

Prior Authorization DRUG Guidelines

EXJADE (Deferasirox)

Effective Date: 1/28/14

Date Developed: 1/28/14 by Catherine Sanders, MD

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Exjade is a chelating agent used in the treatment of chronic iron overload by selectively binding iron, forming a complex which is excreted primarily through the feces.

Pre-Authorization Criteria: 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.

Prescribing and Access Restrictions

Deferasirox (Exjade®) is only available through a restricted distribution program called EPASS™ Complete Care. Prescribers must enroll patients in this program in order to obtain the medication. For patient enrollment, contact 1-888-90-EPASS (1-888-903-7277).

Dosing: Adult:

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

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.

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.

Dosing: Pediatric:

Note: Calculate dose to the nearest whole tablet size.

Chronic iron overload due to blood transfusion: Children ≥ 2 years and Adolescents: Refer to adult dosing.

Chronic iron overload in non-transfusion-dependent thalassemia syndromes: Children ≥ 10 years and Adolescents: Refer to adult dosing.

Dosing: Geriatric:

Refer to adult dosing.

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:

Children ≥ 2 years and Adolescents <16 years: For increase in serum creatinine >33% above the average baseline level and above the age-appropriate ULN: Reduce daily dose by 10 mg/kg

Adolescents ≥ 16 years and Adults: For increase in serum creatinine $\geq 33\%$ above the average baseline, repeat within 1 week; if still elevated by $\geq 33\%$: 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:

Children ≥ 10 years and Adolescents <16 years: For increase in serum creatinine >33% above the average baseline level and above the age-appropriate ULN: Reduce daily dose by 5 mg/kg

Adolescents ≥ 16 years and Adults: For increase in serum creatinine $\geq 33\%$ above the average baseline, repeat within 1 week; if still elevated by $\geq 33\%$: 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.

Dosing: 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 $<50,000/\text{mm}^3$

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.

Dosage Forms: U.S.:

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet Soluble, Oral:

Exjade: 125 mg, 250 mg, 500 mg

Generic Equivalent Available: U.S.-No

Administration

Oral: Administer tablets by making an oral suspension; **do not chew or swallow tablets whole.**

Completely disperse tablets in water, orange juice, or apple juice (use 3.5 ounces for total doses <1 g; 7 ounces for doses ≥ 1 g); stir to form a fine suspension and drink entire contents. Rinse remaining residue with more fluid; drink. Avoid dispersion of tablets in milk (due to slowed dissolution) or carbonated drinks (due to foaming) (Séchaud, 2008). Administer at same time each day on an empty stomach, at least 30 minutes before food. Do not take simultaneously with aluminum-containing antacids.

Exclusions:

Exjade is not to be used in patients with severe hepatic impairment at treatment initiation (Child-Pugh class C)

Exjade is not to be used for transfusional iron overload or non-transfusion-dependent thalassemia syndromes in patients with creatinine clearance <40 mL/minute or serum creatinine >2 times age-appropriate ULN.

Contraindications:

Hypersensitivity to deferasirox or any component of the formulation; platelet counts $<50,000/\text{mm}^3$; poor performance status; high-risk myelodysplastic syndromes; advanced malignancies; creatinine clearance <40 mL/minute or serum creatinine >2 x age-appropriate ULN

Adverse Reactions:

$>10\%$: fever, headache, rash, abdominal pain, nausea, vomiting, diarrhea, serum creatinine increased, proteinuria, cough, nasopharyngitis, pharyngolaryngeal pain, influenza

Other Serious Less Common Reactions: nephrotoxicity, hepatotoxicity, GI hemorrhage, GI ulcer, agranulocytosis, neutropenia, thrombocytopenia, anemia exacerbation, hearing loss, cataracts, lens opacification, IOP elevated, retinal disorders, hypersensitivity reaction, anaphylaxis, leukocytoclastic vasculitis, erythema multiforme.

U.S. BOXED WARNING:

Monitor creatinine and determine CrCl x 2 at baseline, then q month; for patients with renal impairment or acute renal failure risk, monitor creatinine q week x 4 at treatment start, then q month; increased risk of acute renal failure and death in patients with comorbidities or advanced hematological disorder. Monitor ALT, AST, bilirubin at baseline, then q 2 weeks x 2 then q month; decrease dose if Child-Pugh Class B impairment and avoid use if Child-Pugh Class C. Increased risk of gastrointestinal hemorrhage in elderly patients with advanced hematologic malignancies and/or low platelets; monitor patients and discontinue treatment if suspected GI ulcer or hemorrhage.

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