Drug Coverage Policy

Effective Date..... 5/15/2024
Coverage Policy Number IP0271
Title.....Iron Chelators (Oral)

Chelating Agents – Iron Chelators (Oral)

- Exjade® (deferasirox tablets for suspension – Novartis, generic)
- Ferriprox® (deferiprone tablets and oral solution – Chiesi, generic [tablets only])
- Jadenu® (deferasirox tablets – Novartis, generic)
- Jadenu® Sprinkle (deferasirox oral granules – Novartis, generic)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

Oral iron chelators are indicated for the **treatment of iron overload** for specific conditions.[1-4] Exjade and Jadenu have the same chemical entity (deferasirox) in different formulations.[1,2]

Deferasirox products (Exjade, Jadenu/Sprinkle; generics) are indicated for the following uses:[1,2]

- **Chronic iron overload due to blood transfusions** (transfusional hemosiderosis), in patients ≥ 2 years of age.
- **Chronic iron overload in non-transfusion-dependent thalassemia syndromes**, in patients ≥ 10 years of age with a liver iron concentration of at least 5 mg of iron per gram of liver dry weight and a serum ferritin level > 300 mcg/L.

Limitations of Use: The safety and efficacy of deferasirox products when administered with other iron chelation therapy have not been established.[1,2]

Deferiprone tablets (Ferriprox tablets, generic) are indicated for the following uses:[3]

- **Transfusional iron overload with thalassemia syndromes**, in patients ≥ 8 years of age.
- **Transfusional iron overload with sickle cell disease or other anemias**, in patients ≥ 8 years of age.

Ferriprox oral solution is indicated for the following uses:[4]

- **Transfusional iron overload with thalassemia syndromes**, in patients ≥ 3 years of age.
- **Transfusional iron overload with sickle cell disease or other anemias**, in patients ≥ 3 years of age.

Limitations of Use: Safety and effectiveness of deferiprone products have not been established for the treatment of transfusional iron overload in patients with myelodysplastic syndrome (MDS) or in patients with Diamond Blackfan anemia.[3,4]

Table 1. Availability of Oral Iron Chelators.[1-4]

Exjade (deferasirox tablets for suspension)	Ferriprox (deferiprone tablets and oral solution)		Jadenu/Sprinkle (deferasirox granules and tablets)	
• 125 mg • 250 mg • 500 mg	**Tablets** • 500 mg • 1000 mg	**Solution** 100 mg/mL	**Granules** • 90 mg • 180 mg • 360 mg	**Tablets** • 90 mg • 180 mg • 360 mg

Disease 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 chelating therapy. This is because the body does not have an efficient mechanism to excrete iron.[6] 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.

Guidelines

- **Thalassemia Syndromes:**
  - The Thalassemia International Federation published guidelines (2021) for transfusion-dependent thalassemia.[7] Initiation of an iron chelator generally starts after 10 to 20 infusions or when serum ferritin level is > 1,000 mcg/L. Recommendations advise use based on patient characteristics and FDA-approved indications and also advocate for switching, rotating, and combing chelator regimens as needed to control iron balance or distribution.
  - The American Heart Association (AHA) published a consensus statement (2013) on cardiovascular function and treatment in patients with β-thalassemia major.[8] Deferasirox, deferiprone, and deferoxamine (injectable iron chelator) are recommended chelating treatments. The AHA advises the use of Ferriprox monotherapy in patients with cardiac siderosis, patients with reduced left ventricular ejection fraction (LVEF), or asymptomatic left ventricular dysfunction. Exjade and Jadenu monotherapy can be used in patients with detectable cardiac iron levels and

normal cardiac function. However, Exjade and Jadenu are not recommended as first-choice treatment for cardiac siderosis with cardiac iron (T2*) < 6 ms or in patients with reduced LVEF.

- **MDS:** The National Comprehensive Cancer Network (NCCN) guidelines for MDS (version 3.2023 – November 10, 2023) have recommendations for the management of iron overload.[9] NCCN advises consideration of deferasirox or deferoxamine (injectable iron chelator) to decrease iron overload (aiming for target ferritin level < 1,000 mcg/mL) in specific patients with MDS or who are potential transplant candidates. The guidelines note that deferiprone is available; however, controversy remains regarding the use of this agent for MDS due to the Boxed Warning for agranulocytosis.

Medical Necessity Criteria

Oral iron chelating agents are considered medically necessary when ONE of the following are met:

I. Deferasirox products are considered medically necessary when ONE of the following are met:

FDA-Approved Indications

1. **Iron Overload, Chronic – Transfusion-Related.** Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient is receiving blood transfusions at regular intervals for a chronic condition; AND
       Note: Examples of chronic conditions include thalassemia syndromes, myelodysplastic syndrome, chronic anemia, and sickle cell disease.
     - **ii.** Prior to starting chelating therapy, serum ferritin level was > 1,000 mcg/L; AND
     - **iii.** The medication is prescribed by or in consultation with a hematologist
     - **iv.** Preferred product criteria is met for the products listed in the below table(s)
   - **B)** Patient is Currently Receiving a Deferasirox Product. Approve if the patient is benefiting from therapy, as confirmed by the prescriber.
     Note: Examples of benefit from therapy include reduction in serum ferritin levels, stable disease, and reduced organ iron load.

2. **Iron Overload, Chronic – Non-Transfusion-Dependent Thalassemia Syndromes.** Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets BOTH of the following (i, ii, and iii):
     - **i.** Prior to starting chelating therapy, serum ferritin level was > 300 mcg/L; AND
     - **ii.** The medication is prescribed by or in consultation with a hematologist.
     - **iii.** Preferred product criteria is met for the products listed in the below table(s)
   - **B)** Patient is Currently Receiving a Deferasirox Product. Approve if the patient is benefiting from therapy, as confirmed by the prescriber.
     Note: Examples of benefit from therapy include reduction in serum ferritin levels, stable disease, and reduced organ iron load.

II. Deferiprone products are considered medically necessary when ONE of the following are met:

FDA-Approved Indications

1. **Iron Overload, Chronic – Transfusion-Related Due to Thalassemia Syndromes.** Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets BOTH of the following (i, ii, and iii):
     - **i.** Prior to starting chelating therapy, serum ferritin level was > 1,000 mcg/L; AND

ii. The medication is prescribed by or in consultation with a hematologist.
iii. Preferred product criteria is met for the products listed in the below table(s)

B) Patient is Currently Receiving a Deferiprone Product. Approve if the patient is benefiting from therapy, as confirmed by the prescriber.
Note: Examples of benefit from therapy include reduction in serum ferritin levels, stable disease, and reduced organ iron load.

2. Iron Overload, Chronic – Transfusion-Related Due to Sickle Cell Disease or Other Anemias. Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets BOTH of the following (i, ii, and iii):
i. Prior to starting chelating therapy, serum ferritin level was > 1,000 mcg/L; AND
ii. The medication is prescribed by or in consultation with a hematologist.
iii. Preferred product criteria is met for the products listed in the below table(s)

B) Patient is Currently Receiving a Deferiprone Product. Approve if the patient is benefiting from therapy, as confirmed by the prescriber.
Note: Examples of benefit from therapy include reduction in serum ferritin levels, stable disease, and reduced organ iron load.

Other Uses with Supportive Evidence

3. Iron Overload, Chronic – Non-Transfusion-Dependent Thalassemia Syndromes. Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets BOTH of the following (i, ii, and iii):
i. Prior to starting chelating therapy, serum ferritin level was > 300 mcg/L; AND
ii. The medication is prescribed by or in consultation with a hematologist.
iii. Preferred product criteria is met for the products listed in the below table(s)

B) Patient is Currently Receiving a Deferiprone Product. Approve if the patient is benefiting from therapy, as confirmed by the prescriber.
Note: Examples of benefit from therapy include reduction in serum ferritin levels, stable disease, and reduced organ iron load.

Employer Plans:

Non-Covered Product	Criteria
Exjade (deferasirox) tablet for suspension	Trial of **deferasirox tablet for suspension** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction.
Ferriprox (deferiprone) 500 mg and 1000 mg tablets	There is documentation of **ONE** of the following: A. Trial of **deferiprone 500 mg or 1000 mg tablet** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction. [may require prior authorization] B. Failure, contraindication, or intolerance to deferasirox (generic Exjade or generic Jadenu/Jadenu Sprinkle).
Ferriprox Solution (deferiprone) oral solution	There is documentation of **ONE** of the following: A. Failure, contraindication, or intolerance to deferasirox (generic Exjade or generic Jadenu/Jadenu Sprinkle). B. **ONE** of the following: i. Failure, contraindication, or intolerance to deferiprone 500 mg or 1000 mg tablet (generic Ferriprox). [may require prior authorization] ii. Dose prescribed cannot be attained with deferiprone tablet

Non-Covered Product	Criteria
	iii. Patient who cannot swallow or have difficulty swallowing tablets
Jadenu (deferasirox) tablet	Trial of **deferasirox tablet** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction.
Jadenu Sprinkle (deferasirox) oral granules	Trial of **deferasirox granule packet** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction.

Individual and Family Plans:

Non-Covered Product	Criteria
deferiprone 500 mg & 1000 mg tablets	Failure, contraindication, or intolerance to deferasirox (generic Exjade or generic Jadenu/Jadenu Sprinkle). [may require prior authorization]
Exjade (deferasirox) tablet for suspension	Trial of **deferasirox tablet for suspension** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction. [may require prior authorization]
Ferriprox (500 mg & 1000 mg) deferiprone tablets	There is documentation of **ONE** of the following: A. Trial of **deferiprone 500 mg or 1000 mg tablet** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction. [may require prior authorization] B. Failure, contraindication, or intolerance to deferasirox (generic Exjade or generic Jadenu/Jadenu Sprinkle). [may require prior authorization]
Ferriprox Solution (deferiprone) oral solution	There is documentation of **ONE** of the following: A. Failure, contraindication, or intolerance to deferasirox (generic Exjade or generic Jadenu/Jadenu Sprinkle). [may require prior authorization] B. **ONE** of the following: i. Failure, contraindication, or intolerance to deferiprone 500 mg or 1000 mg tablet (generic Ferriprox). [may require prior authorization] ii. Dose prescribed cannot be attained with deferiprone tablet iii. Patient who cannot swallow or have difficulty swallowing tablets
Jadenu (deferasirox) tablet	Trial of **deferasirox tablet** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction. [may require prior authorization]
Jadenu Sprinkle (deferasirox) oral granules	Trial of **deferasirox granule packet** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction. [may require prior authorization]

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based

literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven (criteria will be updated as new published data are available).

References

1. Exjade® tablets for suspension [prescribing information]. East Hanover, NJ: Novartis; August 2023.
2. Jadenu® tablets and Jadenu® Sprinkle oral granules [prescribing information]. East Hanover, NJ: Novartis; March 2023.
3. Ferriprox® tablets [prescribing information]. Cary, NC: Chiesi; July 2023.
4. Ferriprox® oral solution [prescribing information]. Cary, NC: Chiesi; November 2021.
5. Brittenham GM. Iron-chelating therapy for transfusional iron overload. *N Engl J Med.* 2011;364:146-156.
6. Palmer WC, Vishnu P, Sanchez W, et al. Diagnosis and Management of Genetic Iron Overload Disorders. *J Gen Intern Med*. 2018 Dec;33(12):2230-2236.
7. Farmakis D, Porter J, Taher A, et al. 2021 Thalassaemia International Federation Guidelines for the Management of Transfusion-dependent Thalassemia. *Hemasphere*. 2022;6(8):e732. Published 2022 Jul 29.
8. 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.
9. The NCCN Myelodysplastic Syndrome Clinical Practice Guidelines in Oncology (version 3.2023 – November 10, 2023). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 23, 2024.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Iron Overload, Chronic – Transfusion-Related (Deferasirox):** Removed age **Iron Overload, Chronic – Non-Transfusion-Dependent Thalassemia Syndromes (Deferasirox):** Removed age **Iron Overload, Chronic – Non-Transfusion-Dependent Thalassemia Syndromes:** Removed prior to starting chelating therapy, Liver iron (Fe) concentration (LIC) level greater than or equal to 5 mg Fe per gram of dry weight **Ferriprox Solution** for Emp and IFP: Added as a requirement option: Dose prescribed cannot be attained with deferiprone tablet and patient who cannot swallow or have difficulty swallowing tablets	5/1/2024

The policy effective date is in force until updated or retired.