2D Data Matrix to be printed with serial number on each leaflet. The number should not be repeated

Deferasirox Tablets
013-2024-11
2103903
Dummy

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)

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 50×10^9/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: 11/2024

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 to 10 mg/kg	3.5 to 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 to 10 mg/kg	3.5 to 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 50×10^9/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 reduction or interruption may be considered if abnormalities occur in levels of markers of renal tubular function and/or as clinically indicated. Monitor serum ferritin monthly to evaluate for overchelation. Use the minimum dose to establish and maintain a low iron burden. Monitor renal function more frequently in patients with preexisting renal disease or decreased renal function. In pediatric patients, interrupt deferasirox during acute illnesses, which can cause volume depletion such as vomiting, diarrhea, or prolonged decreased oral intake, and monitor renal function more frequently. Promptly correct fluid deficits to prevent renal injury. Resume therapy as appropriate, based on assessments of renal function, when oral intake and volume status are normal *[see Dosage and Administration (2.5), Warnings and Precautions (5.6), Adverse Reactions (6.1, 6.2), Use in Specific Populations (8.4)]*.

5.2 Hepatic Toxicity and Failure
Deferasirox can cause hepatic injury, fatal in some patients. In Study 1, 4 patients (1.3%) discontinued deferasirox because of hepatic toxicity (drug-induced hepatitis in 2 patients and increased serum transaminases in 2 additional patients). Hepatic toxicity appears to be more common in patients greater than 55 years of age. Hepatic failure was more common in patients with significant comorbidities, including liver cirrhosis and multiorgan failure *[see Adverse Reactions (6.1)]*.

Acute liver injury and failure, including fatal outcomes, have occurred in pediatric deferasirox-treated patients. Liver failure occurred in association with acute kidney injury in pediatric patients at risk for overchelation during a volume-depleting event. Interrupt deferasirox therapy when acute liver injury or acute kidney injury is suspected and during volume depletion. Monitor liver and renal function more frequently in pediatric patients who are receiving deferasirox in the 14 to 28 mg/kg/day range and when iron burden is approaching normal. Use the minimum effective dose to achieve and maintain a low iron burden *[see Dosage and Administration (2.5), Warnings and Precautions (5.6), Adverse Reactions (6.1)]*.

Measure transaminases [aspartate transaminase (AST) and alanine transaminase (ALT)] and bilirubin in all patients before the initiation of treatment and every 2 weeks during the first month and at least monthly thereafter. Consider dose modifications or interruption of treatment for severe or persistent elevations.

Avoid the use of deferasirox in patients with severe (Child-Pugh C) hepatic impairment. Reduce the starting dose in patients with moderate (Child-Pugh B) hepatic impairment *[see Dosage and Administration (2.4), Use in Specific Populations (8.7)]*. Patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment may be at higher risk for hepatic toxicity.

5.3 Gastrointestinal (GI) Ulceration, Hemorrhage, and Perforation
GI hemorrhage, including deaths, has been reported, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts. Nonfatal upper GI irritation, ulceration and hemorrhage have been reported in patients, including children and adolescents, receiving deferasirox *[see Adverse Reactions (6.1)]*. Monitor for signs and symptoms of GI ulceration and hemorrhage during deferasirox therapy, and promptly initiate additional evaluation and treatment if a serious GI adverse reaction is suspected. The risk of GI hemorrhage may be increased when administering deferasirox in combination with drugs that have ulcerogenic or hemorrhagic potential, such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, oral bisphosphonates, or anticoagulants. There have been reports of ulcers complicated with GI perforation (including fatal outcome) *[see Adverse Reactions (6.2)]*.

5.4 Bone Marrow Suppression
Neutropenia, agranulocytosis, worsening anemia, and thrombocytopenia, including fatal events, have been reported in patients treated with deferasirox. Preexisting hematologic disorders may increase this risk. Monitor blood counts in all patients. Interrupt treatment with deferasirox in patients who develop cytopenias until the cause of the cytopenia has been determined. Deferasirox is contraindicated in patients with platelet counts below 50×10^9/L.

5.5 Age-Related Risk of Toxicity
Elderly Patients
Deferasirox has been associated with serious and fatal adverse reactions in the postmarketing setting among adults, predominantly in elderly patients. Monitor elderly patients treated with deferasirox more frequently for toxicity *[see Use in Specific Populations (8.5)]*.

Pediatric Patients
Deferasirox has been associated with serious and fatal adverse reactions in pediatric patients in the postmarketing setting. These events were frequently associated with volume depletion or with continued deferasirox tablets for oral suspension doses in the 20 to 40 mg/kg/day range equivalent to 14 to 28 mg/kg/day deferasirox when body iron burden was approaching or in the normal range. Interrupt deferasirox in patients with volume depletion, and resume deferasirox when renal function and fluid volume have normalized. Monitor liver and renal function more frequently during volume depletion and in patients receiving deferasirox in the 14 to 28 mg/kg/day range when iron burden is approaching the normal range. Use the minimum effective dose to achieve and maintain a low iron burden *[see Dosage and Administration (2.4), Warnings and Precautions (5.6), Use in Specific Populations (8.4)]*.

5.6 Overchelation
For patients with transfusional iron overload, measure serum ferritin monthly to assess the patient's response to therapy and minimize the risk of overchelation. An analysis of pediatric patients treated with deferasirox tablets for oral suspension in pooled clinical trials (n = 158), found a higher rate of renal adverse reactions among patients receiving doses greater than 25 mg/kg/day equivalent to 17.5 mg/kg/day deferasirox while their serum ferritin values were less than 1,000 mcg/L. Consider dose reduction or closer monitoring of renal and hepatic function, and serum ferritin levels during these periods. Use the minimum effective dose to maintain a low-iron burden *[see Adverse Reactions (6.1), Use in Specific Populations (8.4)]*.

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)]*. If the serum ferritin falls below 500 mcg/L, interrupt therapy with deferasirox and continue monthly monitoring. Evaluate the need for ongoing chelation for patients whose conditions do not require regular blood transfusions. Use the minimum effective dose to maintain iron burden in the target range. Continued administration of deferasirox in the 14 to 28 mg/kg/day range, when the body iron burden is approaching or within the normal range can result in life-threatening adverse reactions *[see Dosage and Administration (2.1)]*.

For patients with NTDT, measure LIC by liver biopsy or by using an FDA-cleared or approved method for monitoring patients receiving deferasirox therapy every 6 months on treatment. Interrupt deferasirox administration when the LIC is less than 3 mg Fe/g dw. Measure serum ferritin monthly, and if the serum ferritin falls below 300 mcg/L, interrupt deferasirox and obtain a confirmatory LIC *[see Clinical Studies (14)]*.

5.7 Hypersensitivity
Deferasirox may cause serious hypersensitivity reactions (such as anaphylaxis and angioedema), with the onset of the reaction usually occurring within the first month of treatment *[see Adverse Reactions (6.2)]*. If reactions are severe, discontinue deferasirox and institute appropriate medical intervention. Deferasirox is contraindicated in patients with known hypersensitivity to deferasirox products and should not be reintroduced in patients who have experienced previous hypersensitivity reactions on deferasirox products due to the risk of anaphylactic shock.

5.8 Severe Skin Reactions
Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) which could be life-threatening or fatal have been reported during deferasirox therapy *[see Adverse Reactions (6.1, 6.2)]*. Cases of erythema multiforme have been observed. Advise patients of the signs and symptoms of severe skin reactions, and closely monitor. If any severe skin reactions are suspected, discontinue deferasirox immediately and do not reintroduce deferasirox therapy.

5.9 Skin Rash
Rashes may occur during deferasirox treatment *[see Adverse Reactions (6.1)]*. For rashes of mild to moderate severity, deferasirox may be continued without dose adjustment, since the rash often resolves spontaneously. In severe cases, interrupt treatment with deferasirox. Reintroduction at a lower dose with escalation may be considered after resolution of the rash.

5.10 Auditory and Ocular Abnormalities
Auditory disturbances (high frequency hearing loss, decreased hearing), and ocular disturbances (lens opacities, cataracts, elevations in intraocular pressure, and retinal disorders) were reported at a frequency of less than 1% with deferasirox therapy in the clinical studies. The frequency of auditory adverse reactions was increased among pediatric patients, who received deferasirox tablets for oral suspension doses greater than 25 mg/kg/day equivalent to 17.5 mg/kg/day deferasirox when serum ferritin was less than 1,000 mcg/L *[see Warnings and 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)]*. In Study 7, 134 patients with NTDT of 10 years of age or older with iron overload, received deferasirox tablets for oral suspension for up to 5 years, at a starting dose of 10 mg/kg/day followed by dose adjustment at Week4, and then approximately every 6 months thereafter based on LIC levels. 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	Study 7
Any adverse reaction	Deferasirox N = 110 n (%) 31 (28)	Placebo N = 56 n (%) 9 (16)	Deferasirox N = 130 n (%) 27 (21)	Deferasirox N = 134 n (%) 50 (37)
Nausea	7 (6)	4 (7)	2 (2)[a]	7 (5)
Rash	7 (6)	1 (2)	2 (2)[a]	3 (2)[a]
Diarrhea	5 (5)	1 (2)	7 (5)	8 (6)

Abbreviation: NTDT, non-transfusion-dependent thalassemia.
[a] The occurrence of nausea, and rash are included for Study 6 and rash for Study 7 for consistency. There were no additional adverse reactions with a suspected relationship to study drug occurring in >5% of patients in Study 6 and Study 7.

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, Study 6, and Study 7 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	Study 7
Laboratory Parameter	Deferasirox N = 110 n (%)	Placebo N = 56 n (%)	Deferasirox N = 130 n (%)	Deferasirox N = 134 n (%)
Serum creatinine (> 33% increase from baseline and > ULN at ≥ 2 consecutive post-baseline values)	3 (3)	0	2 (2)	2 (2)
SGPT/ALT (> 5 x ULN and > 2 x baseline)	1 (1)	1 (2)	2 (2)	1 (1)

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).
- A 25% increased risk for acute kidney injury was observed with each 250 mcg/L decrease in serum ferritin starting at 1250 mcg/L (95% CI: 1.01 to 1.56).
- Among pediatric patients with a serum ferritin < 1,000 mcg/L, those who received deferasirox tablets for oral suspension dosage > 30 mg/kg/day, equivalent to 21 mg/kg/day deferasirox compared to those who received lower dosages, had a higher risk for acute kidney injury (Odds ratio (OR) = 4.47, 95% CI: 1.25 to 15.95), consistent with overchelation.

In addition, a cohort-based analysis of ARs was conducted in the deferasirox tablets for oral suspension pediatric pooled clinical trial data. Pediatric patients who received deferasirox tablets for oral suspension dose > 25 mg/kg/day equivalent to 17.5 mg/kg/day deferasirox when their serum ferritin was < 1,000 mcg/L (n = 158), had a 6-fold greater rate of renal adverse reactions (Incidence Rate Ratio (IRR) = 6.00, 95% CI: 1.75 to 21.36), and a 2-fold greater rate of dose interruptions (IRR = 2.06, 95% CI: 1.33 to 3.17) compared to the time-period prior to meeting these simultaneous criteria. Adverse reactions of special interest (cytopenia, renal, hearing, and GI disorders) occurred 1.9-fold more frequently when these simultaneous criteria were met, compared to preceding time-periods (IRR = 1.91, 95% CI: 1.05 to 3.48) *[see Warnings and Precautions (5.6)]*.

6.2 Postmarketing Experience
The following adverse reactions have been spontaneously reported during post-approval use of deferasirox in the transfusional iron overload setting. Because these reactions are reported voluntarily from a population of uncertain size, in which patients may have received concomitant medication, it is not always possible to reliably estimate frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome (SJS), leukocytoclastic vasculitis, urticaria, alopecia, toxic epidermal necrolysis (TEN)
Immune System Disorders: hypersensitivity reactions (including anaphylactic reaction and angioedema)
Renal and Urinary Disorders: acute renal failure, tubulointerstitial nephritis
Hepatobiliary Disorders: hepatic failure
GI Disorders: GI perforation
Blood and Lymphatic System Disorders: worsening anemia

5-Year Pediatric Registry
In a 5-year observational study, 267 pediatric patients 2 to < 6 years of age (at enrollment) with transfusional hemosiderosis received deferasirox. Of the 242 patients who had pre- and post-baseline eGFR measurements, 116 (48%) patients had a decrease in eGFR of ≥ 33% observed at least once. Twenty-one (18%) of these 116 patients with decreased eGFR had a dose interruption, and 15 (13%) of these 116 patients had a dose decrease within 30 days. Adverse reactions leading to permanent discontinuation from the study included liver injury (n = 11), vomiting (n = 2), renal tubular disorder (n = 1), proteinuria (n = 1), hematuria (n = 1), upper GI hemorrhage (n = 1), abdominal pain (n = 1), and hypokalemia (n = 1).

7 DRUG INTERACTIONS

7.1 Aluminum-Containing Antacid Preparations
The concomitant administration of deferasirox and aluminum-containing antacid preparations has not been formally studied. Although deferasirox has a lower affinity for aluminum than for iron, do not take deferasirox with aluminum-containing antacid preparations.

7.2 Agents Metabolized by CYP3A4
Deferasirox may induce CYP3A4 resulting in a decrease in CYP3A4 substrate concentration when these drugs are coadministered. Closely monitor patients for signs of reduced effectiveness when deferasirox is administered with drugs metabolized by CYP3A4 (e.g., alfentanil, aprepitant, budesonide, buspirone, conivaptan, cyclosporine, darifenacin, darunavir, dasatinib, dihydroergotamine, dronedarone, eletriptan, eplerenone, ergotamine, everolimus, felodipine, fentanyl, hormonal contraceptive agents, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, pimozide, quetiapine, quinidine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, tolvaptan, tipranavir, triazolam, ticagrelor, and vardenafil) *[see Clinical Pharmacology (12.3)]*.

7.3 Agents Metabolized by CYP2C8
Deferasirox inhibits CYP2C8 resulting in an increase in CYP2C8 substrate (e.g., repaglinide and paclitaxel) concentration when these drugs are coadministered. If deferasirox and repaglinide are used concomitantly, consider decreasing the dose of repaglinide and perform careful monitoring of blood glucose levels. Closely monitor patients for signs of exposure related toxicity when deferasirox is coadministered with other CYP2C8 substrates *[see Clinical Pharmacology (12.3)]*.

7.4 Agents Metabolized by CYP1A2
Deferasirox inhibits CYP1A2 resulting in an increase in CYP1A2 substrate (e.g., alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, theophylline, tizanidine) concentration when these drugs are coadministered. An increase in theophylline plasma concentrations could lead to clinically significant theophylline induced CNS or other adverse reactions. Avoid the concomitant use of theophylline or other CYP1A2 substrates with a narrow therapeutic index (e.g., tizanidine) with deferasirox. Monitor theophylline concentrations and consider theophylline dose modification if you must coadminister theophylline with deferasirox. Closely monitor patients for signs of exposure related toxicity when deferasirox is coadministered with other drugs metabolized by CYP1A2 *[see Clinical Pharmacology (12.3)]*.

7.5 Agents Inducing UDP-glucuronosyltransferase (UGT) Metabolism
Deferasirox is a substrate of UGT1A1 and to a lesser extent UGT1A3. The concomitant use of deferasirox with strong UGT inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in deferasirox efficacy due to a possible decrease in deferasirox concentration. Avoid the concomitant use of strong UGT inducers with deferasirox. Consider increasing the initial dose of deferasirox if you must coadminister these agents together *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

7.6 Bile Acid Sequestrants
Avoid the concomitant use of bile acid sequestrants (e.g., cholestyramine, colesevelam, colestipol) with deferasirox due to a possible decrease in deferasirox concentration. If you must coadminister these agents together, consider increasing the initial dose of deferasirox *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

7.7 Busulfan
Increased exposure of busulfan was observed with concomitant use with deferasirox. Monitor plasma concentrations of busulfan when coadministered with deferasirox to allow dose adjustment of busulfan as needed *[see Clinical Pharmacology (12.3)]*.

MEDICATION GUIDE
Deferasirox (dee fer' a sir ox) Tablets

What is the most important information I should know about deferasirox tablets?
Deferasirox tablets can cause serious side effects, including:
Kidney problems: Deferasirox tablets can cause sudden (acute) kidney problems, including kidney failure that may require treatment with dialysis, and may cause death. Deaths have happened mostly in people who also have other health problems and had a blood disorder that was in an advanced stage. Adults and children who already have kidney problems and are taking certain medicines with deferasirox tablets may also have an increased risk of sudden kidney problems. Be sure to tell your healthcare provider about all the medicines you take during treatment with deferasirox tablets.

Your healthcare provider should do blood and urine tests to check your or your child's kidney function before and during treatment with deferasirox tablets. **Call your healthcare provider right away if:**
- **your child becomes sick with fever, vomiting, or diarrhea and cannot drink fluids normally during treatment with deferasirox tablets.** Your child may be dehydrated. Your healthcare provider may need to temporarily stop treatment with deferasirox tablets and treat your child for dehydration to help prevent kidney problems. Your healthcare provider may monitor your child's kidney function more closely.
- **you notice that you or your child are passing less urine than usual during treatment with deferasirox tablets.**

Liver problems. Deferasirox tablets can cause liver problems, including liver failure that can sometimes cause death. Liver problems with deferasirox tablets may be more common in people who are over 55 years of age but can also happen in children. Liver failure has happened more often in people with cirrhosis of the liver and failure of other organs. Liver failure has also happened along with kidney problems in certain children who become dehydrated. **See "Kidney problems" above.**

Your healthcare provider should do blood tests to check your liver function before you start and regularly during treatment with deferasirox tablets. **Call your healthcare provider right away,** if you develop any of the following signs and symptoms:
- drowsiness
- upper right stomach-area (abdomen) pain
- yellowing or increased yellowing of your skin or eyes
- dark urine

Bleeding, ulcers, and tears of the stomach or intestine. Severe stomach and intestine bleeding (hemorrhage) that have caused death have happened in some people treated with deferasirox tablets, especially in elderly people who have advanced blood cancers or low platelet counts. Some people have also had ulcers of the stomach or intestine, sometimes with tears (perforation) that have caused death. In some people who have taken deferasirox tablets, including children and adolescents, irritation of the upper gastrointestinal tract, ulcers, and bleeding have happened, but did not cause death.

Your risk of severe bleeding (hemorrhage) may be increased if you take deferasirox tablets along with other medicines that can cause ulcers or bleeding, such as:
- nonsteroidal anti-inflammatory drugs (NSAIDs)
- corticosteroids
- certain osteoporosis medicines called oral bisphosphonates
- blood thinner medicines

Before you start taking deferasirox tablets, tell your healthcare provider if you are taking one of these medicines. Ask your healthcare provider if you are not sure.
If you develop an ulcer of the stomach or intestine, or severe bleeding, your healthcare provider may stop deferasirox tablets.

Elderly people may be at a higher risk of developing serious side effects and death due to serious side effects with deferasirox tablets. Your healthcare provider may need to monitor you more closely during treatment with deferasirox tablets.
- Tell your healthcare provider if you get heartburn during treatment with deferasirox tablets.
- **Get emergency medical help right away if you vomit blood or pass black or bloody stools, or if you have severe stomach-area (abdomen) pain during treatment with deferasirox tablets.**

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

What are deferasirox tablets?
Deferasirox tablets are prescription medicines that are used to treat:
- people 2 years of age and older who have an increased amount of iron in their blood for a long period of time (chronic), caused by repeated blood transfusions
- certain people 10 years of age or older with thalassemia who have an increased amount of iron in their blood but who are not receiving regular blood transfusions

It is not known if deferasirox tablets are safe and effective when used with other medicines to treat an increased amount of iron in the blood.

It is not known if deferasirox tablets are safe and effective for treating children under 2 years of age who have an increased amount of iron in their blood for a long period of time (chronic) caused by repeated blood transfusions.

It is not known if deferasirox tablets are safe and effective for treating children under 10 years of age with thalassemia who have an increased amount of iron in their blood, but who are not receiving regular blood transfusions.

Do not take deferasirox tablets if you:
- have certain kidney problems
- have high-risk myelodysplastic syndrome (MDS)
- have advanced cancer
- have a low platelet count
- are allergic to deferasirox or any of the ingredients in deferasirox tablets. See the end of this medication guide for a list of the ingredients in deferasirox tablets.

Ask your healthcare provider if you are not sure if you have any of the medical conditions listed above.

Before taking deferasirox tablets tell your healthcare provider about all of your medical conditions, including if you:
- have kidney problems
- have liver problems
- have advanced cancer. **See "Do not take deferasirox tablets if you?"**
- have a blood disorder that may increase your risk for bleeding
- are pregnant or plan to become pregnant. It is not known if deferasirox tablets can harm your unborn baby. Hormonal forms of birth control may not be as effective if used during treatment with deferasirox tablets. You could become pregnant. Talk to your healthcare provider about other birth control options that you can use during this time. Tell your healthcare provider right away if you become pregnant during treatment with deferasirox tablets.
- are breastfeeding or plan to breastfeed. It is not known if deferasirox passes into your breast milk and can harm your baby. You and your healthcare provider should decide if you will take deferasirox tablets or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription medicines, over-the-counter medicines, vitamins, and herbal supplements. Some medicines may affect how deferasirox tablets work, and deferasirox tablets may affect how other medicines work. Also, **your risk of sudden kidney problems or severe bleeding may be increased if you take deferasirox tablets with certain medicines. See "What is the most important information I should know about deferasirox tablets?"**
- Avoid taking the following medicines during treatment with deferasirox tablets:
  - ○ antacid products (medicines used to treat heartburn) that contain aluminum
  - ○ theophylline
  - ○ certain medicines to lower your cholesterol, called bile acid sequestrants.

Ask your healthcare provider if you are not sure if you take one of these medicines.
Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take deferasirox tablets?
- Take deferasirox tablets exactly as your healthcare provider tells you.
- **Do not** change your dose of deferasirox tablets or stop taking unless your healthcare provider tells you to.
- Deferasirox comes as tablets.
  - ○ You may take deferasirox tablets on an empty stomach or with a light meal.
    Examples of a light meal include:
    - ■ 1 whole wheat English muffin, 1 packet of jelly (0.5 ounce), and skim milk (8 fluid ounces), or
    - ■ A turkey sandwich (2 ounces of turkey on whole wheat bread with lettuce, tomato, and 1 packet of mustard)

Taking deferasirox tablets:
- ○ Take deferasirox tablets by mouth with water or other liquids 1 time every day, preferably at the same time every day.
- ○ If you have trouble swallowing the tablets whole, you may crush deferasirox tablets and mix them with soft foods such as yogurt or applesauce right before taking your dose.

Artwork information

Customer	Camber	Market	USA
Dimensions (mm)	400 x 800 mm	Non Printing Colors	Die cut
Pharma Code No.	Front-992 & Back-993		
Printing Colours (01)	Black		

Others: Pharma code position and Orientation are tentative, will be changed based on folding size.

- 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 moniter 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 load 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 dioxide.

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

CAMBER PHARMACEUTICALS

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