel, spills or lost tablets, call 1-844-347-7200 or log onto ferriproxassist.ca. Resupply is arranged on a case by case basis.

For more information on **FERRIPROX Assist** please call 1-844-347-7200 or log onto ferriproxassist.ca.

If you want more information about FERRIPROX:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website (www.apopharma.com), or by calling 1-866-949-0995.

This leaflet was prepared by ApoPharma Inc.

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