Oral Iron Chelating Agents
EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO017

Description
Deferasirox (Exjade, Jadenu), and deferiprone (Ferriprox) are orally administered iron chelating agents.

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
deferasirox (generic Exjade)	125 mg tablet for suspension	Hemosiderosis (chronic iron overload) – non-transfusion related thalassemia syndrome Hemosiderosis (chronic iron overload) – transfusion thalassemia	Non-transfusion thalassemia syndrome: Monthly quantity to allow for a maximum of 20 mg/kg per day Setting of transfusions: Monthly quantity to allow for a maximum of 40 mg/kg per day
	250 mg tablet for suspension		
	500 mg tablet for suspension		
deferasirox (Exjade)	125 mg tablet for suspension		
	250 mg tablet for suspension		
	500 mg tablet for suspension		
deferasirox (generic Jadenu)	90 mg tablet	Hemosiderosis (chronic iron overload) – non-transfusion related thalassemia syndrome Hemosiderosis (chronic iron overload) – transfusion thalassemia	Non-transfusion thalassemia syndrome: Monthly quantity to allow for a maximum of 14 mg/kg per day Setting of transfusions: Monthly quantity to allow for a maximum of 28 mg/kg per day
	180 mg tablet		
	360 mg tablet		
	90 mg granule		
	180 mg granule		
	360 mg granule		
	90 mg tablet		

deferasirox (Jadenu)	180 mg tablet		
	360 mg tablet		
	90 mg granule (sprinkle)		
	180 mg granule (sprinkle)		
	360 mg granule (sprinkle)		
deferiprone (generic Ferriprox)	500 mg tablet	Hemosiderosis (chronic iron overload) – transfusion thalassemia and transfusions related to sickle cell disease or other anemias	Monthly quantity to allow for a maximum of 99 mg/kg per day
	1000 mg tablet		
deferiprone (Ferriprox)	100 mg/1 mL solution		
	80 mg/1mL solution		
	500 mg tablet		
	1000 mg tablet		

Initial Evaluation

I. **Deferasirox (Exjade, Jadenu), and deferiprone (Ferriprox)** may be considered medically necessary when the following criteria below are met:
   A. Prescribed by, or in consultation with, a specialist (e.g., hematologist); **AND**
   B. Documentation of the members weight that has been measured in the past three months; **AND**
   C. A diagnosis of one of the following:
      1. **Chronic iron overload due to <u>non-transfusion</u> dependent thalassemia (NTDT) syndromes**; **AND**
         i. Member is ten years of age or older; **AND**
         ii. Documentation of a liver iron (Fe) concentration (LIC) of at least 5 mg per gram of dry weight; **AND**
         iii. Documentation serum ferritin levels are greater than 300 mcg/L; **AND**

iv. Generic deferasirox (generic for Exjade OR Jadenu) has been prescribed; **OR**
    a. Brand Exjade or Jadenu is prescribed and **both** generic deferasirox (generic for Exjade) AND deferasirox (generic for Jadenu) have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication) (Please note: deferiprone [Ferriprox] is not FDA-approved for this indication); **OR**

2. **Chronic iron overload due to blood transfusions**; **AND**
    i. Member is two years of age or older and brand or generic deferasirox (Exjade) or deferasirox (Jadenu) are prescribed; **OR**
        a. Member is eight years of age or older and deferiprone (Ferriprox) tablets are prescribed; **OR**
        b. Member is three years of age or older and deferiprone (Ferriprox) solution is prescribed; **AND**
    ii. Documentation is provided that the member has received transfusions that have resulted in consistent serum ferritin level greater than 1000 mcg/L; **OR**
        a. Documentation is provided that the member has received transfusions that have resulted in liver iron concentration (LIC) ≥5mg/g dry weight (dw); **AND**
    iii. Generic deferasirox (generic for Exjade OR Jadenu) has been prescribed; **OR**
        a. Brand Exjade, Jadenu, or generic deferiprone (Ferriprox) is prescribed and **both** generic deferasirox (generic for Exjade) AND deferasirox (generic for Jadenu) have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication)
        b. Brand Ferriprox is prescribed and **both** generic deferasirox (generic for Exjade) **AND** deferasirox (generic for Jadenu) **AND** generic deferiprone have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication)

II. Deferasirox (Exjade), deferasirox (Jadenu) and deferiprone (Ferriprox) are considered not medically necessary when criteria above are not met and/or when used for:
    A. Plasmodium falciparum parasitemia

III. Deferasirox (Exjade), deferasirox (Jadenu) and deferiprone (Ferriprox) are considered investigational when used for all other conditions, including but not limited to:
   A. Hereditary hemochromatosis
   B. Porphyria cutanea tarda

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Documentation of the member's weight, measured in the past three months; **AND**
   A. **Chronic iron overload due to non-transfusion dependent thalassemia syndromes**; **AND**
      1. Documentation of a serum ferritin levels are greater than 300 mcg/L; **AND**
      2. Generic deferasirox (generic for Exjade OR Jadenu) has been prescribed; **OR**
         i. Brand Exjade or Jadenu is prescribed and **both** generic deferasirox (generic for Exjade) AND generic deferasirox (generic for Jadenu) have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication) (deferiprone [Ferriprox] is not FDA-approved for this indication); **AND**
      3. A response to treatment, defined by a decline in serum ferritin level OR liver iron concentration (LIC), has been documented; **OR**
   B. **Chronic iron overload due to blood transfusions**; **AND**
      a. Documentation that the member is continuing to receive transfusions resulting in serum ferritin levels consistently greater than 500 mcg/L; **AND**
      b. Generic deferasirox (generic for Exjade OR Jadenu) has been prescribed; **OR**
         i. Brand Exjade, Jadenu, or generic deferiprone (Ferriprox) is prescribed and **both** generic deferasirox (generic for Exjade) AND generic deferasirox (generic for Jadenu) have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication); **OR**
         ii. Brand Ferriprox is prescribed and both generic deferasirox (generic for Exjade) AND deferasirox (generic for Jadenu) AND generic deferiprone have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication); **AND**
      c. A response to treatment, defined by a decline in serum ferritin level OR liver iron concentration (LIC), has been documented

Supporting Evidence

I. The agents listed in this policy are iron chelating agents indicated for chronic iron overload but have not been shown to improve survival or disease-related symptoms. Of note, the products are not interchangeable on a dose basis. Deferiprone (Ferriprox) is an iron chelator indicated only for transfusional iron overload in patients with thalassemia, sickle cell disease, or other anemias. Although deferiprone (Ferriprox) was previously reserved for use when other chelation therapy had been inadequate, labeling has been updated to no longer require use of other chelation therapy prior to therapy with deferiprone (Ferriprox). Deferasirox (Exjade, Jadenu) remains the most cost-effective therapy in this class; the requirement of trial and failure of therapy with deferasirox (Exjade, Jadenu) prior to coverage of deferiprone (Ferriprox) has been maintained in this policy.

II. Per the package inserts for the medications listed in this policy, doses are based on weight. Safety and efficacy of the medications have been studied for FDA-approved weight-based doses. Doses escalation beyond these limits has not been evaluated.

III. Clinical trials evaluated deferasirox (Exjade) and deferasirox (Jadenu) in patients 10 years of age or older for chronic iron overload due to non-transfusion dependent thalassemias, and for two years of age an older for iron overload due to blood transfusions. Deferiprone (Ferriprox) has not been adequately evaluated for safety and efficacy in patients younger than eight years of age for the tablet formulation and three years of age for the solution formulation.

IV. **Chronic iron overload due to <u>non-transfusion</u> dependent thalassemia (NTDT) syndromes**

- For iron overload not due to transfusion, deferasirox (Exjade) and deferasirox (Jadenu) were studied in patients with an LIC of at least 5 mg of iron per dry weight and a serum ferritin greater than 300 mcg/L. Levels of serum ferritin below 300 mcg/L are considered within normal range and would not meet medical necessity for dosing of iron overload treatment products.

V. **Chronic iron overload due to <u>blood transfusions</u>**

- Although deferasirox (Exjade, Jadenu) has not been approved in chronic iron overload in patients with sickle cell disease specifically, there is evidence of clinical benefit in this indication. Deferasirox (Exjade, Jadenu) was studied in one phase 2, randomized, open-label trial in comparison to deferoxamine in 195 patients age two and older with sickle cell disease and transfusional hemosiderosis. At end of study, the mean change in LIC in the per protocol-1 (PP-1) population, which consisted of patients who had at least 1 post-baseline LIC assessment, was -1.3 mg Fe/g dry weight for patients receiving deferasirox tablets for oral suspension (n = 113) and -0.7 mg Fe/g dry weight for patients receiving deferoxamine (n = 54).

- For iron overload due to transfusion in patients with sickle cell disease and other anemias, deferiprone (Ferriprox) was studied in one randomized, controlled, open-label, non-inferiority trial against deferoxamine in 228 patients age two and older. The primary endpoints were change from baseline in liver iron concentration (LIC) at 12 months; the non-inferiority criteria was met with a mean decrease from baseline in LIC of 4.04 ± 0.48 mg/g dw (deferiprone) vs. 4.45 ± 0.57 mg/g dw (deferoxamine). Adverse drug reactions (ADRs) observed during the clinical trial were consistent with those already seen in the thalassemia population. The rates of agranulocytosis were also comparable to those seen in patients with thalassemia; no new safety signals or concerns were noted.

VI. For transfusion related iron overload, patient with a serum ferritin level greater than or equal to 1000 mcg/L or a liver iron concentration of 3 to 5 mg/g dry weight (dw), or higher, will be considered for iron overload products. Upon renewal, patients with a serum ferritin level below 500 mcg/L will have therapy temporarily discontinued.

VII. As of December 2019, AB-rated generics for Exjade and Jadenu tablets were available on the market.

VIII. As of February 2021, AB-rated generics for Ferriprox 500mg tablets were available on the market. All other strengths and dosage forms remain available in the Brand formulation only.

Investigational or Not Medically Necessary Uses

I. Plasmodium falciparum parasitemia
   A. In a prospective, double-blind, placebo-controlled trial, deferiprone was found to be clinically ineffective against plasmodium falciparum parasitemia.

II. Hereditary hemochromatosis and porphyria cutanea tarda
   A. Clinical trials are investigating iron overload agents in these settings.

References

1. Exjade [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation. May, 2018.
2. Jadenu [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation. May, 2018.
3. Ferriprox [Prescribing Information]. Toronto, Ontario, Canada. Apotex Inc. April, 2021.
4. Cohen AR, Glimm E, Porter JB. Effect of transfusional iron intake on response to chelation therapy in beta-thalassemia major. Blood. 2008;111(2):583-7.
5. Taher AT, Porter JB, Viprakasit V, et al. Deferasirox demonstrates a dose-dependent reduction in liver iron concentration and consistent efficacy across subgroups of non-transfusion-dependent thalassemia patients. Am J Hematol. 2013;88(6):503-6.
6. Vichinsky E, Onyekwere O, Porter J, et al. A randomised comparison of deferasirox versus deferoxamine for the treatment of transfusional iron overload in sickle cell disease. Br J Haematol. 2007;136(3):501-8.

7. Tricta F, Uetrecht J, Galanello R, et al. Deferiprone-induced agranulocytosis: 20 years of clinical observations. Am J Hematol. 2016;91(10):1026-31.
8. Elalfy M, et al. Deferiprone versus deferoxamine for transfusion-dependent anemias (FIRST study). Chiesi [unpublished].
9. Elafly M, et al. Long-term efficacy and safety of deferiprone for patients with sickle cell disease or other anemias (FIRST-EXT study). Chiesi [unpublished].

Policy Implementation/Update:

Action and Summary of Changes	Date
Added 1000mg strength of deferiprone (generic Ferriprox)	02/2022
Addition of generic deferasirox oral granules and generic deferiprone tablets to policy; requirement to have trial and failure or contraindication to both generic Exjade and Jadenu for prior to payment consideration of generic deferiprone, and generic Exjade and Jadenu AND generic deferiprone prior to payment consideration for brand Ferriprox. Criteria updated regarding the following: age for use of deferiprone tablets (8 years old) and deferiprone solution (3 years old), addition of LIC as baseline and renewal measurement for transfusional iron overload. Update to supporting evidence.	09/2021
Addition of generic Jadenu and new strength of deferiprone to the policy, with requirement to have trial and failure or contraindication, to both generic Exjade and Jadenu prior to payment consideration for brand products of this policy.	12/2019
Iron chelating agent policies combined, criteria added regarding the following: weight documentation, ferritin level documentation, addition of a policy to Jadenu, specialist prescribing, additional of generic deferasirox (Exjade) tablet for oral suspension and step through this product. Transition to policy format.	05/2019
Criteria created	08/2013