

PRIOR AUTHORIZATION POLICY

POLICY: Chelating Agents – Iron Chelators (Oral)

- Exjade® (deferasirox tablets for suspension – Novartis; generic)
- Jadenu® (deferasirox tablets – Novartis)
- Jadenu® Sprinkle (deferasirox granules for oral use – Novartis)
- Ferriprox® (deferiprone tablets and oral solution – ApoPharma USA)

TAC APPROVAL DATE: 05/22/2019

OVERVIEW

Iron chelating therapy should be considered in all patients who require long-term blood transfusions.⁵ Patients with sickle cell disease, myelodysplastic syndromes (MDS), thalassemia major, Diamond-Blackfan anemia, aplastic anemia, and other congenital and acquired forms of refractory anemia (e.g., hereditary hemochromatosis) may require regular blood transfusions and as a result may require iron chelation therapy. This is because the body does not have an efficient mechanism to excrete iron.⁴ In patients requiring multiple blood transfusions, iron accumulates and is deposited into multiple organ systems. The long term consequences of chronic iron overload include multiple organ dysfunction (e.g., heart, liver) and/or organ failure. Iron chelation therapy is necessary to prevent organ failure and decrease mortality. In the US, it is estimated that approximately 25,000 patients are transfusion dependent due to various causes such as sickle cell disease and refractory anemias.⁷

Serum ferritin level measurements are the laboratory parameter most often used to assess the iron burden and response to chelation therapy.⁴ Sustained serum ferritin levels > 2,500 mcg/L are associated with organ toxicity and death. Most chelation regimens strive to achieve the goal of ferritin levels < 2,500 mcg/L. Trends in ferritin level are useful in monitoring the direction of body iron loading, but it may not predict cardiac iron loading.⁶ Long-term elevations in ferritin levels predict cardiac mortality, with ferritin levels > 2,500 mcg/L indicating a higher cardiac risk; however, there is no threshold effect, so a ferritin level of 1,000 mcg/L could indicate a risk. Cardiac iron levels have a better predictive value of heart failure.

Exjade, Jadenu (granules and tablets), and Ferriprox are orally administered iron chelators used for the treatment of iron overload.¹⁻³ Exjade and Jadenu have the same chemical entity (deferasirox) in different formulations.¹⁻² Deferoxamine is an intravenously (IV) administered iron chelator that is not covered under this prior authorization policy.

Ferriprox is indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.³ Ferriprox approval was based on a reduction in serum ferritin levels. There are no controlled trials demonstrating a direct treatment benefit, such as an improvement in disease-related symptoms, functioning, or increased survival. Safety and effectiveness of Ferriprox for the treatment of transfusional iron overload in patients with other chronic anemias have not been established.

Exjade and Jadenu (granules and tablets) have the following FDA-approved indications¹⁻²:

- Treatment of chronic iron overload due to blood transfusions (transfusion iron overload) in patients \geq 2 years of age. Exjade/Jadenu therapy should be considered when a patient has evidence of chronic transfusional iron overload (e.g., at least 20 units of packed red blood cells for a 40 kg person or more) and a serum ferritin consistently > 1,000 mcg/L.

- Exjade and Jadenu are also indicated for the treatment of chronic iron overload in patients ≥ 10 years of age 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 > 300 mcg/L. This indication is based on achievement of an LIC < 5 mg Fe/g dw. An improvement in survival or disease-related symptoms has not been established.
- Limitations of Use: Controlled trials of Exjade and Jadenu with myelodysplastic syndrome (MDS) and chronic iron overload due to blood transfusions have not been performed. The safety and efficacy of Exjade and Jadenu when administered with other iron chelation therapy have not been established.

EFFICACY

A 5-year multicenter, randomized, open-label trial assessed the efficacy of Ferriprox compared with deferoxamine intravenous (IV) treatment in patients with sickle cell disease.¹¹ Patients (n = 60) were > 13 years of age and had serum ferritin concentration between 800 to 3,000 mcg/L. By Year 5, 36.6% of patients treated with Ferriprox achieved serum ferritin levels < 400 mcg/L compared with 3.3% of patients treated with deferoxamine (P = 0.002). Overall survival did not differ significantly between the two groups after 5 years or 10 years. A Phase III study is underway comparing the efficacy of Ferriprox vs. Exjade/Jadenu in pediatric patients with transfusion-related iron overload due to thalassemia, sickle cell disease, and other conditions.¹² Studies with Ferriprox use in pediatric patients for various iron overload conditions have been conducted in other countries.¹³

Iron overload in thalassemia intermedia is mainly due to increased intestinal absorption of iron due to chronic anemia.⁹ Transfusions play a minor role in iron overloading in these patients, but iron chelation therapy is indicated for thalassemia intermedia. A 5-year randomized, open-label, long-term trial was conducted in patients (n = 88) with thalassemia intermedia comparing Ferriprox with deferoxamine IV treatment. After 5 years there were no statistically significant differences between Ferriprox and deferoxamine in the decrease in mean serum ferritin levels and overall survival. There are data available from other studies as well with Ferriprox use in iron-loaded non-transfusion dependent thalassemias.¹⁰

The three pivotal studies for Exjade/Jadenu included patients with β -thalassemia, chronic anemias, myelodysplastic syndromes, sickle cell disease, Diamond-Blackfan syndrome and other congenital or acquired anemias.^{1,2} The prospective EPIC study (Evaluation of Patients' Iron Chelation with Exjade) included patients with thalassemia (~70%), myelodysplastic syndrome (20%), aplastic anemia (7%), sickle cell disease (5%) and other rare anemias such as red cell aplasia and hemolytic anemias (~2.5%).¹⁴ Baseline median serum ferritin levels in all subgroups were $> 2,500$ mcg/L. Overall there was a significant reduction in serum ferritin level from baseline (-264 ng/mL) in all subgroups, except sickle cell disease (likely due to low number of patients). The NCCN myelodysplastic syndromes guidelines notes that monitoring serum ferritin levels and aiming to decrease ferritin levels to $< 1,000$ mcg/L may be useful.⁸

GUIDELINES

The American Heart Association published a consensus statement on cardiovascular function and treatment in β -thalassemia major.⁶ Exjade/Jadenu, Ferriprox, and deferoxamine intravenous (IV) iron chelator all remove cardiac iron if given in adequate doses and if patient compliance is good. Optimal therapy must be tailored to each patient. In patients with detectable, asymptomatic cardiac iron overload, the following are noted: retrospective studies suggest that Ferriprox monotherapy may offer superior cardiac protection and improve survival compared with deferoxamine IV chelator. The AHA recommends the use of Ferriprox monotherapy in patients with cardiac siderosis and it is also suitable for patients with reduced left ventricular ejection fraction (LVEF) or asymptomatic left ventricular (LV) dysfunction. Exjade/Jadenu monotherapy can be used successfully in patients with detectable cardiac iron and normal cardiac function; however, no change in LVEF was observed in trials. The AHA recommends Exjade/Jadenu for cardiac

siderosis, but it is not recommended as first-choice treatment for cardiac iron (T2*) < 6 ms or in patients with reduced LVEF because of the limited data on efficacy. Caution is recommended in the use of Exjade/Jadenu monotherapy to treat cardiac siderosis in patients with high liver iron loading, especially if higher doses are required (> 40 mg/kg/day), as cardiac efficacy may be delayed. The use of combination Ferriprox and deferoxamine therapy is noted as widespread, and this combination is used especially in patients with moderate to severe cardiac iron overload or when LVEF is impaired. Exjade/Jadenu has also been used in combination with deferoxamine. There are limited data available for the combination use of daily Ferriprox with daily Exjade/Jadenu.

The National Comprehensive Cancer Network (NCCN) guidelines for myelodysplastic syndromes (version 2.2019 – October 18, 2018) has the following recommendations under supportive care, for the management of iron overload.⁸ For patients with chronic transfusion need, serum ferritin levels and associated organ function should be monitored. It is useful to decrease serum ferritin levels to < 1,000 mcg/L. The NCCN Panel recommends consideration of once-daily deferoxamine subcutaneously or Exjade/Jadenu orally to decrease iron overload (aiming for target ferritin level < 1,000 ng/mL) in lower risk patients with MDS or who are potential transplant candidates and are anticipated to receive > 20 to 30 blood transfusions; and patients with serum ferritin levels > 2,500 ng/mL the aim is to get the levels to < 1,000 ng/mL. The NCCN recommendations notes that a third oral chelating agent, Ferriprox, is available and it was approved based on retrospective analysis of pooled efficacy and safety studies in patients with transfusion-related iron overload refractory to existing chelation therapy. NCCN notes that controversy remains regarding the use of this agent due to the boxed warning for agranulocytosis.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Exjade, Jadenu (granules and tablets), and Ferriprox. Because of the specialized skills required for evaluation and diagnosis of patients treated with these agents as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Exjade, Jadenu (granules and tablets), and Ferriprox to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration listed below.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or laboratory data.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of **Ferriprox** is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Iron Overload, Chronic – Transfusion-Related Due to Thalassemia Syndromes.** Approve Ferriprox for 1 year if the patient meets the following criteria (A or B):
 - A) **Initial Therapy.** Approve Ferriprox if the patient meets all of the following criteria (i and ii):
 - i. Prior to starting Ferriprox therapy, the serum ferritin level was > 2,500 micrograms/liter (mcg/L) **[documentation required]**; AND
 - ii. Ferriprox is prescribed by or in consultation with a hematologist.
 - B) **Patients Currently Receiving Ferriprox.** Approve for 1 year if the patient is benefiting from Ferriprox therapy (e.g., reduction in the serum ferritin levels by at least 20% from baseline, stable disease, reduced cardiac iron load), as confirmed by the prescribing physician.

Other Uses with Supportive Evidence

2. **Iron Overload, Chronic – Transfusion – Related Due to Sickle Cell Disease.** Approve Ferriprox for 1 year if the patient meets the following criteria (A or B).
 - A) **Initial Therapy.** Approve Ferriprox if the patient meets all the following criteria (i and ii):
 - i. Prior to starting Ferriprox therapy, the patient's serum ferritin level was > 1,000 micrograms/liter (mcg/L) **[documentation required]**; AND
 - ii. Ferriprox is prescribed by or in consultation with a hematologist.
 - B) **Patients Currently Receiving Ferriprox.** Approve for 1 year if the patient is benefiting from Ferriprox therapy for sickle cell disease (e.g., reduction in the serum ferritin levels to < 1,000 mcg/L, stable disease, reduced cardiac iron load), as confirmed by the prescribing physician.
3. **Iron Overload, Chronic – Non-Transfusion-Dependent Thalassemia Syndromes.** Approve Ferriprox for 1 year if the patient meets the following criteria (A or B).
 - A) **Initial Therapy.** Approve Ferriprox if the patient meets all the following criteria (i, ii, and iii):
 - i. Prior to starting Ferriprox therapy, the patient's serum ferritin level was > 300 micrograms/liter (mcg/L) **[documentation required]**; AND
 - ii. Ferriprox is prescribed by or in consultation with a hematologist.
 - B) **Patients Currently Receiving Ferriprox.** Approve for 1 year if the patient is benefiting from Ferriprox therapy (e.g., reduction in the serum ferritin levels, stable disease, reduced cardiac iron load), as confirmed by the prescribing physician.

II. Coverage of **Exjade or Jadenu (granules or tablets)** is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Iron Overload, Chronic – Transfusion-Related.** Approve Exjade or Jadenu (granules or tablets) for 1 year if the patient meets the following criteria (A or B):
 - A) **Initial Therapy.** Approve Exjade or Jadenu (granules or tablets) if the patient meets all the following criteria (i, ii, and iii):
 - i. Patient is receiving blood transfusions at regular intervals for various conditions (e.g., thalassemia syndromes, myelodysplastic syndrome, chronic anemia, sickle cell disease); AND

- ii. Prior to starting Exjade or Jadenu (granules or tablets) therapy, the patient’s serum ferritin level was > 1,000 micrograms/liter (mcg/L) **[documentation required]**; AND
 - iii. Exjade or Jadenu (granules or tablets) is prescribed by or in consultation with a hematologist.
 - B) Patients Currently Receiving Exjade or Jadenu (granules or tablets). Approve for 1 year if the patient is benefiting from Exjade or Jadenu (granules or tablets) therapy (e.g., reduction in the serum ferritin levels to < 1,000 mcg/L, stable disease, reduced cardiac iron load), as confirmed by the prescribing physician.
- 2. Iron Overload, Chronic – Non-Transfusion-Dependent Thalassemia Syndromes.** Approve Exjade or Jadenu (granules or tablets) for 1 year if the patient meets the following criteria (A or B).
- A) Initial Therapy. Approve Exjade or Jadenu (granules or tablets) if the patient meets all the following criteria (i and ii):
 - i. Prior to starting Exjade or Jadenu (granules or tablets) therapy, the patient’s serum ferritin level was > 300 micrograms/liter (mcg/L) **[documentation required]**; AND
 - ii. Exjade or Jadenu (granules or tablets) is prescribed by or in consultation with a hematologist.
 - B) Patients Currently Receiving Exjade or Jadenu (granules or tablets). Approve for 1 year if the patient is benefiting from Exjade or Jadenu (granules or tablets) therapy (e.g., reduction in the serum ferritin levels, stable disease, reduced iron load), as confirmed by the prescribing physician.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Exjade, Jadenu (granules or tablets), and Ferriprox have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Exjade® tablets for suspension [prescribing information]. East Hanover, NJ: Novartis; December 2018
2. Jadenu® tablets and Jadenu® Sprinkle for oral use [prescribing information]. East Hanover, NJ: Novartis; December 2018.
3. Ferriprox® tablets [prescribing information]. Rockville, MD: ApoPharma USA, Inc.; February 2015.
4. Algren AD. Review of oral iron chelators (deferiprone and deferasirox) for the treatment of iron overload in pediatric patients. Available at: http://www.who.int/selection_medicines/committees/expert/18/applications/OralIronChelators.pdf. Accessed on May 17, 2019.
5. Brittenham GM. Iron-chelating therapy for transfusional iron overload. *N Engl J Med*. 2011;364:146-156.
6. Pennell DJ, Udelson JE, Arai AE, et al. Cardiovascular function and treatment in β -thalassemia major. A consensus statement from the American Heart Association. *Circulation*. 2013;128:281-308.
7. Chalmers AW, Shammo JM. Evaluation of a new tablet formulation of deferasirox to reduce chronic iron overload after long-term blood transfusions. *Ther Clin Risk Manag*. 2016;12:201-208.
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- 2017 March 22]. Available at: <https://www.clinicaltrials.gov/ct2/show/NCT01825512?term=NCT01825512&rank=1>. NLM Identifier: NCT01825512.
13. Marsella M, Borgna-Pignatti C. Transfusional iron overload and iron chelation therapy in thalassemia major and sickle cell disease. *Hematol Oncol Clin N Am*. 2014;28:703-727.
 14. Cappellini MD, Porter J, El-Beshlawy A, et al. Tailoring iron chelation by iron intake and serum ferritin: the prospective EPIC study of deferasirox in 1744 patients with transfusion-dependent anemias. *Haematologica*. 2010;95:557-566.
 15. Ferriprox® oral solution [prescribing information]. Rockville, MD: ApoPharma USA, Inc.; September 2015.

OTHER REFERENCES UTILIZED

- Bayanzay K, Alzoebe L. Reducing the iron burden and improving survival in transfusion-dependent thalassemia patients: current perspectives. *J Blood Med*. 2016;7:159-169.
- Jang JH, Lee JH, Yoon SS, et al. Korean guidelines for iron chelation therapy in transfusion-induced iron overload. *J Korean Med Sci*. 2013;28:1563-1572.
 - Hider RC, Victor Hoffbrand A. The role of deferoxamine in iron chelation. *N Engl J Med*. 2018;379:2140-2150.
 - Lyle L, Hirose A. Iron overload in myelodysplastic syndromes: pathophysiology, consequences, diagnosis, and treatment. *J Adv Pract Oncol*. 2018;9:392-405.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
New Policy	--	04/26/2017
Selected revision	Added Jadenu Sprinkle to drug target list and wherever appropriate in the policy. No criteria changes.	07/12/2017
Annual revision	No criteria changes	05/02/2018
Annual revision	No criteria changes	05/22/2019

* For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>; TAC – Therapeutic Assessment Committee.