Deferasirox is an orally active chelator that is selective for iron (as Fe³⁺). It is a tridentate ligand that binds iron with high affinity in vivo.

### 2.1 Administration

#### 2.1.1 General Considerations

Deferasirox is administered to patients with transfusional iron overload to reduce iron burden. The recommended dose is 1.5 g once daily or 2.5 g once daily for patients with baseline ferritin levels more than 100,000 mcg/L. Deferasirox is administered during the first two hours of each day, beginning on an empty stomach, and with a full glass of water (8 ounces) to allow for complete swallowing. Deferasirox is not currently available for administration to pediatric patients.

#### 2.1.2 Co-administration of Drugs

The use of deferasirox with ribavirin, mycophenolate (MMF), and antiretrovirals (e.g., rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in deferasirox efficacy due to a possible decrease in plasma concentrations or deferasirox plasma concentrations could lead to clinically significant theophylline-induced CNS or other adverse reactions. Avoid the co-administration of these drugs with deferasirox.

#### 2.1.3 Drug Interactions

- **CYP3A4 inhibitors**: Use with caution, especially with ritonavir.
- **CYP2C8 inhibitors**: No interaction studies conducted.

### 2.2 Dosage and Administration

#### 2.2.1 Initiating Therapy

- **Age-related Dosing**: No dose adjustment needed in elderly patients.
- **Patients with Renal Impairment**: No dose adjustment needed in patients with renal impairment.

#### 2.2.2 Dosing in Patients with Baseline Ferritin Levels

- **Ferritin 50,000 - 100,000 mcg/L**: Initial dose of 1.5 g/day.
- **Ferritin ≥ 100,000 mcg/L**: Initial dose of 2.5 g/day.

#### 2.2.3 Treatment Adjustments

- **Maintenance Dosing**: Adjust the dose of deferasirox based on the patient's transfused iron and ferritin levels.

#### 2.2.4 Discontinuation

- **Discontinue therapy if ferritin levels fall below 500 mcg/L**.

### 2.3 Monitoring

- **Transaminases and Bilirubin**: Measure transaminases (AST and ALT) and bilirubin in all patients before initiating therapy and every 2 weeks during therapy.

### 3. Adverse Reactions

Adverse reactions which most frequently led to dose interruption or dose adjustment during clinical trials were rash, gastrointestinal disorders, and renal disorders. Other adverse reactions which occurred at a frequency of greater than 1% are listed in Table 1. Adverse reactions reported in postmarketing surveillance are also listed in Table 2. Adverse reactions which occurred more frequently in patients under 18 years of age are listed in Table 3. Adverse reactions which have been reported in clinical trials or postmarketing surveillance are also listed in Table 4.

### 4.7 Pregnancy

- **Pregnancy**: Deferasirox is an FDA category B drug.

### 5.2 Nursing Mothers

- **Lactation**: Deferasirox and its metabolites are excreted in rat milk. Because of the potential for serious adverse reactions in nursing infants, the decision to use deferasirox in a nursing woman should be made with consideration of the importance of the drug to the mother.

### 6.7 Transfusional Iron Overload

Deferasirox is indicated for the treatment of transfusional iron overload in patients with chronic transfusion-dependent anemia due to sickle cell disease (SCD) and thalassemia major (TA-M) to reduce iron burden. Deferasirox is not currently available for administration to patients with other causes of iron overload, including but not limited to, myelodysplastic syndrome (MDS) and chronic iron overload due to blood transfusion.

### 6.10.10 References

- **References**

### 6.13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

- **Carcinogenesis**: No studies of carcinogenic potential have been performed.

### 7. Administration

#### 7.1 Cautions

- **Platelet Counts**: Platelet counts below 50 x 10⁹/L are contraindicated.

#### 7.2 Contraindications

- **Hypersensitivity to deferasirox**: Severe hypersensitivity reactions have been observed in patients treated with deferasirox.

### 8.3 Interactions

- **CYP3A4 Inhibitors**: Use with caution, especially with ritonavir.
- **CYP2C8 Inhibitors**: No interaction studies conducted.

### 10.1 Mechanisms of Action

- **Deferasirox**: At the site of absorption, deferasirox is quickly converted to deferoxamine, which is the active metabolite. Absorption of deferoxamine is rapid, and the concentration in tissue fluids and periportal hepatocytes is approximately two-fold higher than in the serum.

### 11.1 Preclinical Pharmacology

- **Pharmacokinetics**: Deferasirox is rapidly and almost completely absorbed after oral administration. The plasma clearance of deferasirox is primarily hepatic, and its elimination is due to metabolism.

### 12.1 Preclinical Toxicology

- **Toxicity Studies**: Deferasirox was toxicologically evaluated in various species, including rats, dogs, and monkeys. Deferasirox was administered orally to rats and dogs at doses of 100 mg/kg/day and to monkeys at doses of 50 mg/kg/day for up to 2 years. In rats, the no-observed-adverse-effect level (NOAEL) was 10 mg/kg/day. In dogs, the NOAEL was 50 mg/kg/day. In monkeys, the NOAEL was 25 mg/kg/day.

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

- **Carcinogenesis**: No studies of carcinogenic potential have been performed.
Deferasirox at oral doses up to 75 mg per kg per day (0.6 times the MRHD on an mg/m² basis) was found to have no adverse positive in 1 of 3.

Deferasirox was negative in the Ames test and chromosome aberration test with human peripheral blood lymphocytes. It was showed to be negative in the micronucleus test in vitro and in vivo. It did not show any teratogenic effects in the rat, rabbit, and mouse. The use of deferasirox was assessed in a study in which the liver was transplanted into mice. No evidence of carcinogenicity was observed in mice when deferasirox was given at doses up to 200 mg per kg per day (0.81 times the MRHD on an mg/m² basis).

Deferasirox is provided as 125 mg, 250 mg and 500 mg Tablets For Oral Suspension.

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 the patient is taking bile acid sequestrants.

The clinical significance of these observations is unknown.

Deferasirox 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.

In instructing pediatric patients and their caregivers to contact their healthcare provider during episodes of acute illness, especially in those patients who are at increased risk for these complications, advise patients to contact their health care provider for signs and symptoms of gastrointestinal ulceration and hemorrhage.

Skin Rash

Bacterial and fungal infections have been reported in patients taking deferasirox, especially in those patients who are at increased risk for these complications.

DRUG INTERACTIONS

Cyclosporin A or Verapamil: The concomitant use of deferasirox with cyclosporin A or verapamil did not result in a decrease in deferasirox exposure.

Colestyramine: The concomitant use of deferasirox with bile acid sequestrants may result in a decrease in deferasirox efficacy.

Potent UDP-glucuronosyltransferase (UGT) inducers such as rifampicin (600 mg/day for 9 days) resulted in a decrease of deferasirox exposure.

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

Cholestyramine: The concomitant use of deferasirox with bile acid sequestrants may result in a decrease in deferasirox efficacy.