DEFERIPRONE- deferiprone tablet, coated
Hikma Pharmaceuticals USA Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DEFERIPRONE TABLETS safely and effectively. See full prescribing information for DEFERIPRONE TABLETS.
DEFERIPRONE tablets, for oral use
Initial U.S. Approval: 2011

WARNING: AGRANULOCYTOSIS AND NEUTROPENIA

See full prescribing information for complete boxed warning.

- **Deferiprone tablets 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 deferiprone tablets and monitor regularly while on therapy. (5.1)**
- **Interrupt deferiprone tablets therapy if neutropenia develops. (5.1)**
- **Interrupt deferiprone tablets if infection develops and monitor the ANC more frequently. (5.1)**
- **Advise patients taking deferiprone tablets to report immediately any symptoms indicative of infection. (5.1)**

INDICATIONS AND USAGE

Deferipronetablets are an iron chelator indicated for the treatment of transfusional iron overload in adult patients with thalassemia syndromes when current chelation therapy is inadequate. (1)
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.

DOSAGE AND ADMINISTRATION

- Deferiprone Tablets are available in a 1,000 mg formulation. (2.1)
- To prevent medication errors, before prescribing and dispensing, ensure that the tablet formulation is appropriate for the dosing regimen. Each tablet has distinct identifying characteristics. (2.1, 3)
- Deferiprone Tablets (three times a day), 1,000 mg:
    - Starting oral dosage: 75 mg/kg/day (actual body weight) in three divided doses (2.3)
    - Maximum oral dosage: 99 mg/kg/day (actual body weight) in three divided doses (2.3)

DOSAGE FORMS AND STRENGTHS

- Tablets (three times a day): 1,000 mg film-coated with functional scoring (3)

CONTRAINDICATIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-800-962-8364 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 deferiprone tablets 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: 8/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: AGRANULOCYTOSIS AND NEUTROPENIA

- **Deferiprone tablets 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 deferiprone tablets therapy and monitor regularly while on therapy.**
- **Interrupt deferiprone tablets therapy if neutropenia develops. *[see Warnings and Precautions (5.1)]***
- **Interrupt deferiprone tablets if infection develops, and monitor the ANC more frequently. *[see Warnings and Precautions (5.1)]***
- **Advise patients taking deferiprone tablets to report immediately any symptoms indicative of infection. *[see Warnings and Precautions (5.1)]***

1 INDICATIONS AND USAGE

Deferiprone tablets are indicated for the treatment of transfusional iron overload in adult patients with thalassemia syndromes when current chelation therapy is inadequate.

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.

Pediatric use information is approved for Chiesi USA, Inc.'s FERRIPROX® (deferiprone) tablets. However, due to Chiesi USA, Inc.'s marketing exclusivity rights, this drug product is not labeled with that information.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

- Deferiprone Tablets (three times a day) - 1,000 mg - given three times a day *[see Dosage and Administration (2.3)]*

To prevent medication errors, before prescribing and dispensing, ensure that the tablet formulation is appropriate for the dosing regimen. Each tablet has distinct identifying characteristics *[see Dosage Forms and Strengths (3)]*.

Monitoring for Safety:

Due to the risk of agranulocytosis, monitor ANC before and during deferiprone tablets therapy.

Test ANC prior to start of deferiprone tablets therapy and monitor on the following schedule during treatment:

- First six months of therapy: Monitor ANC weekly;
- Next six months of therapy: Monitor ANC once every two weeks;
- After one year of therapy: Monitor ANC every two to four weeks (or at the patient's blood transfusion interval in patients that have not experienced an interruption due to any decrease in ANC *[see Warnings and Precautions (5.1)]*.

Due to the risk of hepatic transaminase elevations, monitor ALT before and monthly during deferiprone tablets therapy *[see Warnings and Precautions (5.2)]*.

Due to the risk of zinc deficiency, monitor zinc levels before and regularly during deferiprone tablets therapy *[see Warnings and Precautions (5.3)]*.

2.3 Recommended Dosage for 1,000 mg Deferiprone Tablets (three times a day) for Adult Patients with Transfusional Iron Overload due to Thalassemia Syndromes

Starting Dosage for Three Times a Day Tablets:

The recommended starting oral dosage of deferiprone tablets (three times a day) is 75 mg/kg/day (actual body weight), in three divided doses per day. Table 3 describes the number of deferiprone tablets (three times a day) needed to achieve the 75 mg/kg/day total starting dosage. Round dose to the nearest 500 mg (half-tablet).

Table 3: Number of Deferiprone 1,000 mg Tablets (three times a day) Needed to Achieve the Total Starting Daily Dosage of 75 mg/kg (rounded to the nearest half-tablet)

Body Weight (kg)	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

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 for Three Times Daily Tablets:

Tailor dosage adjustments for deferiprone tablets (three times a day) to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). The maximum oral dosage is 99 mg/kg/day (actual body weight), in three divided doses per day. Table 4 describes the number of deferiprone tablets (three times a day) needed to achieve the 99 mg/day total maximum daily dosage.

Table 4: Number of Deferiprone 1,000 mg Tablets (three times a day) Needed to Achieve the Maximum Total Daily Dosage of 99 mg/kg (rounded to the nearest half-tablet)

Body Weight (kg)	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

Pediatric use information is approved for Chiesi USA, Inc.'s FERRIPROX® (deferiprone) tablets. However, due to Chiesi USA, Inc.'s marketing exclusivity rights, this drug product is not labeled with that information.

2.5 Monitoring Ferritin Levels to Assess Efficacy

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

2.6 Dosage Modification for Drug Interactions

Allow at least a 4-hour interval between administration of deferiprone tablets 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 (three times a day): 1,000 mg film-coated, modified capsule shaped, white to off-white with functional scoring and debossed with 54 [score] 23 on one side and plain on the other.

4 CONTRAINDICATIONS

Deferiprone tablets are 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 deferiprone tablets use. Deferiprone tablets can also cause neutropenia, which may foreshadow agranulocytosis. Measure the absolute neutrophil count (ANC) before starting deferiprone tablets therapy and monitor it regularly while on therapy *[see Dosage and Administration (2.1)]*.

Reduction in the frequency of ANC monitoring should be considered on an individual patient basis, according to the health care provider's assessment of the patient's understanding of the risk minimization measures required during therapy.

Interrupt deferiprone tablets therapy if neutropenia develops (ANC $< 1.5 \times 10^9$/L).

Interrupt deferiprone tablets if infection develops and monitor the ANC frequently.

Advise patients taking deferiprone tablets 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. The mechanism of deferiprone-associated agranulocytosis is unknown. Agranulocytosis and neutropenia usually resolve upon discontinuation of deferiprone tablets, 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 deferiprone tablets treatment.

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

Consider hospitalization and other management as clinically appropriate.

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

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

Instruct the patient to immediately discontinue deferiprone tablets 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).

5.2 Liver Enzyme Elevations

In pooled clinical trials, 7.5% of 642 patients with thalassemia syndromes treated with deferiprone tablets developed increased ALT values. Four (0.62%) deferiprone tablet-

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 deferiprone tablets and consider interruption of therapy if there is a persistent increase in the serum transaminase levels *[see Dosage and Administration (2.1)]*.

5.3 Zinc Deficiency

Decreased plasma zinc concentrations have been observed on deferiprone tablets therapy. Monitor plasma zinc annually, and supplement in the event of a deficiency *[see Dosage and Administration (2.1)]*.

5.4 Embryo-Fetal Toxicity

Based on findings from animal reproduction studies and evidence of genotoxicity, deferiprone tablets can cause fetal harm when administered to a pregnant woman. The available data on the use of deferiprone tablets 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 deferiprone tablets 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 deferiprone tablets 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 deferiprone tablets (three times a day).

Thalassemia Syndromes:

The safety of deferiprone tablets was evaluated in the pooled clinical trial database *[see Clinical Studies (14.1)]*. Patients received deferiprone tablets (three times a day). Deferiprone tablets were administered orally three times a day (total daily dose either 50, 75, or 99 mg/kg), N=642. Among 642 patients receiving deferiprone tablets, 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 deferiprone tablets 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 deferiprone tablets 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 deferiprone tablets in clinical trials in patients with thalassemia syndromes.

Table 7: Adverse reactions occurring in ≥ 1% of deferiprone tablets-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 deferiprone tablets 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 deferiprone tablets. 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, edema peripheral, multi-organ failure.

Hepatobiliary disorders: jaundice, hepatomegaly.

Immune system disorders: anaphylactic shock, hypersensitivity.

Infections and infestations: cryptococcal cutaneous infection, enteroviral encephalitis, pharyngitis, pneumonia, sepsis, furuncle, infectious hepatitis, rash pustular, subcutaneous abscess.

Investigations: blood bilirubin increased, blood creatinine phosphokinase increased.

Metabolism and nutrition disorders: metabolic acidosis, dehydration.

Musculoskeletal and connective tissue disorders: myositis, chondropathy, trismus.

Nervous system disorders: cerebellar syndrome, cerebral hemorrhage, convulsion, gait disturbance, intracranial pressure increased, psychomotor skills impaired, pyramidal tract syndrome, somnolence.

Psychiatric disorders: bruxism, depression, obsessive-compulsive disorder.

Renal disorders: glycosuria, hemoglobinuria.

Respiratory, thoracic and mediastinal disorders: acute respiratory distress syndrome, epistaxis, hemoptysis, pulmonary embolism.

Skin, subcutaneous tissue disorders: hyperhidrosis, periorbital edema, photosensitivity reaction, pruritis, urticaria, rash, Henoch-Schönlein purpura.

Vascular disorders: hypotension, hypertension.

7 DRUG INTERACTIONS

7.1 Drugs Associated with Neutropenia or Agranulocytosis

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

7.2 Effect of Other Drugs on Deferiprone Tablets

UDP-Glucuronosyltransferases (UGTs):

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

Polyvalent Cations:

Deferiprone has the potential to bind polyvalent cations (e.g., iron, aluminum, and zinc); allow at least a 4-hour interval between deferiprone tablets and other medications (e.g., antacids), or supplements containing these polyvalent cations *[see Dosage and Administration(2.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary:

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

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

Data:

Human Data:

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

Of the 39 pregnancies in deferiprone-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 deferiprone-treated patients, 5 resulted in healthy newborns, 1 resulted in a healthy newborn with slight hypospadias, 1 was electively terminated, 1 resulted in the intrauterine death of twins, and 2 had unknown outcomes.

Animal Data:

During organogenesis, pregnant rats and rabbits received deferiprone at oral doses of 0, 30, 80 or 200 mg/kg/day, and 0, 10, 50, or 150 mg/kg/day, respectively. The daily dose was administered as two equal divided doses approximately 7 hours apart. Doses of 200 mg/kg/day in rats and 150 mg/kg/day in rabbits, approximately 33% and 49% of the MRHD, respectively, resulted in increased post-implantation loss and reduced fetal weights in the presence of maternal toxicity (reduced maternal body weight and body weight gain in both rats and rabbits; abnormal large placenta at low incidence in rats). The 200 mg/kg/day dose in rats resulted in external, visceral and skeletal fetal malformations, such as cranial malformations, cleft palate, limb malrotation, anal atresia, internal hydrocephaly, anophthalmia, and fused bones. The dose of 150 mg/kg/day in rabbits resulted in external fetal malformations (partially opened eyes) and minor blood vessel and skeletal variations.

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

8.2 Lactation

Risk Summary:

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

Because of the potential for serious adverse reactions in the breastfed child, including the potential for tumorigenicity shown for deferiprone in animal studies, advise patients that breastfeeding is not recommended during treatment with deferiprone tablets, and for at least 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing:

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

Contraception:

Females:

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

Males:

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with deferiprone tablets and for at least 3 months after the last dose *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of deferiprone tablets have not been established in pediatric

patients with chronic iron overload due to blood transfusions who are less than 8 years of age.

Pediatric use information is approved for Chiesi USA, Inc.'s FERRIPROX® (deferiprone) tablets. However, due to Chiesi USA, Inc.'s marketing exclusivity rights, this drug product is not labeled with that information.

8.5 Geriatric Use

Clinical studies of deferiprone 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.

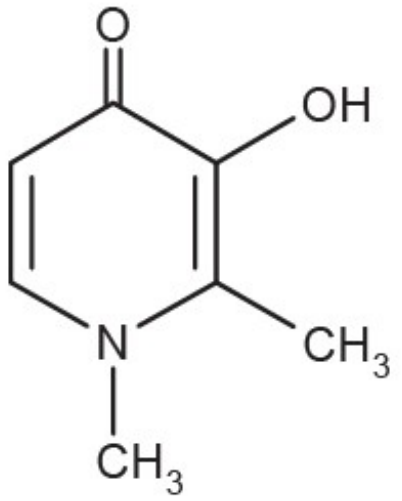
10 OVERDOSAGE

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

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 crystalline powder. It is slightly soluble in deionized water and has

a melting point range of 271°C - 273°C.

Deferiprone Tablets (three times a day), 1,000 mg:

Deferiprone tablets, 1,000 mg are white to off-white, modified capsule shaped, biconvex, film coated tablet, debossed with 54 [score] 23 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, magnesium stearate; *Coating:* hypromellose, polyethylene glycol, polysorbate 80, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Deferiprone is a chelating agent with an affinity for ferric ions (iron III). Deferiprone binds with ferric ions to form neutral 3:1 (deferiprone:iron) complexes that are stable at physiological pH.

12.2 Pharmacodynamics

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

Cardiac Electrophysiology:

At the maximum approved recommended dose, deferiprone does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Deferiprone Tablets (three times a day), 1,000 mg:

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

Absorption:

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

Effect of Food:

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

Elimination:

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

Metabolism:

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

Excretion:

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

Specific Populations:

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

Drug Interaction Studies:

In Vitro Studies:

UGT1A6 Inhibitors: Phenylbutazone (UGT1A6 inhibitor) decreased glucuronidation of deferiprone by up to 78%.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

14 CLINICAL STUDIES

The following information is based on studies with deferiprone tablets (three times a day).

14.1 Transfusional Iron Overload in Patients with Thalassemia Syndromes

In a prospective, planned, pooled analysis of patients with thalassemia syndromes from

several studies, the efficacy of deferiprone 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 deferiprone. Deferiprone therapy (35-99 mg/kg/day) was considered successful in individual patients who experienced a ≥ 20% decline in serum ferritin within one year of starting therapy.

Data from a total of 236 patients were analyzed. Of the 224 patients with thalassemia who received deferiprone monotherapy and were eligible for serum ferritin analysis, 105 (47%) were male and 119 (53%) were female. The mean age of these patients was 18.2 years (range 2 to 62; 91 patients were <17).

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

Deferiprone Tablets (three times a day), 1,000 mg:

Deferiprone Tablets (three times a day) are white to off-white, modified capsule shaped, biconvex, film coated tablets, debossed with 54 [score] 23 on one side and plain on the other. They are provided in a 50 count, 150 count, and 300 count HDPE bottle with a child-resistant cap.

NDC 0054-0711-19: Bottle of 50 Tablets

NDC 0054-0711-23: Bottle of 150 Tablets

NDC 0054-0711-28: Bottle of 300 Tablets

Storage:

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. 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 deferiprone tablets at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].
- *Deferiprone Tablets (three times a day), 1,000 mg:*

  Store in the originally supplied bottle, closed tightly to protect from moisture.

  Advise patients to take the first dose of deferiprone in the morning, the second

dose at midday, and the third dose in the evening. Clinical experience suggests that taking deferiprone tablets with meals may reduce nausea.

Embryo-Fetal toxicity:

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

Lactation:

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

Distributed by:

Hikma Pharmaceuticals USA Inc.

Berkeley Heights, NJ 07922

C50001130/03

Revised August 2023

Medication Guide
Deferiprone (de fer' i prone) Tablets

What is the most important information I should know about deferiprone tablets?

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

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

Stop taking deferiprone tablets and call your healthcare provider or get medical help right away if you develop any of these symptoms of infection:

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

It is important for you to have your white blood cell count checked within 24 hours of developing symptoms of an infection to see if you have severe neutropenia (agranulocytosis). Do not delay getting medical care if you are unable to reach your healthcare provider.
See **"What are the possible side effects of deferiprone tablets?"** for more information about side effects.

What are deferiprone tablets?
Deferiprone tablets are a prescription medicine used to treat iron overload from blood transfusions in adults with thalassemia syndromes when current iron removal (chelation) therapy does not work well enough.
It is not known if deferiprone tablets are safe and effective to treat iron overload due to blood transfusions:

- in people with myelodysplastic syndrome or Diamond Blackfan anemia
- in children less than 8 years of age

Do not take deferiprone tablets if you are allergic to deferiprone or any of the ingredients in deferiprone tablets.
See the end of this Medication Guide for a complete list of ingredients in deferiprone tablets.

Before taking deferiprone tablets, tell your healthcare provider about all of your medical conditions, including if you:

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

Females who are able to become pregnant:

- Your healthcare provider should do a pregnancy test before you start treatment with deferiprone tablets.
- You should use effective birth control during treatment with deferiprone tablets and for at least 6 months after the last dose.

Males with female partners who are able to become pregnant:

- You should use effective birth control during treatment with deferiprone tablets and for at least 3 months after the last dose.

- are breastfeeding or plan to breastfeed. It is not known if deferiprone passes into your breast milk. Do not breastfeed during treatment with deferiprone tablets and for at least 2 weeks after the last dose.

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

How should I take deferiprone tablets?

- Take deferiprone tablets exactly as your healthcare provider tells you.
- Your healthcare provider will prescribe deferiprone tablets based on your body weight.
- Your healthcare provider will check your body iron level during treatment with deferiprone tablets and may change your dose if needed. Your healthcare provider

may also change your dose of deferiprone tablets if you have certain side effects. Do not change your dose of deferiprone tablets unless your healthcare provider tells you to.
- **Take these deferiprone tablets 3 times each day.** Take your first dose in the morning, the second dose at mid-day, and the third dose in the evening.
- Taking deferiprone tablets with meals may help reduce nausea.
- **If you must take a medicine to treat indigestion (antacid), or supplements that contain iron, aluminum, or zinc during treatment with deferiprone tablets, allow at least 4 hours between taking deferiprone tablets and these products.**
- If you take too many deferiprone tablets, call your healthcare provider.
- If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and then continue with your regular schedule. Do not try to catch-up or take 2 doses at the same time to make up for a missed dose.

What are the possible side effects of deferiprone tablets?
Deferiprone tablets can cause serious side effects, including:

- **See "What is the most important information I should know about deferiprone tablets?"**
- **Increased liver enzyme levels in your blood.** Your healthcare provider should do blood tests to check your liver function before you start and then monthly during treatment with deferiprone tablets. Your healthcare provider may temporarily stop treatment with deferiprone tablets if you develop increased liver enzyme levels and they continue to be increased.
- **Decreased levels of zinc in your blood.** Your healthcare provider will do blood tests to check your zinc levels before you start and during treatment with deferiprone tablets, and may prescribe a zinc supplement for you if your zinc levels are low.

The most common side effects of deferiprone tablets in people with thalassemia include:

- nausea
- vomiting
- stomach-area (abdominal) pain
- joint pain
- abnormal liver function tests
- low white blood cells

Deferiprone tablets may cause a change in urine color to reddish-brown. This is not harmful and is expected during treatment with deferiprone tablets.
These are not all of the possible side effects of deferiprone tablets.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store deferiprone tablets?
Deferiprone Tablets, 1,000 mg (3 times each day)

- Store at room temperature between 68°F to 77°F (20°C to 25°C). Store deferiprone tablets in the original bottle and tightly closed to protect from moisture.

Keep deferiprone tablets and all medicines out of the reach of children.

General information about the safe and effective use of deferiprone tablets.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use deferiprone tablets for a condition for which they were not prescribed. Do not give deferiprone tablets to other people, even if they have the same symptoms that you have. They may harm them. You can ask your pharmacist or healthcare provider for information about deferiprone tablets that is written for health professionals.

What are the ingredients in deferiprone tablets?
Deferiprone Tablets, 1,000 mg (3 times each day)
Active ingredient: deferiprone
Inactive ingredients:

Tablet core: methylcellulose, crospovidone, magnesium stearate.
Coating: hypromellose, polyethylene glycol, polysorbate 80, and titanium dioxide.
Distributed by:
Hikma Pharmaceuticals USA Inc.
Berkeley Heights, NJ 07922
C50001130/03
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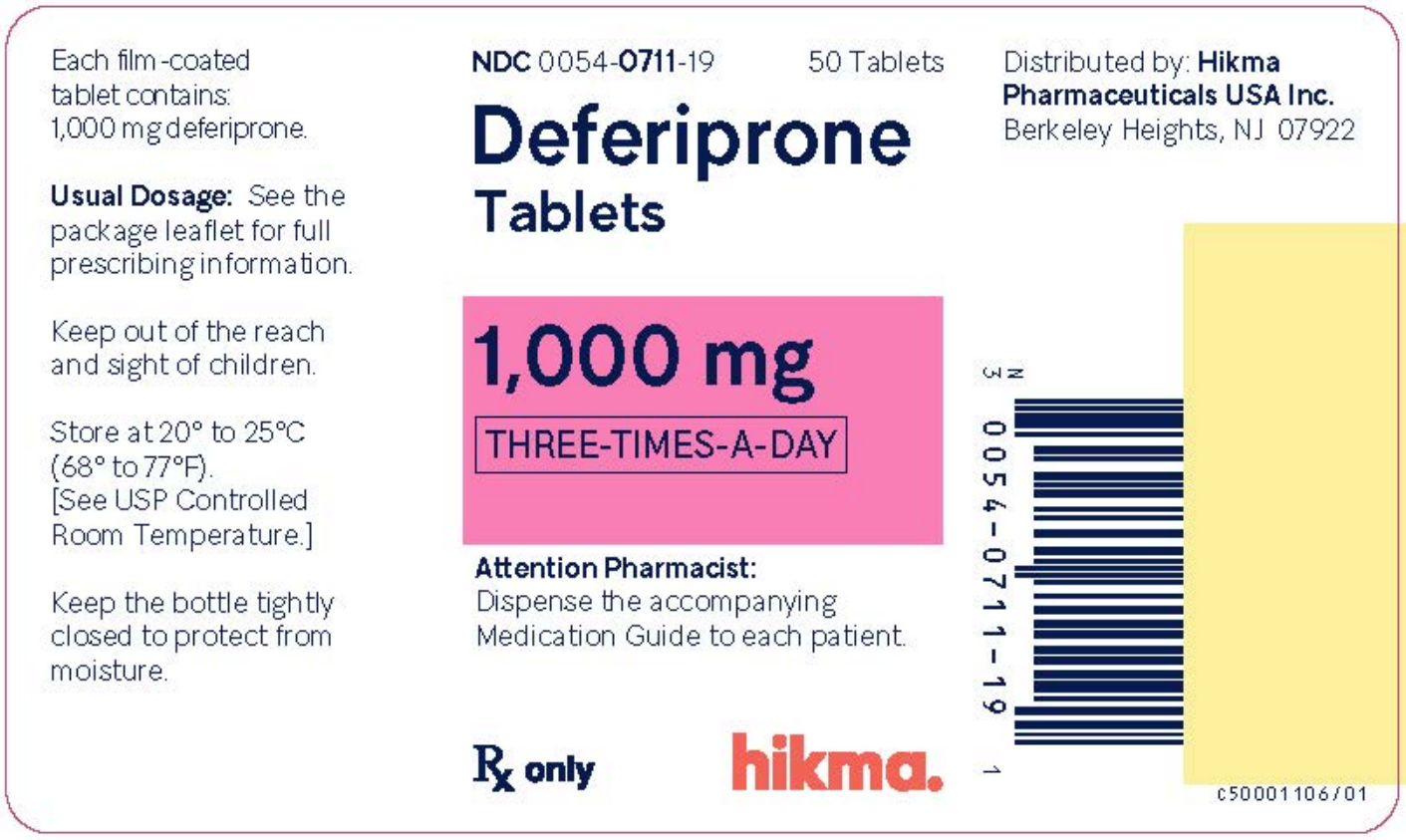
This Medication Guide has been approved by the U.S. Food and Drug Administration.

Pediatric use information is approved for Chiesi USA, Inc.'s FERRIPROX® (deferiprone) tablets. However, due to Chiesi USA, Inc.'s marketing exclusivity rights, this drug product is not labeled with that information.

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

Deferiprone Tablets, 1,000 mg Three-Time-A-Day Bottle of 50 NDC 0054-0711-19



PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

Deferiprone Tablets, 1,000 mg Three-Times-A-Day Bottle of 150 NDC 0054-0711-23

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

Deferiprone Tablets, 1,000 mg Three-Times-A-Day Bottle of 300 NDC 0054-0711-28

DEFERIPRONE

deferiprone tablet, coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0054-0711
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DEFERIPRONE (UNII: 2BTY8KH53L) (DEFERIPRONE - UNII:2BTY8KH53L)	DEFERIPRONE	1000 mg

Inactive Ingredients	
Ingredient Name	**Strength**
METHYLCELLULOSE (15 MPA.S) (UNII: NPU9M2E6L8)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	

POLYETHYLENE GLYCOL 1000 (UNII: U076Q6Q621)	
CROSPOVIDONE, UNSPECIFIED (UNII: 2S7830E561)	

Product Characteristics

Color	WHITE	**Score**	2 pieces
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	54;23
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0054-0711-19	50 in 1 BOTTLE; Type 0: Not a Combination Product	02/08/2022	
2	NDC:0054-0711-23	150 in 1 BOTTLE; Type 0: Not a Combination Product	02/08/2022	
3	NDC:0054-0711-28	300 in 1 BOTTLE; Type 0: Not a Combination Product	02/08/2022	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA213239	02/08/2022	

Labeler - Hikma Pharmaceuticals USA Inc. (080189610)

Establishment

Name	Address	ID/FEI	Business Operations
West-Ward Columbus Inc.		058839929	MANUFACTURE(0054-0711)

Revised: 8/2023 Hikma Pharmaceuticals USA Inc.