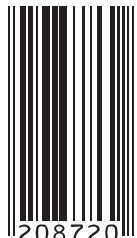


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Deferiprone Tablets 500 mg Rx only

WHITE

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DEFERIPRONE TABLETS safely and effectively.

DEFERIPRONE tablets, for oral use
Initial U.S. Approval: 2011

WARNING: AGRANULOCYTOSIS AND NEUTROPENIA
See full prescribing information for complete boxed warning.

- Deferiprone can cause agranulocytosis that can lead to serious infections and death. Neutropenia may precede the development of agranulocytosis.
Measure the absolute neutrophil count (ANC) before starting deferiprone and monitor weekly while on therapy.
Interrupt deferiprone if infection develops and monitor the ANC more frequently.
Advise patients taking deferiprone to report immediately any symptoms indicative of infection.

INDICATIONS AND USAGE

Deferiprone is an iron chelator indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.

Approval is based on a reduction in serum ferritin levels. There are no controlled trials demonstrating a direct treatment benefit, such as improvement in disease-related symptoms, functioning, or increased survival.

Limitations of Use

Safety and effectiveness have not been established for the treatment of transfusional iron overload in patients with other chronic anemias.

DOSAGE AND ADMINISTRATION

25 mg/kg to 33 mg/kg actual body weight, orally, three times per day, for a total daily dose of 75 mg/kg to 99 mg/kg body weight.

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: AGRANULOCYTOSIS AND NEUTROPENIA

- 1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS

FULL PRESCRIBING INFORMATION

WARNING: AGRANULOCYTOSIS AND NEUTROPENIA
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1 INDICATIONS AND USAGE

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Limitations of Use

- Safety and effectiveness have not been established for the treatment of transfusional iron overload in patients with other chronic anemias.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Starting Dose

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

DOSAGE FORMS AND STRENGTHS

Tablets: 500 mg with functional scoring. (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

The most common adverse reactions are (incidence ≥ 5%) nausea, vomiting and abdominal pain, alanine aminotransferase increased, arthralgia and neutropenia.

To report SUSPECTED ADVERSE REACTIONS, contact Taro Pharmaceuticals U.S.A., Inc. at 1-866-923-4914 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Drugs Associated with Neutropenia or Agranulocytosis: Avoid co-administration.
UGT1A6 inhibitors: Avoid co-administration.
Polyvalent Cations: Allow at least a 4-hour interval between administration of deferiprone and drugs or supplements containing polyvalent cations.

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2020

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
13 NONCLINICAL TOXICOLOGY
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

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

Table with 3 columns: Body Weight (kg), Dose (mg), Number of 500 mg tablets. Rows for 20, 30, 40, 50, 60, 70, 80, 90 kg.

Dose Adjustments

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

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

Table with 3 columns: Body Weight (kg), Dose (mg), Number of 500 mg tablets. Rows for 20, 30, 40, 50, 60, 70, 80, 90 kg.

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

2.2 Dosage Modification for Drug Interactions

Allow at least a 4-hour interval between administration of deferiprone and other drugs or supplements containing polyvalent cations such as iron, aluminum, or zinc.

3 DOSAGE FORMS AND STRENGTHS

Tablets, 500 mg are white to pinkish-white, capsule-shaped tablets; scored on one side, engraved "T" on the left of the score line and "5" on the right and plain on the other side.

4 CONTRAINDICATIONS

Deferiprone is contraindicated in patients with known hypersensitivity to deferiprone or to any of the excipients in the formulation. The following reactions have been reported in association with the administration of deferiprone: Henoch-Schönlein purpura; urticaria; and periorbital edema with skin rash.

5 WARNINGS AND PRECAUTIONS

5.1 Agranulocytosis and Neutropenia

Fatal agranulocytosis can occur with deferiprone use. Deferiprone can also cause neutropenia, which may foreshadow agranulocytosis. Measure the absolute neutrophil count (ANC) before starting deferiprone therapy and monitor it weekly while on therapy.

Interrupt deferiprone therapy if neutropenia develops (ANC < 1.5 x 10^9/L). Interrupt deferiprone if infection develops and monitor the ANC frequently. Advise patients taking deferiprone to immediately interrupt therapy and report to their physician if they experience any symptoms indicative of infection.

In pooled clinical trials, the incidence of agranulocytosis was 1.7% of patients. The mechanism of deferiprone-associated agranulocytosis is unknown. Agranulocytosis and neutropenia usually resolve upon discontinuation of deferiprone, 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 treatment.

For agranulocytosis (ANC < 0.5 x 10^9/L):

Consider hospitalization and other management as clinically appropriate. Do not resume deferiprone in patients who have developed agranulocytosis unless potential benefits outweigh potential risks. Do not rechallenge patients who have developed neutropenia with deferiprone unless potential benefits outweigh potential risks.

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

Instruct the patient to immediately discontinue deferiprone and all other medications with a potential to cause neutropenia. Obtain a complete blood cell (CBC) count, including a white blood cell (WBC) count corrected for the presence of nucleated red blood cells, an absolute neutrophil count (ANC), and a platelet count daily until recovery (ANC ≥ 1.5 x 10^9/L).

5.2 Liver Enzyme Elevations

In clinical studies, 7.5% of 642 patients treated with deferiprone developed increased ALT values. Four (0.62%) deferiprone-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 and consider interruption of therapy if there is a persistent increase in the serum transaminase levels.

5.3 Zinc Deficiency

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

5.4 Embryo-Fetal Toxicity

Based on findings from animal reproduction studies and evidence of genotoxicity, deferiprone can cause fetal harm when administered to a pregnant woman. The available data on the use of deferiprone in pregnant women are insufficient to inform risk. In animal studies, administration of deferiprone during the period of organogenesis resulted in embryofetal death and malformations at doses lower than equivalent human clinical doses. Advise pregnant women and females of reproductive potential of the potential risk to the fetus.

Advise females of reproductive potential to use an effective method of contraception during treatment with deferiprone 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 and for at least three months after the last dose.

6 ADVERSE REACTIONS

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

- Agranulocytosis and Neutropenia
Liver Enzyme Elevations
Zinc Deficiency

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reaction information for deferiprone represents the pooled data collected from 642 patients who participated in single arm or active-controlled clinical trials.

The most serious adverse reaction reported in clinical trials with deferiprone was agranulocytosis.

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

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

Table 2: Adverse drug reactions occurring in ≥ 1% of deferiprone-treated patients

Table with 2 columns: Body System Adverse Reaction, % Subjects (N=642). Rows for BLOOD AND LYMPHATIC SYSTEM DISORDERS, GASTROINTESTINAL DISORDERS.

cut here

Dispense with Medication Guide available at: https://www.taro.com/usa-medication-guides

Medication Guide
Deferiprone (de-fer-ip-rone) Tablets

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

Deferiprone 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.

Your healthcare provider should do a blood test before you start deferiprone and weekly during treatment to check your neutrophil count. If you develop neutropenia, your healthcare provider should check your blood counts every day until your white blood cell count improves.

Stop taking deferiprone and get medical help right away if you develop any of these symptoms of infection:

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

See "What are the possible side effects of deferiprone?" for more information about side effects.

What is deferiprone?

Deferiprone is a prescription medicine used to treat people with thalassemia syndromes who have iron overload from blood transfusions, when current iron removal (chelation) therapy does not work well enough.

It is not known if deferiprone is safe and effective:

- to treat iron overload due to blood transfusions in people with any other type of anemia that is long lasting (chronic)
in children

Do not take 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 you take 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 can harm your unborn baby. You should avoid becoming pregnant during treatment with deferiprone. Tell your healthcare provider right away if you become pregnant during treatment with deferiprone.

Females who are able to become pregnant:

- Your healthcare provider should do a pregnancy test before you start treatment with deferiprone.
You should use effective birth control during treatment with deferiprone 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 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 and for 2 weeks after the last dose.

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

How should I take deferiprone?

- Take deferiprone exactly as your healthcare provider tells you.
- Your healthcare provider will prescribe deferiprone based on your body weight.
- Your healthcare provider will check your body iron level during treatment with deferiprone and may change your dose if needed. Your healthcare provider may also change your dose of deferiprone if you have certain side effects. Do not change your dose of deferiprone unless your healthcare provider tells you to.
- Take deferiprone 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 with meals may help reduce nausea.
- **If you must take a medicine to treat indigestion (antacid), or mineral supplements that contain iron, aluminum, or zinc during treatment with deferiprone, allow at least 4 hours between taking deferiprone and these products.**
- If you take too much deferiprone, 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?

Deferiprone can cause serious side effects, including:

- **See “What is the most important information I should know about deferiprone?”**
- **Increased liver enzyme levels in your blood.** Your healthcare provider should do monthly blood tests to check your liver function during treatment with deferiprone.
- **Decreased levels of zinc in your blood.** Your healthcare provider will do blood tests to check your zinc levels during treatment with deferiprone and may prescribe a zinc supplement for you if your zinc levels are low.

The most common side effects of deferiprone include:

- nausea
- vomiting
- stomach-area (abdominal) pain
- joint pain

Deferiprone may cause a change in urine color to reddish-brown. This is not harmful and is expected during treatment with deferiprone.

These are not all the possible side effects of deferiprone.

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?

- Store deferiprone tablets at room temperature, 68°F to 77°F (20°C to 25°C) [see USP Controlled Room Temperature].

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

General information about the safe and effective use of deferiprone.

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

What are the ingredients in deferiprone tablets?

Active ingredient: deferiprone

Inactive ingredients: colloidal silicon dioxide, magnesium stearate, and microcrystalline cellulose.

Mfd. by: Taro Pharmaceutical Industries Ltd., Haifa Bay, Israel, 2624761

Dist. by: **Taro Pharmaceuticals U.S.A., Inc.**, Hawthorne, NY, 10532

Revised: March 2020 20872-0320-1

For more information, call 1-866-923-4914 or visit www.taro.com.

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 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. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: thrombocytosis, pancytopenia.

Cardiac disorders: atrial fibrillation, cardiac failure.

Congenital, familial and genetic disorders: hypospadias.

Eye disorders: diplopia, papilledema, retinal toxicity.

Gastrointestinal disorders: enterocolitis, rectal hemorrhage, gastric ulcer, pancreatitis, parotid gland enlargement.

General disorders and administration site conditions: chills, pyrexia, edema peripheral, multi-organ failure.

Hepatobiliary disorders: jaundice, hepatomegaly.

Immune system disorders: anaphylactic shock, hypersensitivity.

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

Investigations: blood bilirubin increased, blood creatinine phosphokinase increased.

Metabolism and nutrition disorders: metabolic acidosis, dehydration.

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

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

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

Renal disorders: glycosuria, hemoglobinuria.

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

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

Vascular disorders: hypotension, hypertension.

7 DRUG INTERACTIONS

7.1 Drugs Associated with Neutropenia or Agranulocytosis

Avoid co-administration of deferiprone 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

UDP-Glucuronosyltransferases (UGTs)

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

Polyvalent Cations

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

In animal reproduction studies, oral administration of deferiprone to pregnant rats and rabbits during organogenesis at doses 33% and 49%, respectively, of the maximum recommended human dose (MRHD) resulted in structural abnormalities, embryo-fetal mortality and alterations to growth [see *Data*].

The limited data from deferiprone use in pregnant women are insufficient to inform a drug-associated risk of major birth defects and miscarriage. Based on evidence of genotoxicity and developmental toxicity in animal studies, deferiprone 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 to 4% and 15 to 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 MRHD, 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, 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.

Contraception

Females

Deferiprone 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 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 and for at least 3 months after the last dose [see *Nonclinical Toxicology* (13.1)].

8.4 Pediatric Use

The safety and effectiveness of deferiprone in pediatric patients have not been established.

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.

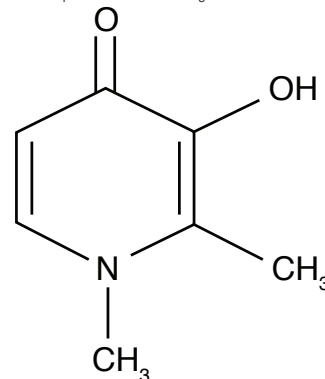
10 OVERDOSAGE

No cases of acute overdose have been reported. There is no specific antidote to deferiprone 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 500 mg deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one), a synthetic, orally active, iron-chelating agent. The molecular formula for deferiprone is C₁₁H₁₂N₂O, and its molecular weight is 193.15 g/mol. Deferiprone has the following structural formula:



Deferiprone is a white to pinkish-white powder. It is sparingly soluble in deionized water and has a melting point range of 272 °C to 278 °C.

Deferiprone tablets are white to pinkish-white, capsule-shaped tablets; scored on one side, engraved "T" on the left of the score line and "5" on the right and plain on the other side. The tablets can be broken in half along the score line. Each tablet contains 500 mg deferiprone and the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, and microcrystalline cellulose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Deferiprone is a chelating agent that binds with ferric ions (iron III) to form neutral 3:1 (deferiprone:iron) complexes that are stable over a wide range of pH values. Deferiprone has a lower binding affinity for other metals (e.g., copper, aluminum and zinc) than for iron.

12.2 Pharmacodynamics

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

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

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

Absorption

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

Effect of Food

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

Elimination

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

Metabolism

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

Excretion

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

Specific Populations

No clinically significant differences in the pharmacokinetics of deferiprone were observed based on sex, race/ethnicity, body weight, mild to severe (eGFR 15 to 89 mL/min/1.73 m²) renal impairment, or mild (Child Pugh Class A) to

moderate (Child Pugh Class B) hepatic impairment. The effect of age, including geriatric or pediatric populations, end stage renal disease, or severe (Child Pugh Class C) hepatic impairment on the pharmacokinetics of deferiprone is unknown.

Drug Interaction Studies

In Vitro Studies

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

14 CLINICAL STUDIES

Transfusional Iron Overload

In a prospective, planned, pooled analysis of patients from several studies, the efficacy of 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 to 99 mg/kg/day) was considered successful in individual patients who experienced a ≥ 20% decline in serum ferritin within one year of starting therapy.

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

For the patients in the analysis, the endpoint of at least a 20% reduction in serum ferritin was met in 50% (of 236 subjects), with a 95% confidence interval of 43% to 57%.

A small number of patients with thalassemia and iron overload were assessed by measuring the change in the number of milliseconds (ms) in the cardiac MRI T2* value before and after treatment with deferiprone for one year. There was an increase in cardiac MRI T2* from a mean at baseline of 11.8 ± 4.9 ms to a mean of 15.1 ± 7.0 ms after approximately one year of treatment. The clinical significance of this observation is not known.

16 HOW SUPPLIED/STORAGE AND HANDLING

Deferiprone Tablets, 500 mg are white to pinkish-white, capsule-shaped tablets; scored on one side, engraved "T" on the left of the score line and "5" on the right and plain on the other side. They are provided in a 100 count HDPE bottle with a child-resistant cap.

500 mg tablets, 100 tablets NDC 51672-4196-1

Store at 20° to 25°C (68° to 77°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 at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. Instruct patients and their caregivers to store deferiprone out of the reach and sight of children.
- Inform patients of the risks of developing agranulocytosis and instruct them to immediately interrupt therapy and report to their physician if they experience any symptoms of infection such as fever, sore throat or flu-like symptoms.
- Inform patients that their blood will be checked to monitor liver function and zinc levels. A zinc supplement may be prescribed if zinc levels are low.
- Advise patients to take the first dose of deferiprone in the morning, the second dose at midday, and the third dose in the evening. Clinical experience suggests that taking deferiprone with meals may reduce nausea. If a dose of this medicine has been missed, take it as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not catch-up or double doses.
- Advise patients to contact their physician in the event of overdose.
- Inform patients that their urine might show a reddish/brown discoloration due to the excretion of iron. This is a very common sign of the desired effect of deferiprone, and it is not harmful.

Embryo-Fetal toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions* (5.4) and *Use in Specific Populations* (8.1)]. Advise female patients of reproductive potential to use effective contraception during treatment with deferiprone 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 and for at least 2 weeks after the last dose [see *Use in Specific Populations* (8.2)].

Mfd. by: Taro Pharmaceutical Industries Ltd., Haifa Bay, Israel, 2624761

Dist. by: **Taro Pharmaceuticals U.S.A., Inc.**, Hawthorne, NY, 10532

Revised: March 2020 20872-0320-1

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