DEFERASIROX

Class: Chelating Agent

Indications : Chronic iron overload: Treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) or due to non-transfusion-dependent thalassemia syndromes and with a liver iron concentration (LIC) of at least 5 mg iron per gram of liver dry weight (mg Fe/g dw) and serum ferritin >300 mcg/L.

Available dosage form in the hospital:

- DEFERASIROX 250MG DISP.TAB

- DEFERASIROX 500MG DISP.TAB

Dosage: **Note**: Calculate dose to the nearest whole tablet size.

- **Chronic iron overload due to blood transfusion**: Oral: **Note**: Treatment should only be initiated with evidence of chronic iron overload (ie, transfusion of ≥100 mL/kg of packed red blood cells [eg, ≥20 units for a 40 kg individual] and serum ferritin consistently >1000 mcg/L).

  -***U.S. labeling:*** Initial: 20 mg/kg once daily
  -***Canadian labeling:*** Dosing based on treatment goal and patient's individual transfusion rate:
  -Treatment goal: Maintenance of acceptable body iron levels:
  - Initial: 10 mg/kg once daily if transfused packed red blood cells (pRBCs) <7 mL/kg/month (approximately <2 units per month for an adult)
  - Initial: 20 mg/kg once daily if transfused pRBCs ≥7 mL/kg/month (approximately >2 units per month for an adult)

  -Treatment goal: Iron overload reduction:
  - Initial: 20 mg/kg once daily if transfused pRBCs <14 mL/kg/month (approximately <4 units per month for an adult)
  - Initial: 30 mg/kg once daily if transfused pRBCs ≥14 mL/kg/month (approximately >4 units per month for an adult)

  Maintenance: Adjust dose every 3-6 months based on serum ferritin trends; adjust by 5 or 10 mg/kg/day; titrate to individual response and treatment goals. Usual range: 20-30 mg/kg/day; doses up to 40 mg/kg/day may be considered for serum ferritin levels persistently >2500 mcg/L (doses above 40 mg/kg/day are not recommended). Note: Consider interrupting therapy for serum ferritin <500 mcg/L (risk of toxicity may be increased).
- **Chronic iron overload in non-transfusion-dependent thalassemia syndromes**: Oral:

  -U.S. labeling: Note: Treatment should only be initiated with evidence of chronic iron overload (hepatic iron concentration ≥5 mg Fe/g dry weight and serum ferritin >300 mcg/L).

  - Initial: 10 mg/kg once daily. Consider increasing to 20 mg/kg once daily after 4 weeks if baseline hepatic iron concentration is >15 mg Fe/g dry weight.
  - Maintenance: Monitor serum ferritin monthly; if serum ferritin is <300 mcg/L, interrupt therapy and obtain hepatic iron concentration. Monitor hepatic iron concentration every 6 months; interrupt therapy when hepatic iron concentration <3 mg Fe/g dry weight. After 6 months of therapy, consider dose adjustment to 20 mg/kg/day if hepatic iron concentration >7

mg Fe/g dry weight. Reduce dose to ≤10 mg/kg when hepatic iron concentration is 3-7 mg Fe/g dry weight. Doses above 20 mg/kg/day are not recommended. After interruption, resume treatment when hepatic iron concentration >5 mg Fe/g dry weight.

-Canadian labeling: **Note:** Treatment should only be initiated with evidence of chronic iron overload (hepatic iron concentration ≥5 mg Fe/g dry weight or serum ferritin consistently >800 mcg/L).

- Initial: 10 mg/kg/day
- Maintenance: Do not exceed 10 mg/kg/day in patients whose hepatic iron concentration was not evaluated and if serum ferritin ≤2000 mcg/L. Monitor serum ferritin monthly; consider dose adjustment by 5 or 10 mg/kg/day every 3-6 months if hepatic iron concentration ≥7 mg Fe/g dry weight or serum transferrin levels consistently >2000 mcg/L. Patients receiving >10 mg/kg should have their dose reduced to ≤10 mg/kg when hepatic iron concentration <7 mg Fe/g dry weight or serum ferritin <2000 mcg/L. Interrupt therapy when hepatic iron concentration <3 mg Fe/g dry weight or serum ferritin <300 mcg/L. Doses above 20 mg/kg/day are not recommended.

-Dosage adjustment with concomitant bile acid sequestrants (eg,cholestyramine, colesevelam, colestipol) or potent UGT inducers (eg, rifampin, phenytoin, phenobarbital, ritonavir): Avoid concomitant use; if coadministration necessary, consider increasing the initial dose of deferasirox dose by 50%; monitor serum ferritin and clinical response.

Geriatric
Refer to adult dosing.

Renal Impairment: Creatinine clearance should be estimated using the Cockcroft-Gault formula.

-Renal impairment at treatment initiation:

- Cl_{cr} >60 mL/minute: No dosage adjustment necessary
- Cl_{cr} 40-60 mL/minute: Reduce initial dose by 50%.
- Cl_{cr} <40 mL/minute or serum creatinine >2 times age-appropriate ULN: Use is contraindicated.

-Renal toxicity during treatment:

U.S. labeling:

-Transfusional iron overload:

- Adults: For increase in serum creatinine ≥33% above the average baseline, repeat within 1 week; if still elevated by ≥33%: Reduce daily dose by 10 mg/kg
- All patients: Cl_{cr} <40 mL/minute or serum creatinine >2 times age-appropriate ULN: Discontinue treatment.

-Non-transfusion-dependent thalassemia syndromes:

- Adults: For increase in serum creatinine ≥33% above the average baseline, repeat within 1 week; if still elevated by ≥33%: Interrupt therapy if the dose is 5 mg/kg; reduce dose by 50% if the dose is 10-20 mg/kg
- All patients: Cl_{cr} <40 mL/minute or serum creatinine >2 times age-appropriate ULN: Discontinue treatment.

-Canadian labeling:

- Adults: For increase in serum creatinine >33% above the average pretreatment level for 2 consecutive weekly levels, reduce daily dose by 10 mg/kg.
- All patients: Progressive increase serum creatinine beyond ULN: Withhold treatment.

Hepatic Impairment:

-Hepatic impairment at treatment initiation:

- Mild impairment (Child-Pugh class A): No dosage adjustment necessary; monitor closely for efficacy and for adverse reactions requiring dosage reduction.
- Moderate impairment (Child-Pugh class B): Initial: Reduce dose by 50%; monitor closely for efficacy and for adverse reactions requiring dosage reduction.
- Severe impairment (Child-Pugh class C): Avoid use.

-Hepatic toxicity during treatment: Severe or persistent increases in transaminases/bilirubin: Reduce dose or temporarily interrupt treatment.

Dosing: Adjustment for Toxicity

- Bone marrow suppression: Interrupt treatment; may reinitiate once cause of cytopenia has been determined; use contraindicated if platelet count <50,000/mm3
- Dermatologic toxicity (suspected erythema multiforme): Discontinue and evaluate.
- Gastrointestinal: Discontinue treatment for suspected GI ulceration or hemorrhage.
- Hearing loss or visual disturbance: Consider dose reduction or treatment interruption
- Severe rash: Interrupt treatment; may reintroduce at a lower dose (with future dose escalation) and short-term oral corticosteroids. Permanently discontinue treatment if erythema multiforme is suspected.

Common side effect:

Central nervous system: Fever, headache.
Dermatologic: Rash (dose related; 2% to 11%)
Gastrointestinal: Abdominal pain (dose related; 21% to 28%), nausea (dose related; 2% to 23%), vomiting (dose related; 10% to 21%), diarrhea (dose related; 5% to 20%)
Renal: Serum creatinine increased (dose related; 2% to 38%), proteinuria (19%)
Respiratory: Cough (14%), nasopharyngitis (13%), pharyngolaryngeal pain (11%)
Miscellaneous: Influenza (11%).

Pregnancy Risk Factor: C