013-2021-05

Deferasirox Tablets

2101009

2D Code

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

DEFERASIROX tablets, for oral use

Initial U.S. Approval: 2005

WARNING: RENAL FAILURE, HEPATIC FAILURE, and GASTROINTESTINAL HEMORRHAGE
See full prescribing information for complete boxed warning.

Deferasirox may cause serious and fatal:

- **acute kidney injury, including acute renal failure requiring dialysis and renal tubular toxicity including Fanconi syndrome (5.1)**
- **hepatic toxicity, including failure (5.2)**
- **gastrointestinal hemorrhage (5.3)**

Deferasirox therapy requires close patient monitoring, including laboratory tests of renal and hepatic function. (5)

RECENT MAJOR CHANGES

Indications and Usage, Limitations of Use (1.3) 7/2019

INDICATIONS AND USAGE

Deferasirox tablets are an iron chelator indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. (1.1)

Deferasirox tablets are indicated for the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion-dependent thalassemia (NTDT) syndromes, and with a liver iron (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight (Fe/g dw) and a serum ferritin greater than 300 mcg/L. (1.2)

Limitations of Use:

The safety and efficacy of deferasirox tablets when administered with other iron chelation therapy have not been established. (1.3)

DOSAGE AND ADMINISTRATION

- Transfusional Iron Overload: Initial dose for patients with estimated glomerular filtration rate (eGFR) greater than 60 mL/min/1.73 m^2 is 14 mg per kg (calculated to nearest whole tablet) once daily. (2.1)
- NTDT Syndromes: Initial dose for patients with eGFR greater than 60 mL/min/1.73 m^2 is 7 mg per kg (calculated to nearest whole tablet) once daily. (2.2)
- See full prescribing information for information regarding monitoring, administration, and dose-reductions for organ impairment. (2.1, 2.2, 2.3, 2.4)

DOSAGE FORMS AND STRENGTHS

Tablets: 90 mg, 180 mg, 360 mg. (3)

CONTRAINDICATIONS

- Estimated GFR less than 40 mL/min/1.73 m^2. (4)
- Patients with poor performance status. (4)
- Patients with high-risk myelodysplastic syndrome (MDS). (4)
- Patients with advanced malignancies. (4)
- Patients with platelet counts less than 50 x 10^9/L. (4)
- Known hypersensitivity to deferasirox or any component of deferasirox tablets. (4)

WARNINGS AND PRECAUTIONS

- Acute Kidney Injury: Measure serum creatinine in duplicate before starting therapy. Monitor renal function during deferasirox therapy and reduce dose or interrupt therapy for toxicity. (2.1, 2.4, 5.1)
- Hepatic Toxicity: Monitor hepatic function. Reduce dose or interrupt therapy for toxicity. (5.2)
- Fatal and Nonfatal Gastrointestinal (GI) Bleeding, Ulceration, and Irritation: Risk may be greater in patients who are taking deferasirox in combination with drugs that have known ulcerogenic or hemorrhagic potential. (5.3)
- Bone Marrow Suppression: Neutropenia, agranulocytosis, worsening anemia, and thrombocytopenia, including fatal events; monitor blood counts during deferasirox therapy. Interrupt therapy for toxicity. (5.4)
- Age-related Risk of Toxicity: Monitor elderly and pediatric patients closely for toxicity. (5.5)
- Hypersensitivity Reactions: Discontinue deferasirox for severe reactions and institute medical intervention. (5.7)
- Severe Skin Reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS): Discontinue deferasirox. (5.8)

ADVERSE REACTIONS

In patients with transfusional iron overload, the most frequently occurring (greater than 5%) adverse reactions are diarrhea, vomiting, nausea, abdominal pain, skin rashes, and increases in serum creatinine. In deferasirox-treated patients with NTDT syndromes, the most frequently occurring (greater than 5%) adverse reactions are diarrhea, rash, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Annora Pharma Private Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Do not take deferasirox with aluminum-containing antacid preparations. (7.1)
- Deferasirox increases the exposure of repaglinide. Consider repaglinide dose reduction and monitor blood glucose levels. (7.3)
- Avoid the use of deferasirox with theophylline as theophylline levels could be increased. (7.4)
- Deferasirox increases exposure of busulfan. Monitor plasma concentrations of busulfan when coadministered with deferasirox to allow dose adjustment of busulfan, as needed. (7.7)

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: RENAL FAILURE, HEPATIC FAILURE, and GASTROINTESTINAL HEMORRHAGE

Renal Failure

- **Deferasirox can cause acute renal failure and death, particularly in patients with comorbidities and those who are in the advanced stages of their hematologic disorders.**
- **Evaluate baseline renal function prior to starting or increasing deferasirox dosing in all patients. Deferasirox is contraindicated in adult and pediatric patients with eGFR less than 40 mL/min/1.73 m^2. Measure serum creatinine in duplicate prior to initiation of therapy. Monitor renal function at least monthly. For patients with baseline renal impairment or increased risk of acute renal failure, monitor renal function weekly for the first month, then at least monthly. Reduce the starting dose in patients with preexisting renal disease. During therapy, increase the frequency of monitoring and modify the dose for patients with an increased risk of renal impairment, including use of concomitant nephrotoxic drugs, and pediatric patients with volume depletion or overchelation *[see Dosage and Administration (2.1, 2.4, 2.5), Warnings and Precautions (5.1), Adverse Reactions (6.1, 6.2)].***

Hepatic Failure

- **Deferasirox can cause hepatic injury including hepatic failure and death.**
- **Measure serum transaminases and bilirubin in all patients prior to initiating treatment, every 2 weeks during the first month, and at least monthly thereafter.**
- **Avoid use of deferasirox in patients with severe (Child-Pugh C) hepatic impairment and reduce the dose in patients with moderate (Child-Pugh B) hepatic impairment *[see Dosage and Administration (2.4), Warnings and Precautions (5.2)]*.**

Gastrointestinal Hemorrhage

- **Deferasirox can cause gastrointestinal (GI) hemorrhages, which may be fatal, especially in elderly patients who have advanced hematologic malignancies and/or low platelet counts.**
- **Monitor patients and discontinue deferasirox for suspected GI ulceration or hemorrhage *[see Warnings and Precautions (5.3)]*.**

1 INDICATIONS AND USAGE

1.1 Treatment of Chronic Iron Overload Due to Blood Transfusions (Transfusional Iron Overload)

Deferasirox tablets are indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older.

1.2 Treatment of Chronic Iron Overload in Non-Transfusion-Dependent Thalassemia Syndromes

Deferasirox tablets are indicated for the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion-dependent thalassemia (NTDT) syndromes and with a liver iron concentration (LIC) of at least 5 milligrams of iron per gram of liver dry weight (mg Fe/g dw) and a serum ferritin greater than 300 mcg/L.

1.3 Limitations of Use

The safety and efficacy of deferasirox tablets when administered with other iron chelation therapy have not been established.

2 DOSAGE AND ADMINISTRATION

2.1 Transfusional Iron Overload

Deferasirox therapy should only be considered when a patient has evidence of chronic transfusional iron overload. The evidence should include the transfusion of at least 100 mL/kg of packed red blood cells (e.g., at least 20 units of packed red blood cells for a 40 kg person or more in individuals weighing more than 40 kg), and a serum ferritin consistently greater than 1,000 mcg/L.

Prior to starting therapy, or increasing dose, evaluate:

- Serum ferritin level
- Baseline renal function:
  - o Obtain serum creatinine in duplicate (due to variations in measurements).
  - o Calculate the estimated glomerular filtration rate (eGFR). Use a prediction equation appropriate for adult patients (e.g., CKD-EPI, MDRD method) and in pediatric patients (e.g., Schwartz equations).
  - o Obtain urinalyses and serum electrolytes to evaluate renal tubular function *[see Dosage and Administration (2.4), Warnings and Precautions (5.1)]*.
- Serum transaminases and bilirubin *[see Dosage and Administration (2.4), Warnings and Precautions (5.2)]*
- Baseline auditory and ophthalmic examinations *[see Warnings and Precautions (5.10)]*

Initiating Therapy:

The recommended initial dose of deferasirox tablets for patients 2 years of age and older with eGFR greater than 60 mL/min/1.73 m^2 is 14 mg per kg body weight orally, once daily. Calculate doses (mg per kg per day) to the nearest whole tablet. Changes in weight of pediatric patients over time must be taken into account when calculating the dose.

During Therapy:

- Monitor serum ferritin monthly and adjust the dose of deferasirox, if necessary, every 3 to 6 months based on serum ferritin trends.
- Use the minimum effective dose to achieve a trend of decreasing ferritin.
- Make dose adjustments in steps of 3.5 or 7 mg per kg and tailor adjustments to the individual patient's response and therapeutic goals.
- In patients not adequately controlled with doses of 21 mg per kg (e.g., serum ferritin levels persistently above 2,500 mcg/L and not showing a decreasing trend over time), doses of up to 28 mg per kg may be considered. Doses above 28 mg per kg are not recommended *[see Warnings and Precautions (5.6)].*
- Adjust dose based on serum ferritin levels
  - o If the serum ferritin falls below 1,000 mcg/L at 2 consecutive visits, consider dose reduction especially if the deferasirox dose is greater than 17.5 mg/kg/day *[see Adverse Reactions (6.1)]*.
  - o If the serum ferritin falls below 500 mcg/L, interrupt deferasirox therapy to minimize the risk of overchelation, and continue monthly monitoring *[see Warnings and Precautions (5.6)].*
  - o Evaluate the need for ongoing chelation therapy for patients whose conditions no longer require regular blood transfusions.
  - o Use the minimum effective dose to maintain iron burden in the target range *[see Warnings and Precautions (5.6)].*
- Monitor blood counts, liver function, renal function and ferritin monthly *[see Warnings and Precautions (5.1, 5.2, 5.4)]*.
- Interrupt deferasirox for pediatric patients who have acute illnesses, which can cause volume depletion, such as vomiting, diarrhea, or prolonged decreased oral intake, and monitor more frequently. Resume therapy as appropriate, based on assessments of renal function, when oral intake and volume status are normal *[see Dosage and Administration (2.4, 2.5), Warnings and Precautions (5.1), Use in Specific Populations (8.4), Clinical Pharmacology (12.3)].*

2.2 Iron Overload in Non-Transfusion-Dependent Thalassemia Syndromes

Deferasirox therapy should only be considered when a patient with NTDT syndrome has an LIC of at least 5 mg Fe/g dw and a serum ferritin greater than 300 mcg/L.

Prior to starting therapy, obtain:

- LIC by liver biopsy or by an FDA-cleared or approved method for identifying patients for treatment with deferasirox therapy
- Serum ferritin level on at least 2 measurements 1-month apart *[see Clinical Studies (14)]*
- Baseline renal function:
  - o Obtain serum creatinine in duplicate (due to variations in measurements).
  - o Calculate the estimated glomerular filtration rate (eGFR). Use a prediction equation appropriate for adult patients (e.g., CKD-EPI, MDRD method) and in pediatric patients (e.g., Schwartz equations).
  - o Obtain urinalyses and serum electrolytes to evaluate renal tubular function *[see Dosage and Administration (2.4), Warnings and Precautions (5.1)]*.
- Serum transaminases and bilirubin *[see Dosage and Administration (2.4), Warnings and Precautions (5.2)]*
- Baseline auditory and ophthalmic examinations *[see Warnings and Precautions (5.10)]*

Initiating Therapy:

- The recommended initial dose of deferasirox for patients with eGFR greater than 60 mL/min/1.73 m^2 is 7 mg per kg body weight orally once daily. Calculate doses (mg per kg per day) to the nearest whole tablet.
- If the baseline LIC is greater than 15 mg Fe/g dw, consider increasing the dose to 14 mg/kg/day after 4 weeks.

During Therapy:

- Monitor serum ferritin monthly to assess the patient's response to therapy and to minimize the risk of overchelation *[see Warnings and Precautions (5.6)]*. Interrupt treatment when serum ferritin is less than 300 mcg/L and obtain an LIC to determine whether the LIC has fallen to less than 3 mg Fe/g dw.
- Use the minimum effective dose to achieve a trend of decreasing ferritin.
- Monitor LIC every 6 months.
- After 6 months of therapy, if the LIC remains greater than 7 mg Fe/g dw, increase the dose of deferasirox to a maximum of 14 mg/kg/day. Do not exceed a maximum of 14 mg/kg/day.
- If after 6 months of therapy, the LIC is 3 to 7 mg Fe/g dw, continue treatment with deferasirox at no more than 7 mg/kg/day.
- When the LIC is less than 3 mg Fe/g dw, interrupt treatment with deferasirox and continue to monitor the LIC.
- Monitor blood counts, liver function, renal function and ferritin monthly *[see Warnings and Precautions (5.1, 5.2, 5.4)]*.
- Increase monitoring frequency for pediatric patients who have acute illness, which can cause volume depletion, such as vomiting, diarrhea, or prolonged decreased oral intake. Consider dose interruption until oral intake and volume status are normal *[see Dosage and Administration (2.4, 2.5), Warnings and Precautions (5.1), Use in Specific Populations (8.4), Clinical Pharmacology (12.3)]*.

Restart treatment when the LIC rises again to more than 5 mg Fe/g dw.

2.3 Administration

Swallow deferasirox tablets once daily with water or other liquids, preferably at the same time each day. Take deferasirox tablets on an empty stomach or with a light meal (contains less than 7% fat content and approximately 250 calories). Examples of light meals include 1 whole wheat English muffin, 1 packet jelly (0.5 ounces), and skim milk (8 fluid ounces) or a turkey sandwich (2 oz. turkey on whole wheat bread w/ lettuce, tomato, and 1 packet mustard). Do not take deferasirox tablets with aluminum-containing antacid products *[see Drug Interactions (7.1)]*. For patients who have difficulty swallowing whole tablets, deferasirox tablets may be crushed and mixed with soft foods (e.g., yogurt or applesauce) immediately prior to use and administered orally. Commercial crushers with serrated surfaces should be avoided for crushing a single 90 mg tablet. The dose should be immediately and completely consumed and not stored for future use.

For patients who are currently on chelation therapy with deferasirox tablets for oral suspension and converting to deferasirox tablets, the dose should be about 30% lower, rounded to the nearest whole tablet. The table below provides additional information on dosing conversion to deferasirox tablets.

	Deferasirox Tablets for oral suspension	Deferasirox Tablets
Transfusion-Dependent Iron Overload		
Starting Dose	20 mg/kg/day	14 mg/kg/day
Titration Increments	5-10 mg/kg	3.5-7 mg/kg
Maximum Dose	40 mg/kg/day	28 mg/kg/day
Non-Transfusion-Dependent Thalassemia Syndromes		
Starting Dose	10 mg/kg/day	7 mg/kg/day
Titration Increments	5-10 mg/kg	3.5-7 mg/kg
Maximum Dose	20 mg/kg/day	14 mg/kg/day

2.4 Use in Patients With Baseline Hepatic or Renal Impairment

Patients with Baseline Hepatic Impairment

Mild (Child-Pugh A) Hepatic Impairment: No dose adjustment is necessary.

Moderate (Child-Pugh B) Hepatic Impairment: Reduce the starting dose by 50%.

Severe (Child-Pugh C) Hepatic Impairment: Avoid deferasirox tablets *[see Warnings and Precautions (5.2), Use in Specific Populations (8.7)]*.

Patients with Baseline Renal Impairment

Do not use deferasirox in adult or pediatric patients with eGFR less than 40 mL/min/1.73 m^2 *[see Dosage and Administration (2.5), Contraindications (4)].*

For patients with renal impairment (eGFR 40 to 60 mL/min/1.73 m^2), reduce the starting dose by 50% *[see Use in Specific Populations (8.6)]*.

Exercise caution in pediatric patients with eGFR between 40 and 60 mL/minute/1.73 m^2. If treatment is needed, use the minimum effective dose and monitor renal function frequently. Individualize dose titration based on improvement in renal injury *[see Use in Specific Populations (8.6)]*.

2.5 Dose Modifications for Decreases in Renal Function While on Deferasirox Tablets

Deferasirox tablets are contraindicated in patients with eGFR less than 40 mL/min/1.73 m^2 *[see Contraindications (4)]*.

For decreases in renal function while receiving deferasirox tablets *[see Warnings and Precautions (5.1)]*, modify the dose as follows:

Transfusional Iron Overload

Adults:

- If the serum creatinine increases by 33% or more above the average baseline measurement, repeat the serum creatinine within 1 week, and if still elevated by 33% or more, reduce the dose by 7 mg per kg.

Pediatric Patients (ages 2 years to 17 years):

- Reduce the dose by 7 mg per kg if eGFR decreases by greater than 33% below the average baseline measurement and repeat eGFR within 1 week.
- Interrupt deferasirox tablets for acute illnesses, which can cause volume depletion, such as vomiting, diarrhea, or prolonged decreased oral intake, and monitor more frequently. Resume therapy as appropriate, based on assessments of renal function, when oral intake and volume status are normal. Avoid use of other nephrotoxic drugs *[see Warnings and Precautions (5.1)].*
- In the setting of decreased renal function, evaluate the risk benefit profile of continued deferasirox tablets use. Use the minimum effective deferasirox tablets dose and monitor renal function more frequently, by evaluating tubular and glomerular function. Titrate dosing based on renal injury. Consider dose reduction or interruption and less nephrotoxic-therapies until improvement of renal function. If signs of renal tubular or glomerular injury occur in the presence of other risk factors such as volume depletion, reduce or interrupt deferasirox tablets to prevent severe and irreversible renal injury *[see Warnings and Precautions (5.1)]*.

All Patients (regardless of age):

- Discontinue therapy for eGFR less than 40 mL/min/1.73 m^2 *[see Contraindications (4)].*

Non-Transfusion-Dependent Thalassemia Syndromes

Adults:

- If the serum creatinine increases by 33% or more above the average baseline measurement, repeat the serum creatinine within 1 week, and if still elevated by 33% or more, interrupt therapy if the dose is 3.5 mg per kg, or reduce by 50% if the dose is 7 or 14 mg per kg.

Pediatric Patients (ages 10 years to 17 years):

- Reduce the dose by 3.5 mg per kg if eGFR decreases by greater than 33% below the average baseline measurement and repeat the eGFR within 1 week.
- Increase monitoring frequency for pediatric patients who have acute illnesses, which can cause volume depletion, such as vomiting, diarrhea, or prolonged decreased oral intake. Consider dose interruption until oral intake and volume status are normal. Avoid use of other nephrotoxic drugs *[see Warnings and Precautions (5.1)]*.
- In the setting of decreased renal function, evaluate the risk benefit profile of continued deferasirox tablets use. Use the minimum effective deferasirox tablets dose and monitor renal function more frequently, by evaluating tubular and glomerular function. Titrate dosing based on renal injury. Consider dose reduction or interruption and less nephrotoxic therapies until improvement of renal function. If signs of renal tubular or glomerular injury occur in the presence of other risk factors such as volume depletion, reduce or interrupt deferasirox tablets to prevent severe and irreversible renal injury *[see Warnings and Precautions (5.1)]*.

All Patients (regardless of age):

- Discontinue therapy for eGFR less than 40 mL/min/1.73 m^2 *[see Contraindications (4)]*.

2.6 Dose Modifications Based on Concomitant Medications

UDP-glucuronosyltransferases (UGT) Inducers

Concomitant use of UGT inducers decreases systemic exposure. Avoid the concomitant use of strong UGT inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir). If you must administer deferasirox tablets with a strong UGT inducer, consider increasing the initial dose by 50%, and monitor serum ferritin levels and clinical responses for further dose modification *[see Dosage and Administration (2.1, 2.2), Drug Interactions (7.5)]*.

Bile Acid Sequestrants

Concomitant use of bile acid sequestrants decreases systemic exposure. Avoid the concomitant use of bile acid sequestrants (e.g., cholestyramine, colesevelam, colestipol). If you must administer deferasirox tablets with a bile acid sequestrant, consider increasing the initial dose by 50%, and monitor serum ferritin levels and clinical responses for further dose modification *[see Dosage and Administration (2.1, 2.2), Drug Interactions (7.6)]*.

3 DOSAGE FORMS AND STRENGTHS

- 90 mg deferasirox tablets are white to off white, film coated, oval biconvex tablets, debossed with '56' on one side and 'V' on the other side.
- 180 mg deferasirox tablets are white to off white, film coated, oval biconvex tablets, debossed with '57' on one side and 'V' on the other side.
- 360 mg deferasirox tablets are white to off white, film coated, oval biconvex tablets, debossed with '58' on one side and 'V' on the other side.

4 CONTRAINDICATIONS

Deferasirox tablets are contraindicated in patients with:

- Estimated GFR less than 40 mL/min/1.73 m^2 *[see Dosage and Administration (2.5), Warnings and Precautions (5.1)]*;
- Poor performance status *[see Warnings and Precautions (5.1, 5.3)]*;
- High-risk myelodysplastic syndromes *(this patient population was not studied and is not expected to benefit from chelation therapy)*;
- Advanced malignancies *[see Warnings and Precautions (5.1, 5.3)]*;
- Platelet counts less than 50 x 10^9/L *[see Warnings and Precautions (5.3, 5.4)]*;
- Known hypersensitivity to deferasirox or any component of deferasirox tablets *[see Warnings and Precautions (5.7), Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Kidney Injury, Including Acute Renal Failure Requiring Dialysis and Renal Tubular Toxicity Including Fanconi Syndrome

Deferasirox is contraindicated in patients with eGFR less than 40 mL/min/1.73 m^2. Exercise caution in pediatric patients with eGFR between 40 and 60 mL/min/1.73 m^2. If treatment is needed, use the minimum effective dose and monitor renal function frequently. Individualize dose titration based on improvement in renal injury *[see Use in Specific Populations (8.6)]*. For patients with renal impairment (eGFR 40 to 60 mL/min/1.73 m^2) reduce the starting dose by 50% *[see Dosage and Administration (2.4, 2.5), Use in Specific Populations (8.6)]*.

Deferasirox can cause acute kidney injury including renal failure requiring dialysis that has resulted in fatal outcomes. Based on postmarketing experience, most fatalities have occurred in patients with multiple comorbidities and who were in advanced stages of their hematological disorders. In the clinical trials, adults and pediatric deferasirox-treated patients with no preexisting renal disease experienced dose-dependent mild, non-progressive increases in serum creatinine and proteinuria. Preexisting renal disease and concomitant use of other nephrotoxic drugs may increase the risk of acute kidney injury in adult and pediatric patients. Acute illnesses associated with volume depletion and overchelation may increase the risk of acute kidney injury in pediatric patients. In pediatric patients, small decreases in eGFR can result in increases in deferasirox exposure, particularly in younger patients with body surface area typical of patients less than age 7 years. This can lead to a cycle of worsening renal function and further increases in deferasirox tablets for oral suspension exposure, unless the dose is reduced or interrupted. Renal tubular toxicity, including acquired Fanconi syndrome, has been reported in patients treated with deferasirox, most commonly in pediatric patients with beta-thalassemia and serum ferritin levels less than 1,500 mcg/L *[see Warnings and Precautions (5.6), Adverse Reactions (6.1, 6.2), Use in Specific Populations (8.4), Clinical Pharmacology (12.3)]*.

Evaluate renal glomerular and tubular function before initiating therapy or increasing the dose. Use prediction equations validated for use in adult and pediatric patients to estimate GFR. Obtain serum electrolytes and urinalysis in all patients to evaluate renal tubular function *[see Dosage and Administration (2.1, 2.2)]*.

Monitor all patients for changes in eGFR and for renal tubular toxicity weekly during the first month after initiation or modification of therapy and at least monthly thereafter. Dose [illegible]

[illegible]

Precautions (5.6)].

Perform auditory and ophthalmic testing (including slit lamp examinations and dilated fundoscopy) before starting deferasirox treatment and thereafter at regular intervals (every 12 months). If disturbances are noted, monitor more frequently. Consider dose reduction or interruption.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are also discussed in other sections of the labeling:

- Acute Kidney Injury, Including Acute Renal Failure Requiring Dialysis, and Renal Tubular Toxicity Including Fanconi Syndrome *[see Warnings and Precautions (5.1, 5.6)]*
- Hepatic Toxicity and Failure *[see Warnings and Precautions (5.2, 5.6)]*
- GI Hemorrhage *[see Warnings and Precautions (5.3)]*
- Bone Marrow Suppression *[see Warnings and Precautions (5.4)]*
- Hypersensitivity *[see Warnings and Precautions (5.7)]*
- Severe Skin Reactions *[see Warnings and Precautions (5.8)]*
- Skin Rash *[see Warnings and Precautions (5.9)]*
- Auditory and Ocular Abnormalities *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials 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. Deferasirox was evaluated in healthy volunteer trials. Currently, there are no clinical data in patients with deferasirox tablets. Deferasirox tablets contains the same active ingredient as deferasirox tablets for oral suspension. The following adverse reactions have been reported with deferasirox tablets for oral suspension.

Transfusional Iron Overload

A total of 700 adult and pediatric patients were treated with deferasirox for 48 weeks in premarketing studies. These included 469 patients with beta-thalassemia, 99 with rare anemias, and 132 with sickle cell disease. Of these patients, 45% were male, 70% were Caucasian, and 292 patients were less than 16 years of age. In the sickle cell disease population, 89% of patients were black. Median treatment duration among the sickle cell patients was 51 weeks. Of the 700 patients treated, 469 (403 beta-thalassemia and 66 rare anemias) were entered into extensions of the original clinical protocols. In ongoing extension studies, median durations of treatment were 88 to 205 weeks.

Six hundred twenty-seven (627) patients with myelodysplastic syndrome (MDS) were enrolled across 5 uncontrolled trials. These studies varied in duration from 1 to 5 years. The discontinuation rate across studies in the first year was 46% (Adverse Events (AEs) 20%, withdrawal of consent 10%, death 8%, other 4%, lab abnormalities 3%, and lack of efficacy 1%). Among 47 patients enrolled in the study of 5-year duration, 10 remained on deferasirox at the completion of the study.

Table 1 displays adverse reactions occurring in greater than 5% of deferasirox-treated beta-thalassemia patients (Study 1), sickle cell disease patients (Study 3), and patients with MDS (MDS pool). Abdominal pain, nausea, vomiting, diarrhea, skin rashes, and increases in serum creatinine were the most frequent adverse reactions reported with a suspected relationship to deferasirox. Gastrointestinal symptoms, increases in serum creatinine, and skin rash were dose related.

Table 1. Adverse Reactions[a] Occurring in > 5% of Deferasirox-treated Patients in Study 1, Study 3, and MDS Pool

	Study 1 (Beta-thalassemia)		Study 3 (Sickle Cell Disease)		MDS Pool
Adverse Reactions	**Deferasirox N = 296 n (%)**	**Deferoxamine N = 290 n (%)**	**Deferasirox N = 132 n (%)**	**Deferoxamine N = 63 n (%)**	**Deferasirox N = 627 n (%)**
Abdominal Pain[b]	63 (21)	41 (14)	37 (28)	9 (14)	145 (23)
Diarrhea	35 (12)	21 (7)	26 (20)	3 (5)	297 (47)
Creatinine Increased[c]	33 (11)	0 (0)	9 (7)	0	89 (14)
Nausea	31 (11)	14 (5)	30 (23)	7 (11)	161 (26)
Vomiting	30 (10)	28 (10)	28 (21)	10 (16)	83 (13)
Rash	25 (8)	9 (3)	14 (11)	3 (5)	83 (13)

Abbreviation: MDS, myelodysplastic syndrome.
[a] Adverse reaction frequencies are based on AEs reported regardless of relationship to study drug.
[b] Includes 'abdominal pain', 'abdominal pain lower', and 'abdominal pain upper'.
[c] Includes 'blood creatinine increased' and 'blood creatinine abnormal'. See also Table 2.

In Study 1, a total of 113 (38%) patients treated with deferasirox had increases in serum creatinine greater than 33% above baseline on 2 separate occasions (Table 2) and 25 (8%) patients required dose reductions. Increases in serum creatinine appeared to be dose related *[see Warnings and Precautions (5.1)]*. In this study, 17 (6%) patients treated with deferasirox developed elevations in serum glutamic-pyruvic transaminase (SGPT)/ALT levels greater than 5 times the upper limit of normal (ULN) at 2 consecutive visits. Of these, 2 patients had liver biopsy proven drug-induced hepatitis and both discontinued deferasirox therapy *[see Warnings and Precautions (5.2)]*. An additional 2 patients, who did not have elevations in SGPT/ALT greater than 5 times the ULN, discontinued deferasirox because of increased SGPT/ALT. Increases in transaminases did not appear to be dose related. Adverse reactions that led to discontinuations included abnormal liver function tests (2 patients) and drug-induced hepatitis (2 patients), skin rash, glycosuria/proteinuria, Henoch Schönlein purpura, hyperactivity/insomnia, drug fever, and cataract (1 patient each).

In Study 3, a total of 48 (36%) patients treated with deferasirox had increases in serum creatinine greater than 33% above baseline on 2 separate occasions (Table 2) *[see Warnings and Precautions (5.1)]*. Of the patients who experienced creatinine increases in Study 3, 8 deferasirox-treated patients required dose reductions. In this study, 5 patients in the deferasirox group developed elevations in SGPT/ALT levels greater than 5 times the ULN at 2 consecutive visits and 1 patient subsequently had deferasirox permanently discontinued. Four additional patients discontinued due to adverse reactions with a suspected relationship to study drug, including diarrhea, pancreatitis associated with gallstones, atypical tuberculosis, and skin rash.

In the MDS pool, in the first year, a total of 229 (37%) patients treated with deferasirox had increases in serum creatinine greater than 33% above baseline on 2 consecutive occasions (Table 2) and 8 (3.5%) patients permanently discontinued *[see Warnings and Precautions (5.1)]*. A total of 5 (0.8%) patients developed SGPT/ALT levels greater than 5 times the ULN at 2 consecutive visits. The most frequent adverse reactions that led to discontinuation included increases in serum creatinine, diarrhea, nausea, rash, and vomiting. Death was reported in the first year in 52 (8%) of patients *[see Clinical Studies (14)]*.

Table 2. Number (%) of Patients with Increases in Serum Creatinine or SGPT/ALT in Study 1, Study 3, and MDS Pool

	Study 1 (Beta-thalassemia)		Study 3 (Sickle Cell Disease)		MDS Pool
Laboratory Parameter	**Deferasirox N = 296 n (%)**	**Deferoxamine N = 290 n (%)**	**Deferasirox N = 132 n (%)**	**Deferoxamine N = 63 n (%)**	**Deferasirox N = 627 n (%)**
Serum Creatinine					
Creatinine increase > 33% at 2 consecutive post-baseline visits	113 (38)	41 (14)	48 (36)	14 (22)	229 (37)
Creatinine increase > 33% and > ULN at 2 consecutive post-baseline visits	7 (2)	1 (0)	3 (2)	2 (3)	126 (20)
SGPT/ALT					
SGPT/ALT > 5 x ULN at 2 post-baseline visits	25 (8)	7 (2)	2 (2)	0	9 (1)
SGPT/ALT > 5 x ULN at 2 consecutive post-baseline visits	17 (6)	5 (2)	5 (4)	0	5 (1)

Abbreviations: ALT, alanine transaminase; MDS, myelodysplastic syndrome; SGPT, serum glutamic-pyruvic transaminase; ULN, upper limit of normal.

Non-Transfusion-Dependent Thalassemia Syndromes

In Study 5, 110 patients with NTDT received 1 year of treatment with deferasirox 5 or 10 mg/kg/day and 56 patients received placebo in a double-blind, randomized trial. In Study 6, 130 of the patients who completed Study 5 were treated with open-label deferasirox at 5, 10, or 20 mg/kg/day (depending on the baseline LIC) for 1 year *[see Clinical Studies (14)]*. Table 3 and 4 display the frequency of adverse reactions in patients with NTDT. Adverse reactions with a suspected relationship to study drug were included in Table 3 if they occurred at ≥ 5% of patients in Study 5.

Table 3. Adverse Reactions Occurring in Greater Than 5% Patients with NTDT

	Study 5		Study 6
	Deferasirox N = 110 n (%)	**Placebo N = 56 n (%)**	**Deferasirox N = 130 n (%)**
Any adverse reaction	**31 (28)**	**9 (16)**	**27 (21)**
Nausea	7 (6)	4 (7)	2 (2)[a]
Rash	7 (6)	1 (2)	2 (2)[a]
Diarrhea	5 (5)	1 (2)	7 (5)

Abbreviation: NTDT, non-transfusion-dependent thalassemia.
[a] The occurrence of nausea, and rash are included for Study 6. There were no additional adverse reactions with a suspected relationship to study drug occurring in >5% of patients in Study 6.

In Study 5, 1 patient in the placebo 10 mg/kg/day group experienced an ALT increase to greater than 5 times ULN and greater than 2 times baseline (Table 4). Three deferasirox-treated patients (all in the 10 mg/kg/day group) had 2 consecutive serum creatinine level increases greater than 33% from baseline and greater than ULN. Serum creatinine returned to normal in all 3 patients (in 1 spontaneously and in the other 2 after drug interruption). Two additional cases of ALT increase and 2 additional cases of serum creatinine increase were observed in the 1-year extension of Study 5. The number (%) of patients with NTDT with increase in serum creatinine or SGPT/ALT in Study 5 and Study 6 are presented in Table 4 below.

Table 4. Number (%) of Patients with NTDT with Increases in Serum Creatinine or SGPT/ALT

	Study 5		Study 6
Laboratory Parameter	**Deferasirox N = 110 n (%)**	**Placebo N = 56 n (%)**	**Deferasirox N = 130 n (%)**
Serum creatinine (> 33% increase from baseline and > ULN at ≥ 2 consecutive post-baseline values)	3 (3)	0	2 (2)
SGPT/ALT (> 5 x ULN and > 2 x baseline)	1 (1)	1 (2)	2 (2)

Abbreviations: ALT, alanine transaminase; NTDT, non-transfusion-dependent thalassemia; SGPT, serum glutamic-pyruvic transaminase; ULN, upper limit of normal.

Proteinuria

In clinical studies, urine protein was measured monthly. Intermittent proteinuria (urine protein/creatinine ratio greater than 0.6 mg/mg) occurred in 18.6% of deferasirox-treated patients compared to 7.2% of deferoxamine-treated patients in Study 1 *[see Warnings and Precautions (5.1)].*

Other Adverse Reactions

In the population of more than 5,000 patients with transfusional iron overload, who have been treated with deferasirox during clinical trials, adverse reactions occurring in 0.1% to 1% of patients included gastritis, edema, sleep disorder, pigmentation disorder, dizziness, anxiety, maculopathy, cholelithiasis, pyrexia, fatigue, laryngeal pain, cataract, hearing loss, GI hemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, renal tubular disorder (Fanconi syndrome), and acute pancreatitis (with and without underlying biliary conditions). Adverse reactions occurring in 0.01% to 0.1% of patients included optic neuritis, esophagitis, erythema multiforme, and drug reaction with eosinophilia and systemic symptoms (DRESS). Adverse reactions, which most frequently led to dose interruption or dose adjustment during clinical trials were rash, GI disorders, infections, increased serum creatinine, and increased serum transaminases.

Pooled Analysis of Pediatric Clinical Trial Data

A nested case control analysis was conducted within a deferasirox tablets for oral suspension pediatric-pooled clinical trial dataset to evaluate the effects of dose and serum ferritin level, separately and combined, on kidney function. Among 1213 children (aged 2 to 15 years) with transfusion-dependent thalassemia, 162 cases of acute kidney injury (eGFR ≤ 90 mL/min/1.73 m^2) and 621 matched-controls with normal kidney function (eGFR ≥ 120 mL/min/1.73 m^2) were identified. The primary findings were:

- A 26% increased risk of acute kidney injury was observed with each 5 mg/kg increase in daily deferasirox tablets for oral suspension dosage equivalent to 3.5 mg/kg deferasirox, starting at 20 mg/kg/day equivalent to 14 mg/kg/day deferasirox (95% confidence interval (CI): 1.08 to 1.48).

[illegible]

MEDICATION GUIDE

Deferasirox (dee fer' a sir' ox) Tablets

[illegible]

Size: 400 x 800 mm
Pharma Code: Front-61 & Back-62
Spec.: Printed on 40 GSM Bible paper, front & back side printing
Note: Pharma code position and Orientation are tentative, will be changed based on folding size.
No of Colours: 01 - Black

Administration of deferasirox to rats during pregnancy resulted in decreased offspring viability and an increase in renal anomalies in male offspring at doses that were about or less than the recommended human dose on a mg/m^2 basis. No fetal effects were noted in pregnant rabbits at doses equivalent to the human recommended dose on an mg/m^2 basis. Deferasirox should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies had a background risk of birth defect, loss, or other adverse outcomes. However, the background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

In embryo-fetal developmental studies, pregnant rats and rabbits received oral deferasirox during the period of organogenesis at doses up to 100 mg/kg/day in rats and 50 mg/kg/day in rabbits (1.2 times the maximum recommended human dose (MRHD) on an mg/m^2 basis). These doses resulted in maternal toxicity but no fetal harm was observed.

In a prenatal and postnatal developmental study, pregnant rats received oral deferasirox daily from organogenesis through lactation day 20 at doses of 10, 30, and 90 mg/kg/day (0.1, 0.3, and 1.0 times the MRHD on a mg/m^2 basis). Maternal toxicity, loss of litters, and decreased offspring viability occurred at 90 mg/kg/day (1.0 times the MRHD on a mg/m^2 basis), and increases in renal anomalies in male offspring occurred at 30 mg/kg/day (0.3 times the MRHD on a mg/m^2 basis).

8.2 Lactation

Risk Summary

No data are available regarding the presence of deferasirox or its metabolites in human milk, the effects of the drug on the breastfed child, or the effects of the drug on milk production. Deferasirox and its metabolites were excreted in rat milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in a breastfeeding child from deferasirox and its metabolites, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother.

8.3 Females and Males of Reproductive Potential

Contraception

Counsel patients to use non-hormonal method(s) of contraception since deferasirox can render hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.

8.4 Pediatric Use

Transfusional Iron Overload

The safety and effectiveness of deferasirox have been established in pediatric patients 2 years of age and older for the treatment of transfusional iron overload *[see Dosage and Administration (2.1)]*.

Safety and effectiveness have not been established in pediatric patients less than 2 years of age for the treatment of transfusional iron overload.

Pediatric approval for treatment of transfusional iron overload was based on clinical studies of 292 pediatric patients 2 years to less than 16 years of age with various congenital and acquired anemias. Seventy percent of these patients had beta-thalassemia *[see Indications and Usage (1), Dosage and Administration (2.1), Clinical Studies (14)]*. In those clinical studies, 173 children (ages 2 to < 12 years) and 119 adolescents (ages 12 to < 17 years) were exposed to deferasirox.

Iron Overload in Non-Transfusion-Dependent Thalassemia Syndromes

The safety and effectiveness of deferasirox have been established in patients 10 years of age and older for the treatment of chronic iron overload with non-transfusion-dependent thalassemia (NTDT) syndromes *[see Dosage and Administration (2.2)]*.

Safety and effectiveness have not been established in patients less than 10 years of age with chronic iron overload in NTDT syndromes.

Pediatric approval for treatment of NTDT syndromes with liver iron (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight and a serum ferritin greater than 300 mcg/L was based on 16 pediatric patients treated with deferasirox therapy (10 years to less than 16 years of age) with chronic iron overload and NTDT. Use of deferasirox in these age groups is supported by evidence from adequate and well-controlled studies of deferasirox in adult and pediatric patients *[see Indications and Usage (1.2), Dosage and Administration (2.2), Clinical Studies (14)]*.

In general, risk factors for deferasirox-associated kidney injury include preexisting renal disease, volume depletion, overchelation, and concomitant use of other nephrotoxic drugs. Acute kidney injury, and acute liver injury and failure has occurred in pediatric patients. In a pooled safety analysis, pediatric patients with higher deferasirox exposures had a greater probability of renal toxicity and decreased renal function, resulting in increased deferasirox exposure and progressive renal toxicity/kidney injury. Higher rates of renal AEs have been identified among pediatric patients receiving deferasirox tablets for oral suspension doses greater than 25 mg/kg/day equivalent to 17.5 mg/kg/day deferasirox when their serum ferritin values were less than 1,000 mcg/L *[see Dosage and Administration (2.5), Warnings and Precautions (5.1, 5.6), Adverse Reactions (6.1, 6.2)]*.

Monitoring recommendations for all pediatric patients with Transfusional Iron Overload and NTDT

It is recommended that serum ferritin be monitored every month to assess the patient's response to therapy and to minimize the risk of overchelation *[see Warnings and Precautions (5.6)]*.

Monitor renal function by estimating GFR using an eGFR prediction equation appropriate for pediatric patients and evaluate renal tubular function. Monitor renal function more frequently in pediatric patients in the presence of renal toxicity risk factors, including episodes of dehydration, fever and acute illness that may result in volume depletion or decreased renal perfusion. Use the minimum effective dose *[see Warnings and Precautions (5.1)]*.

Interrupt deferasirox in pediatric patients with transfusional iron overload, and consider dose interruption in pediatric patients with non-transfusion-dependent iron overload, for acute illnesses, which can cause volume depletion, such as vomiting, diarrhea, or prolonged decreased oral intake, and monitor more frequently. Resume therapy as appropriate, based on assessments of renal function, when oral intake and volume status are normal. Evaluate the risk benefit profile of continued deferasirox use in the setting of decreased renal function. Avoid use of other nephrotoxic drugs *[see Dosage and Administration (2.5), Warnings and Precautions (5.1)]*.

Juvenile Animal Toxicity Data

Renal toxicity was observed in adult mice, rats, and marmoset monkeys administered deferasirox at therapeutic doses. In a neonatal and juvenile toxicity study in rats, deferasirox was administered orally from postpartum Day 7 through 70, which equates to a human age range of term neonate through adolescence. Increased renal toxicity was identified in juvenile rats compared to adult rats at a dose based on mg/m^2 approximately 0.4 times the recommended dose of 20 mg/kg/day. A higher frequency of renal abnormalities was noted when deferasirox was administered to non-iron overloaded animals compared to iron overloaded animals.

Additional pediatric use information is approved for Novartis Pharmaceuticals Corporation's JADENU (deferasirox) tablets and granules. However, due to Novartis Pharmaceuticals Corporation's marketing exclusivity rights, this drug product is not labeled with that information.

8.5 Geriatric Use

Four hundred thirty-one (431) patients greater than or equal to 65 years of age were studied in clinical trials of deferasirox in the transfusional iron overload setting. Two hundred twenty-five (225) of these patients were between 65 and 75 years of age while 206 were greater than or equal to 75 years of age. The majority of these patients had myelodysplastic syndrome (MDS) (n = 393). In these trials, elderly patients experienced a higher frequency of adverse reactions than younger patients. Monitor elderly patients for early signs or symptoms of adverse reactions that may require a dose adjustment. Elderly patients are at increased risk for toxicity due to the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

In elderly patients, including those with MDS, individualize the decision to remove accumulated iron based on clinical circumstances and the anticipated clinical benefit and risks of deferasirox tablets for oral suspension therapy.

8.6 Renal Impairment

Deferasirox is contraindicated in patients with eGFR less than 40 mL/min/1.73 m^2 *[see Contraindications (4)]*. For patients with renal impairment (eGFR 40 to 60 mL/min/1.73 m^2), reduce the starting dose by 50% *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*. Exercise caution in pediatric patients with an eGFR between 40 and 60 mL/min/1.73 m^2 *[see Dosage and Administration (2.4)]*. If treatment is needed, use the minimum effective dose with enhanced monitoring of glomerular and renal tubular function. Individualize dose titration based on improvement in renal injury *[see Dosage and Administration (2.4, 2.5)]*.

Deferasirox can cause glomerular dysfunction, renal tubular toxicity, or both, and can result in acute renal failure. Monitor all patients closely for changes in eGFR and renal tubular dysfunction during deferasirox treatment. If either develops, consider dose reduction, interruption or discontinuation of deferasirox until glomerular or renal tubular function returns to baseline *[see Dosage and Administration (2.4, 2.5), Warnings and Precautions (5.1)]*.

8.7 Hepatic Impairment

Avoid use in patients with severe (Child-Pugh C) hepatic impairment. For patients with moderate (Child-Pugh B) hepatic impairment, reduce the starting dose by 50%. Closely monitor patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment for efficacy and adverse reactions that may require dose titration *[see Dosage and Administration (2.4), Warnings and Precautions (5.2), Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

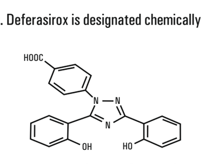
Cases of overdose (2 to 3 times the prescribed dose for several weeks) have been reported. In one case, this resulted in hepatitis which resolved without long-term consequences after a dose interruption. In one pediatric case, a dose of 2 to 3 times the prescribed dose for 6 days resulted in acute renal failure requiring hemofiltration and acute liver injury/failure, which were reversible with intensive care support. Single doses of deferasirox up to 80 mg per kg per day with the tablet for oral suspension formulation in iron-overloaded beta-thalassemic patients have been tolerated with nausea and diarrhea noted. In healthy subjects, single doses of up to 40 mg per kg per day with the tablet for oral suspension formulation were tolerated.

Early signs of acute overdose are digestive effects such as abdominal pain, diarrhea, nausea, and vomiting. Hepatic and renal disorders have been reported, including cases of liver enzyme and creatinine increased with recovery after treatment discontinuation. An erroneously administered single dose of 90 mg/kg led to Fanconi syndrome which resolved after treatment.

There is no specific antidote for deferasirox. In case of overdose, it may be treated with induction of vomiting or gastric lavage, and by symptomatic treatment.

11 DESCRIPTION

Deferasirox is an iron-chelating agent provided as a tablet for oral use. Deferasirox is designated chemically as 4-[3,5-Bis(2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl]benzoic acid and has the following structural formula:



Deferasirox is an off white to slight yellow color crystalline powder. It has a molecular formula $C_{21}H_{15}N_3O_4$ and molecular weight of 373.36 g/mol. It is insoluble in water with a pH of suspension of 4.1.

Deferasirox tablets contain 90 mg, 180 mg, or 360 mg deferasirox. Inactive ingredients include colloidal silicon dioxide, crospovidone, microcrystalline cellulose, poloxamer 188, povidone, and sodium stearyl fumarate. The film coating contains hypromellose, polyethylene glycol, talc and titanium dioxde.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Deferasirox is an orally active chelator that is selective for iron (as Fe^{3+}). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Although deferasirox has very low affinity for zinc and copper, there are variable decreases in the serum concentration of these trace metals after the administration of deferasirox. The clinical significance of these decreases is uncertain.

12.2 Pharmacodynamics

Pharmacodynamic effects tested in an iron balance metabolic study with the tablet for oral suspension formulation showed that deferasirox (10, 20, and 40 mg per kg per day) was able to induce a mean net iron excretion (0.119, 0.329, and 0.445 mg Fe/kg body weight per day, respectively) within the clinically relevant range (0.1 to 0.5 mg per kg per day). Iron excretion was predominantly fecal.

An analysis of pooled pediatric clinical trial data found a statistically significant relationship between exposure and the probability of renal toxicity (increase in serum creatinine and urinary protein), resulting in a decrease in renal function. Decreases in renal function resulted in an increase in deferasirox exposure which may increase the probability of renal toxicity.

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

Absorption

Based on studies in patients with the tablet for oral suspension, deferasirox is absorbed following oral administration with median times to maximum plasma concentration (T_{max}) of about 1.5 to 4 hours. In healthy subjects, deferasirox showed comparable T_{max}. The maximal concentrations (C_{max}) and area under the curve ($AUC_{0\ to\ 24h,}$ AUC_{τ}) of deferasirox increase approximately linearly with dose after both single administration and under steady-state conditions. Exposure to deferasirox increased by an accumulation factor of 1.3 to 2.3 after multiple doses with the tablet for oral suspension formulation.

Tablets

The absolute bioavailability [as measured by area under the curve over time to infinity (AUC_{inf})] of deferasirox tablets for oral suspension is 70% compared to an intravenous dose. The bioavailability (as measured by AUC_{inf}) of deferasirox tablets was 36% greater than with deferasirox tablets for oral suspension. After strength-adjustment, the mean AUC_{inf} of deferasirox tablets (i.e., 360 mg strength) was similar to that of deferasirox tablets for oral suspension (i.e., 500 mg strength) under fasting conditions; however the mean C_{max} was increased by 30%. The 30% increase in C_{max} observed with deferasirox tablets is not clinically meaningful.

The administration of deferasirox tablets with a light meal (approximately 250 calories with fat content less than 7% of total calories) indicated that the AUC_{inf} and C_{max} were similar to that under fasting conditions. The administration of deferasirox tablets with a high-fat meal (approximately 1,000 calories with fat content greater than 50% of total calories), increased AUC_{inf} by 18% and C_{max} by 29% compared to that under fasting conditions *[see Dosage and Administration (2.3)]*.

Distribution

Deferasirox is highly (~99%) protein bound almost exclusively to serum albumin. The percentage of deferasirox confined to the blood cells was 5% in humans. The volume of distribution at steady state (V_{ss}) of deferasirox is 14.37 ± 2.69 L in adults.

Metabolism

Glucuronidation is the main metabolic pathway for deferasirox, with subsequent biliary excretion. Deconjugation of glucuronidates in the intestine and subsequent reabsorption (enterohepatic recycling) is likely to occur. Deferasirox is mainly glucuronidated by UGT1A1 and to a lesser extent UGT1A3. CYP450-catalyzed (oxidative) metabolism of deferasirox appears to be minor in humans (about 8%). Deconjugation of glucuronide metabolites in the intestine and subsequent reabsorption (enterohepatic recycling) was confirmed in a healthy subjects study in which the administration of cholestyramine 12 g twice daily (strongly binds to deferasirox and its conjugates) 4 and 10 hours after a single dose of deferasirox resulted in a 45% decrease in deferasirox exposure (AUC_{inf}) by interfering with the enterohepatic recycling of deferasirox.

Excretion

Deferasirox and metabolites are primarily (84% of the dose) excreted in the feces. Renal excretion of deferasirox and metabolites is minimal (8% of the dose). The mean elimination half-life ($t_{1/2}$) ranged from 8 to 16 hours following oral administration.

Drug Interactions

Midazolam: The concomitant administration of deferasirox tablets for oral suspension and CYP3A4 probe substrate midazolam resulted in a decrease of midazolam C_{max} by 23% and AUC_{inf} by 17%. In the clinical setting, this effect may be more pronounced, as the study was not adequately designed to conclusively assess the potential induction of CYP3A4 by deferasirox *[see Drug Interactions (7.2)]*.

Repaglinide: The concomitant administration of deferasirox tablets for oral suspension (30 mg per kg/day for 4 days) and the CYP2C8 probe substrate repaglinide (single dose of 0.5 mg) increased repaglinide AUC_{inf} to 2.3-fold and C_{max} of 1.6-fold *[see Drug Interactions (7.3)]*.

Theophylline: The concomitant administration of deferasirox tablets for oral suspension (repeated dose of 30 mg per kg/day) and the CYP1A2 substrate theophylline (single dose of 120 mg) resulted in an approximate doubling of the theophylline AUC_{inf} and elimination half-life. The single dose C_{max} was not affected, but an increase in theophylline C_{max} is expected to occur with chronic dosing *[see Drug Interactions (7.4)]*.

Rifampicin: The concomitant administration of deferasirox tablets for oral suspension (single dose of 30 mg per kg) and the strong uridine diphosphate glucuronosyltransferase (UGT) inducer rifampicin (600 mg per day for 9 days) decreased deferasirox AUC_{inf} by 44% *[see Drug Interactions (7.5)]*.

Cholestyramine: The concomitant administration of cholestyramine after a single dose of deferasirox tablets for oral suspension decreased deferasirox AUC_{inf} by 45% *[see Drug Interactions (7.6)]*.

Busulfan: Concomitant administration of deferasirox and busulfan resulted in an increase of busulfan exposure (AUC).

In vitro Studies: Deferasirox inhibited human CYP2A6, CYP2D6, and CYP2C19 *in vitro*.

Deferasirox is not a substrate of P-glycoprotein, MRP1 or MRP2.

Pharmacokinetics in Specific Populations

Pediatric: Following oral administration of single or multiple doses, systemic exposure of adolescents and children to deferasirox was less than in adult patients. In children less than 6 years of age, systemic exposure was about 50% lower than in adults.

Sex: The apparent clearance is 17.5% lower in females compared to males.

Renal Impairment: Compared to patients with MDS and eGFR greater than 60 mL/min/1.73 m^2, patients with MDS and eGFR 40 to 60 mL/min/1.73 m^2 (n = 34) had approximately 50% higher mean deferasirox trough plasma concentrations.

Hepatic Impairment: In a single dose (20 mg/kg) study in patients with varying degrees of hepatic impairment, deferasirox exposure was increased compared to patients with normal hepatic function. The average total (free and bound) AUC_{inf} of deferasirox increased 16% in 6 patients with mild (Child-Pugh A) hepatic impairment, and 76% in 6 patients with moderate (Child-Pugh B) hepatic impairment compared to 6 patients with normal hepatic function. The impact of severe (Child-Pugh C) hepatic impairment was assessed in only 1 patient.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week oral carcinogenicity study in Wistar rats showed no evidence of carcinogenicity from deferasirox at doses up to 60 mg/kg/day (0.7 times the MRHD on an mg/m^2 basis). A 26-week oral carcinogenicity study in p53 (+/-) transgenic mice has shown no evidence of carcinogenicity from deferasirox at doses up to 200 mg/kg/day (1.2 times the MRHD on a mg/m^2 basis) in males and 300 mg/kg/day (1.7 times the MRHD on a mg/m^2 basis) in females.

Deferasirox was negative in the Ames test and chromosome aberration test with human peripheral blood lymphocytes. It was positive in 1 of 3 *in vivo* oral rat micronucleus tests.

Deferasirox at oral doses up to 75 mg/kg/day (0.9 times the MRHD on a mg/m^2 basis) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

14 CLINICAL STUDIES

Deferasirox was evaluated in healthy subjects. There are no clinical data in patients with deferasirox. Deferasirox contains the same active ingredient as deferasirox tablets for oral suspension. The following information is based on clinical trials conducted with deferasirox tablets for oral suspension.

Transfusional Iron Overload

The primary efficacy study, Study 1 (NCT00061750), was a multicenter, open-label, randomized, active-comparator control study to compare deferasirox tablets for oral suspension and deferoxamine in patients with beta-thalassemia and transfusional hemosiderosis. Patients greater than or equal to 2 years of age were randomized in a 1:1 ratio to receive either oral deferasirox tablets for oral suspension at starting doses of 5, 10, 20, or 30 mg per kg once daily or subcutaneous deferoxamine at starting doses of 20 to 60 mg per kg for at least 5 days per week based on LIC at baseline (2 to 3, greater than 3 to 7, greater than 7 to 14, and greater than 14 mg Fe/g dry weight). Patients randomized to deferoxamine who had LIC values less than 7 mg Fe/g dry weight were permitted to continue on their prior deferoxamine dose, even though the dose may have been higher than specified in the protocol.

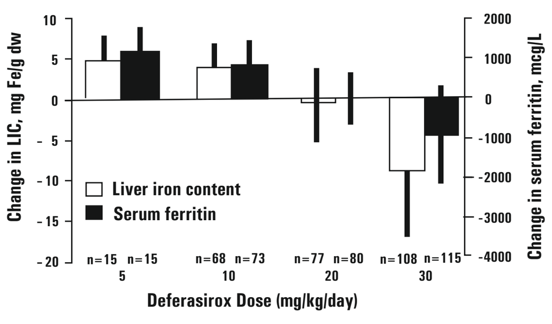
Patients were to have a liver biopsy at baseline and end of study (after 12 months) for LIC. The primary efficacy endpoint was defined as a reduction in LIC of greater than or equal to 3 mg Fe/g dry weight for baseline values greater than or equal to 10 mg Fe/g dry weight, reduction of baseline values between 7 and less than 10 to less than 7 mg Fe/g dry weight, or maintenance or reduction for baseline values less than 7 mg Fe/g dry weight.

A total of 586 patients were randomized and treated, 296 with deferasirox tablets for oral suspension and 290 with deferoxamine. The mean age was 17.1 years (range, 2 to 53 years); 52% were females and 88% were Caucasian. The primary efficacy population consisted of 553 patients (deferasirox tablets for oral suspension n = 276; deferoxamine n = 277) who had LIC evaluated at baseline and 12 months or discontinued due to an adverse reaction. The percentage of patients achieving the primary endpoint was 52.9% for deferasirox tablets for oral suspension and 66.4% for deferoxamine. The relative efficacy of deferasirox to deferoxamine cannot be determined from this study.

In patients who had an LIC at baseline and at end of study, the mean change in LIC was -2.4 mg Fe/g dry weight in patients treated with deferasirox tablets for oral suspension and -2.9 mg Fe/g dry weight in patients treated with deferoxamine.

Reduction of LIC and serum ferritin was observed with deferasirox tablet for oral suspension doses of 20 to 30 mg per kg per day. Deferasirox tablets for oral suspension doses below 20 mg per kg per day failed to provide consistent lowering of LIC and serum ferritin levels (Figure 1). Therefore, a starting dose of 20 mg per kg per day is recommended *[see Dosage and Administration (2.1)]*.

Figure 1. Changes in Liver Iron Concentration and Serum Ferritin Following Deferasirox Tablets for Oral Suspension (5 to 30 mg per kg per day) in Study 1



Study 2 (NCT00061763) was an open-label, noncomparative trial of efficacy and safety of deferasirox tablets for oral suspension given for 1 year to patients with chronic anemias and transfusional hemosiderosis. Similar to Study 1, patients received 5, 10, 20, or 30 mg per kg per day of deferasirox tablets for oral suspension based on baseline LIC.

A total of 184 patients were treated in this study: 85 patients with beta-thalassemia and 99 patients with other congenital or acquired anemias (myelodysplastic syndromes, n = 47; Diamond-Blackfan syndrome, n = 30; other, n = 22). Nineteen percent (19%) of patients were less than 16 years of age and 16% were greater than or equal to 65 years of age. There was a reduction in the absolute LIC from baseline to end of study (-4.2 mg Fe/g dry weight).

Study 3 (NCT00067080) was a multicenter, open-label, randomized trial of the safety and efficacy of deferasirox tablets for oral suspension relative to deferoxamine given for 1 year in patients with sickle cell disease and transfusional hemosiderosis. Patients were randomized to deferasirox tablets for oral suspension at doses of 5, 10, 20, or 30 mg per kg per day or subcutaneous deferoxamine at doses of 20 to 60 mg per kg per day for 5 days per week according to baseline LIC.

A total of 195 patients were treated in this study: 132 with deferasirox tablets for oral suspension and 63 with deferoxamine. Forty-four percent (44%) of patients were less than 16 years of age and 91% were black. At end of study, the mean change in LIC (as measured by magnetic susceptometry by a superconducting quantum interference device) in the per protocol-1 (PP-1) population, which consisted of patients who had at least 1 post-baseline LIC assessment, was -1.3 mg Fe/g dry weight for patients receiving deferasirox tablets for oral suspension (n = 113) and -0.7 mg Fe/g dry weight for patients receiving deferoxamine (n = 54).

One-hundred five (105) patients with thalassemia major and cardiac iron overload were enrolled in a study assessing the change in cardiac magnetic resonance imaging (MRI) T2* value (measured in milliseconds, [ms]) before and after treatment with deferasirox. Cardiac T2* values at baseline ranged from 5 to less than 20 ms. The geometric mean of cardiac T2* in the 68 patients who completed 3 years of deferasirox tablets for oral suspension therapy increased from 11.98 ms at baseline to 17.12 ms at 3 years. Cardiac T2* values improved in patients with severe cardiac iron overload (less than 10 ms) and in those with mild to moderate cardiac iron overload (greater than or equal to 10 to less than 20 ms). The clinical significance of these observations is unknown.

Six hundred twenty-seven (627) patients with MDS were enrolled across 5 uncontrolled trials. Two hundred thirty-nine of the 627 patients were enrolled in trials that limited enrollment to patients with IPSS Low or Intermediate 1 risk MDS, and the remaining 388 patients were enrolled in trials that did not specify MDS risk stratification but required a life expectancy of greater than 1 year. Planned duration of treatment in these trials ranged from 1 year (365 patients) to 5 years (47 patients). These trials evaluated the effects of deferasirox tablets for oral suspension therapy on parameters of iron overload, including LIC (125 patients) and serum ferritin (627 patients). The percent of patients completing planned duration of treatment was 51% in the largest 1-year study, 52% in the 3-year study and 22% in the 5-year study. The major causes for treatment discontinuation were withdrawal of consent, adverse reaction, and death. Over 1 year of follow-up across these pooled studies, mean change in serum ferritin was -332.8 (±2615.59) mcg/L (n = 593) and mean change in LIC was -5.9 (±8.32) mg Fe/g dw (n = 68). Results of these pooled studies in 627 patients with MDS suggest a progressive decrease in serum ferritin and LIC beyond 1 year in those patients who are able to continue deferasirox tablets for oral suspension.

Non-Transfusion-Dependent Thalassemia

Study 5 (NCT00873041) was a randomized, double-blind, placebo-controlled trial of treatment with deferasirox tablets for oral suspension for patients 10 years of age or older with NTDT syndromes and iron overload. Eligible patients had an LIC of at least 5 mg Fe/g dw measured by R2 MRI and a serum ferritin exceeding 300 mcg/L at screening (2 consecutive values at least 14 days apart from each other). A total of 166 patients were randomized, 55 to the deferasirox tablets for oral suspension 5 mg/kg/day dose group, 55 to the deferasirox tablets for oral suspension 10 mg/kg/day dose group, and 56 to placebo (28 to each matching placebo group). Doses could be increased after 6 months if the LIC exceeded 7 mg Fe/g dw and the LIC reduction from baseline was less than 15%. The patients enrolled included 89 males and 77 females. The underlying disease was beta-thalassemia intermedia in 95 (57%) patients, HbE beta-thalassemia in 49 (30%) patients, and alpha-thalassemia in 22 (13%) patients. There were 17 pediatric patients in the study. Caucasians comprised 57% of the study population and Asians comprised 42%. The median baseline LIC (range) for all patients was 12.1 (2.6 to 49.1) mg Fe/g dw. Follow-up was for 1 year. The primary efficacy endpoint of change in LIC from baseline to Week 52 was statistically significant in favor of both deferasirox dose groups compared with placebo (p less than or equal to 0.001) (Table 5). Furthermore, a statistically significant dose effect of deferasirox was observed in favor of the 10 mg/kg/day dose group (10 versus 5 mg/kg/day, p = 0.009). In a descriptive analysis, the target LIC (less than 5 mg Fe/g dw) was reached by 15 (27%) of 55 patients in the 10 mg/kg/day arm, 8 (15%) of 55 patients in the 5 mg/kg/day arm and 2 (4%) of 56 patients in the combined placebo groups.

Study 6 (NCT00873041) was an open-label trial of deferasirox tablets for oral suspension for the treatment of patients previously enrolled on Study 5, including cross-over to active treatment for those previously treated with placebo. The starting dose of deferasirox tablets for oral suspension in Study 6 was assigned based on the patient's LIC at completion of Study 5, being 20 mg/kg/day for an LIC exceeding 15 mg Fe/g dw, 10 mg/kg/day for LIC 3 to 15 mg Fe/g dw, and observation if the LIC was less than 3 mg Fe/g dw. Patients could continue on 5 mg/kg/day if they had previously exhibited at least a 30% reduction in LIC. Doses could be increased to a maximum of 20 mg/kg/day after 6 months if the LIC was more than 7 mg Fe/g dw and the LIC reduction from baseline was less than 15%. The primary efficacy endpoint in Study 6 was the proportion of patients achieving an LIC less than 5 mg Fe/g dw. A total of 133 patients were enrolled. Twenty patients began Study 6 with an LIC less than 5 mg Fe/g dw. Of the 113 patients with a baseline LIC of at least 5 mg Fe/g dw in Study 6, the target LIC (less than 5 mg Fe/g dw) was reached by 39 patients (35%). The responders included 4 (10%) of 39 patients treated at 20 mg/kg/day for a baseline LIC exceeding 15 mg Fe/g dw, and 31 (51%) of 61 patients treated at 10 mg/kg/day for a baseline LIC between 5 and 15 mg Fe/g dw. The absolute change in LIC at Week 52 by starting dose is shown in Table 5 below.

Table 5. Absolute Change in LIC at Week 52 in Patients with NTDT

	Deferasirox Tablets for Oral Suspension Starting Dose[a]			
	Placebo	5 mg/kg/day	10 mg/kg/day	20 mg/kg/day
Study 5[b]				
Number of Patients	n = 54	n = 51	n = 54	.
Mean LIC at Baseline (mg Fe/g dw)	16.1	13.4	14.4	.
Mean Change (mg Fe/g dw)	+0.4	-2.0	-3.8	.
(95% Confidence Interval)	(-0.6, +1.3)	(-2.9, -1.0)	(-4.8, -2.9)	.
Study 6				
Number of Patients	.	n = 8	n = 77	n = 43
Mean LIC at Baseline (mg Fe/g dw)	.	5.6	8.8	23.5
Mean Change (mg Fe/g dw)	.	-1.5	-2.8	-9.1
(95% Confidence Interval)	.	(-3.7, +0.7)	(-3.4, -2.2)	(-11.0, -7.3)

Abbreviation: LIC, liver iron concentration; NTDT, non-transfusion-dependent thalassemia.
[a] Randomized dose in Study 5 or assigned starting dose in Study 6.
[b] Least square mean change for Study 5.

Additional pediatric use information is approved for Novartis Pharmaceuticals Corporation's JADENU (desferasirox) tablets and granules. However, due to Novartis Pharmaceuticals Corporation's marketing exclusivity rights, this drug product is not labeled with that information.

16 HOW SUPPLIED/STORAGE AND HANDLING

Deferasirox tablets 90 mg are white to off white, film coated, oval biconvex tablets, debossed with '56' on one side and 'V' on the other side. They are available in
Bottle of 30 tablets NDC 31722-011-30

Deferasirox tablets 180 mg are white to off white, film coated, oval biconvex tablets, debossed with '57' on one side and 'V' on the other side. They are available in
Bottle of 30 tablets NDC 31722-012-30

Deferasirox tablets 360 mg are white to off white, film coated, oval biconvex tablets, debossed with '58' on one side and 'V' on the other side. They are available in
Bottle of 30 tablets NDC 31722-013-30

Store deferasirox tablets at 20°C to 25°C (68°F to 77°F); excursions are permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Dosing Instructions

Advise patients to take deferasirox tablets with water or other liquids. Advise patients to swallow deferasirox tablets once daily with water or other liquids, preferably at the same time each day. Advise patients to take deferasirox tablets on an empty stomach or with a light meal (contains less than 7% fat content and approximately 250 calories). Examples of light meals include 1 whole wheat English muffin, 1 packet jelly (0.5 ounces), and skim milk (8 fluid ounces) or a turkey sandwich (2 oz. turkey on whole wheat bread w/lettuce, tomato, and 1 packet mustard). For patients who have difficulty swallowing whole tablets, deferasirox tablets may be crushed and mixed with soft foods (e.g., yogurt or applesauce) immediately prior to use and administered orally. Advise against the use of commercial crushers with serrated surfaces for crushing a single 90 mg tablet. Advise patients to immediately and completely consume the dose and not store it for future use *[see Dosage and Administration (2.3)]*.

Blood Testing

Advise patients that blood tests will be performed frequently to check for damage to kidneys, liver, or blood cells *[see Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5)]*.

Acute Kidney Injury, Including Acute Renal Failure

Caution patients about the potential for kidney toxicity when taking deferasirox tablets. Inform patients of the signs and symptoms of kidney injury. Advise patients to contact their healthcare provider immediately if they experience any of these symptoms *[see Warnings and Precautions (5.1)]*.

Hepatic Toxicity and Failure

Caution patients about the potential for hepatic toxicity when taking deferasirox tablets. Inform patients of the signs and symptoms of hepatic toxicity. Advise patients to contact their healthcare provider immediately if they experience any of these symptoms *[see Warnings and Precautions (5.2)]*.

GI Ulceration and Hemorrhage

Caution patients about the potential for the development of GI ulcers or bleeding when taking deferasirox in combination with drugs that have ulcerogenic or hemorrhagic potential, such as NSAIDs, corticosteroids, oral bisphosphonates, or anticoagulants. Inform patients of the signs and symptoms of GI ulcers or bleeding. Advise patients to contact their healthcare provider for symptoms of heartburn but to seek immediate medical attention for symptoms of GI hemorrhage *[see Warnings and Precautions (5.3)]*.

Allergic Reactions

Serious allergic reactions (which include swelling of the throat) have been reported in patients taking deferasirox, usually within the first month of treatment. If reactions are severe, advise patients to stop taking deferasirox immediately and seek immediate medical attention *[see Warnings and Precautions (5.7)]*.

Severe Skin Reactions

Severe skin reactions have been reported in patients taking deferasirox tablets. Inform patients of the signs and symptoms of severe skin reactions. If reactions are severe, advise patients to stop taking deferasirox tablets immediately and seek immediate medical attention *[see Warnings and Precautions (5.8)]*.

Skin Rash

Skin rashes may occur during deferasirox treatment. If the skin rash is severe, advise patients to stop taking deferasirox and seek medical attention *[see Warnings and Precautions (5.9)]*.

Pediatric Patients with Acute Illness

Instruct pediatric patients and their caregivers to contact their healthcare provider during episodes of acute illness, especially if the patient has not been drinking fluids or the patient has volume depletion due to fever, vomiting, or diarrhea *[see Warnings and Precautions (5.1)]*.

Auditory and Ocular Testing

Because auditory and ocular disturbances have been reported with deferasirox, conduct auditory testing and ophthalmic testing before starting deferasirox treatment and thereafter at regular intervals. Advise patients to contact their healthcare provider if they develop visual or auditory changes during treatment *[see Warnings and Precautions (5.10)]*.

Drug Interactions

Caution patients not to take aluminum containing antacids and deferasirox tablets simultaneously *[see Drug Interactions (7.1)]*.

Caution patients about potential loss of effectiveness of drugs metabolized by CYP3A4 (e.g., cyclosporine, simvastatin, hormonal contraceptive agents) when deferasirox is administered with these drugs *[see Drug Interactions (7.2)]*.

Caution patients about potential loss of effectiveness of deferasirox when administered with drugs that are potent UGT inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir). Based on serum ferritin levels and clinical response, consider increases in the dose of deferasirox when concomitantly used with potent UGT inducers *[see Drug Interactions (7.5)]*.

Caution patients about potential loss of effectiveness of deferasirox when administered with drugs that are bile acid sequestrants (e.g., cholestyramine, colesevelam, colestipol). Based on serum ferritin levels and clinical response, consider increases in the dose of deferasirox when concomitantly used with bile acid sequestrants *[see Drug Interactions (7.6)]*.
Caution patients with diabetes to monitor their glucose levels more frequently when repaglinide is used concomitantly with deferasirox *[see Drug Interactions (7.3)]*.

Handling Instructions

Advise patients to store deferasirox tablets in a dry, room-temperature environment *[see How Supplied/Storage and Handling (16)]*.

Driving and Using Machines

Caution patients experiencing dizziness to avoid driving or operating machinery *[see Adverse Reactions (6.1)]*.

CAMBER PHARMACEUTICALS, INC.

2101009

Manufactured for:
Camber Pharmaceuticals, Inc.
Piscataway, NJ 08854

By: Annora Pharma Pvt. Ltd.
Sangareddy - 502313, Telangana, India.

Revised: 05/2021

- Take the dose right away. Do not save any of the deferasirox and soft food mixture for later use.
- **Do not** use store-bought pill crushers with serrated surfaces for crushing deferasirox 90 mg tablets.

- Do not take deferasirox tablets with aluminum-containing antacid products. See "**Before taking deferasirox tablets".**
- Tell your healthcare provider if you or your child gain or lose any weight. Your or your child's dose of deferasirox tablets may need to be adjusted.
- If you take the diabetes medicine repaglinide during treatment with deferasirox tablets, you may need to test your blood sugar (glucose) levels more often. Follow your healthcare provider's instructions about how often to test your blood sugar during this time.
- Your healthcare provider should do blood and urine tests before, and during treatment to check how you respond to deferasirox tablets, and to monitor you for side effects. Your healthcare provider may change your dose, or temporarily or permanently stop deferasirox tablets if you have certain side effects.
- In people who have thalassemia, your healthcare provider will check the amount of iron in your liver before and during treatment with deferasirox tablets.
- If you or your child take too much deferasirox tablets, call your healthcare provider right away or go to the nearest hospital emergency room. Symptoms that can happen if you take too much deferasirox tablets include: stomach-area (abdominal) pain, diarrhea, nausea and vomiting.

What should I avoid while taking deferasirox tablets?

- Deferasirox tablets may cause dizziness. Avoid driving or operating machinery until you know how deferasirox tablets affects you. Do not drive or operate machinery if deferasirox tablets makes you dizzy.

What are the possible side effects of deferasirox tablets?

Deferasirox tablets can cause serious side effects, including:

- **See "What is the most important information I should know about deferasirox tablets?"**
- **Effects on your bone marrow.** Deferasirox tablets can affect your bone marrow and cause you to have low white blood cell count which can be serious, decreased platelets, or worsening of your anemia, and may lead to death. Your risk for effects on your bone marrow may be increased if you already have other blood disorders. Your healthcare provider will do blood tests to monitor your blood cell counts for these problems.
- **Serious allergic reactions.** Deferasirox tablets may cause serious allergic reactions, which usually start within the first month of treatment. **Get medical help right away if you develop any of the following symptoms of a serious allergic reaction including:**
  - difficulty in breathing or swallowing
  - chest pain
  - rapid heartbeat
  - feeling faint
  - swelling of the face, lips, mouth, tongue, or throat
  - severe itching of the skin with a red rash or raised bumps
  - hives
- **Skin rash and severe skin reactions.** Skin rashes are common with deferasirox tablets. If you get a more severe rash, your healthcare provider may temporarily stop deferasirox tablets.

  Severe skin reactions can also happen with deferasirox tablets and can be life-threatening or lead to death. Get medical help right away if you develop any one or more of the following signs and symptoms of a severe skin reaction, including:
  - rash or red skin
  - blisters on your lips, or around your mouth or eyes
  - mouth sores
  - skin peeling
  - high fever or flu-like symptoms
  - enlarged lymph nodes
- **Hearing and vision problems.** Deferasirox tablets can cause decreased hearing and changes in your vision including cataracts, increased pressure in your eye, and problems with your retinas. Your healthcare provider should do hearing and vision tests before you start and then regularly during treatment. Your healthcare provider may decrease your dose or stop deferasirox tablets if you develop hearing or vision problems.

The most common side effects in anyone who takes deferasirox tablets include: diarrhea and nausea.

Other common side effects in people with too much iron in their blood due to repeated blood transfusions include: vomiting, stomach-area (abdomen) pain, and an abnormal kidney function blood test.

These are not all the possible side effects of deferasirox 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 deferasirox tablets?

- Store deferasirox tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep the bottle closed tightly and away from moisture.

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

General information about the safe and effective use of deferasirox tablets

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

For more information, call 1-866-495-1995.

What are the ingredients in deferasirox tablets?

Deferasirox tablets:

Active ingredient: deferasirox

Inactive ingredients: Colloidal silicon dioxide, crospovidone, microcrystalline cellulose, poloxamer 188, povidone, and sodium stearyl fumarate. The film coating contains hypromellose, polyethylene glycol, talc and titanium dioxde.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Medication Guide available at http://camberpharma.com/medication-guides

CAMBER PHARMACEUTICALS, INC.

Manufactured for:
Camber Pharmaceuticals, Inc.
Piscataway, NJ 08854

By: Annora Pharma Pvt. Ltd.
Sangareddy - 502313, Telangana, India.

Revised: 05/2021

Size: 400 x 800 mm
Pharma Code: Front-61 & Back-62
Spec.: Printed on 40 GSM Bible paper, front & back side printing
Note: Pharma code position and Orientation are tentative, will be changed based on folding size.
No of Colours: 01 - Black