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Iron Chelating Agents (Oral)

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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. 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.

Overview

This policy supports medical necessity review for the following oral iron chelating agents:

- **deferasirox** (granule packets, tablets, and tablets for suspension)
- **deferiprone** (500 mg and 1000 mg tablets only)
- **Exjade®** (deferasirox tablets for suspension)
- **Ferriprox®** (deferiprone tablets and oral solution)
- **Jadenu®** (deferasirox tablets)
- **Jadenu® Sprinkle** (deferasirox oral granules)

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

Medical Necessity Criteria

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

I. **Deferasirox (Exjade, Jadenu/Jadenu Sprinkle).** Individual meets **ONE** of the following (1 or 2):

1. **Iron Overload, Chronic – Transfusion-Related.** Individual meets **ALL** of the following criteria (A, B, C, D and E):
    A. Individual is age 2 years or older.
    B. Individual is receiving blood transfusions at regular intervals for chronic condition (for example, thalassemia syndromes, myelodysplastic syndrome, chronic anemia, and sickle cell disease).
    C. Prior to starting chelating therapy, serum ferritin level greater than 1,000 micrograms/liter (mcg/L).
    D. The medication is prescribed by, or in consultation with, a hematologist or hepatologist.
    E. Individual meets the preferred covered alternative(s) criteria as indicated in the table below

2. **Iron Overload, Chronic – Non-Transfusion-Dependent Thalassemia Syndromes.** Individual meets **ALL** of the following criteria (A, B, C and D):
    A. Individual is age 10 years or older.
    B. Prior to starting chelating therapy, **BOTH** of the following (i and ii):
        i. Liver iron (Fe) concentration (LIC) level greater than or equal to 5 mg Fe per gram of dry weight
        ii. Serum ferritin level greater than 300 micrograms/liter (mcg/L)
    C. The medication is prescribed by, or in consultation with, a hematologist or hepatologist.
    D. Individual meets the preferred covered alternative(s) criteria as indicated in the table below

II. **Deferiprone (Ferriprox).** Individual meets **ONE** of the following (1, 2, or 3):

1. **Iron Overload, Chronic – Transfusion-Related Due to Thalassemia Syndromes.** Individual meets **BOTH** of the following criteria (A, B, and C):
    A. Prior to starting chelating therapy, serum ferritin level greater than 1,000 micrograms/liter (mcg/L).
    B. The medication is prescribed by, or in consultation with, a hematologist or hepatologist.
    C. Individual meets the preferred covered alternative(s) criteria as indicated in the table below

2. **Iron Overload, Chronic – Transfusion-Related Due to Sickle Cell Disease or Other Anemias.** Individual meets **BOTH** of the following criteria (A, B, and C);
    A. Prior to starting chelating therapy, serum ferritin level greater than 1,000 micrograms/liter (mcg/L).
    B. The medication is prescribed by, or in consultation with, a hematologist or hepatologist.
    C. Individual meets the preferred covered alternative(s) criteria as indicated in the table below

3. **Iron Overload Chronic – Non-Transfusion-Dependent Thalassemia Syndromes.** Individual meets **BOTH** of the following criteria (A, B, and C):
    A. Prior to starting chelating therapy, **BOTH** of the following (i and ii):
        i. Liver iron (Fe) concentration (LIC) level greater than or equal to 5 mg Fe per gram of dry weight
        ii. Serum ferritin level greater tha 300 micrograms/liter (mcg/L)
    B. The medication is prescribed by, or in consultation with, a hematologist or hepatologist.
    C. Individual meets the preferred covered alternative(s) criteria as indicated in the table below.

Coverage varies across plans and requires the use of preferred products. Refer to the customer's benefit plan document for coverage details.

Employer Group Non-Covered Products and the Preferred Covered Alternatives:

Non-Covered Product	Criteria
Exjade (deferasirox) tablet for suspension	The individual has tried **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 or B): A. The individual has tried **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. The individual has had an inadequate response, contraindication, or is intolerant to deferasirox (generic Exjade or generic Jadenu/Jadenu Sprinkle).
Ferriprox Solution (deferiprone) oral solution	There is documentation of **ONE** of the following (A or B): A. The individual has had an inadequate response, contraindication, or is intolerant to deferasirox (generic Exjade or generic Jadenu/Jadenu Sprinkle). B. The individual has had an inadequate response, or is intolerant to deferiprone 500 mg or 1000 mg tablet (generic Ferriprox). [may require prior authorization]
Jadenu (deferasirox) tablet	The individual has tried **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	The individual has tried **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 Plan Non-Covered Products and Covered Alternative(s):

Non-Covered Product	Criteria
deferiprone 500 mg & 1000 mg tablets	The individual has had an inadequate response, contraindication, or is intolerant to deferasirox (generic Exjade or generic Jadenu/Jadenu Sprinkle). [may require prior authorization]
Exjade (deferasirox) tablet for suspension	The individual has tried **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 or B): A. The individual has tried **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. The individual has had an inadequate response, contraindication, or is intolerant 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 or B): A. The individual has had an inadequate response, contraindication, or is intolerant to deferasirox (generic Exjade or generic Jadenu/Jadenu Sprinkle). [may require prior authorization]

Non-Covered Product	Criteria
	B. The individual has had an inadequate response, or is intolerant to deferiprone 500 mg or 1000 mg tablet (generic Ferriprox). [may require prior authorization]
Jadenu (deferasirox) tablet	The individual has tried **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	The individual has tried **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.

Reauthorization Criteria

Oral iron chelating agents is considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response (for example, reduction in serum ferritin levels, or reduced organ iron load).

Authorization Duration

Initial and reauthorization approval duration: up to 12 months

Conditions Not Covered

Any other use is considered experimental, investigational or unproven.

Background

OVERVIEW
*Oral iron chelator products are indicated for the **treatment of iron overload** for specific conditions.*[1-4]

Deferasirox products are indicated for the following uses:[1,2]
- ***Chronic iron overload due to blood transfusions**, 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 > 300 mcg/L.*

Deferiprone tablets 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.

Deferiprone 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.

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 1.2023 – September 12, 2022) 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.

References

1. Exjade® tablets for suspension [prescribing information]. East Hanover, NJ: Novartis; July 2020.
2. Jadenu® tablets and Jadenu® Sprinkle oral granules [prescribing information]. East Hanover, NJ: Novartis; July 2020.
3. Ferriprox® tablets [prescribing information]. Cary, NC: Chiesi; April 2021.
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 1.2023 – September 12, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 15, 2023.