Iron Chelating Agents

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Related Coverage Resources

Dimercaprol and Edetate Calcium Disodium
Penicillamine and trientine hydrochloride

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.

Medical Necessity Criteria

Iron chelating agents include the following products:

I. Exjade (deferasirox), Jadenu (deferasirox) granules and tablets
II. Ferriprox (deferiprone)

I. Exjade® (deferasirox) and Jadenu®/Jadenu Sprinkle® (deferasirox) are considered medically necessary when ANY of the following criteria are met:
  • Treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) AND ALL of the following are met:
    o Individual is 2 years of age or older
    o Prior to starting Exjade or Jadenu (granules or tablets) therapy, serum ferritin level was documented at greater than 1,000 micrograms/liter (mcg/L)
  • Treatment of chronic iron overload with non-transfusion-dependent thalassemia (NTDT) syndromes AND ALL of the following are met:
    o Individual is 10 years of age or older
    o Prior to starting Exjade or Jadenu (granules or tablets) therapy, serum ferritin level was documented at greater than 300 micrograms/liter (mcg/L)
Coverage for Exjade and Jadenu varies across plans. Refer to the customer’s benefit plan document for coverage details.

Where coverage requires the use of preferred products, the following criteria apply:

**For Employer Group Plans and Individual and Family Plans (IFP): (IFP EFFECTIVE 1/1/2021)**

All of the following:
- Documented intolerance or inability to use deferasirox

## II. Ferriprox® (deferiprone) is considered medically necessary when ANY of the following criteria are met:

- Treatment of transfusional iron overload due to thalassemia syndromes AND the following is met:
  - Prior to starting Ferriprox therapy, the serum ferritin level was greater than 2,500 micrograms/liter (mcg/L)
- Treatment of transfusional iron overload due to Sickle Cell Disease AND the following is met:
  - Prior to starting Ferriprox therapy, serum ferritin level was documented at greater than 1,000 micrograms/liter (mcg/L)
- Treatment of chronic iron overload due to Non-Transfusion-Dependent Thalassemia Syndromes AND the following is met:
  - Prior to starting Ferriprox therapy, serum ferritin level was documented at greater than 300 micrograms/liter (mcg/L)

Coverage for Ferriprox varies across plans. Refer to the customer’s benefit plan document for coverage details.

Where coverage requires the use of preferred products, the following criteria apply:

**For Employer Group Plans and Individual and Family Plan:**

All of the following:
- Documented failure/inadequate response, contraindication per FDA label, intolerance, or not a candidate for deferasirox

**Initial authorization is up to 12 months**

Exjade (deferasirox), Ferriprox (deferiprone), and Jadenu (deferasirox) are considered medically necessary for continued use when the following criteria are met:
- Individual demonstrates benefit from the iron chelation agent (for example: reduction in the serum ferritin levels, stable disease, reduced cardiac iron load), as confirmed by the prescribing physician.

**Reauthorization for up to 12 months**

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.

Exjade (deferasirox), Ferriprox (deferiprone), and Jadenu (deferasirox) considered experimental, investigational or unproven for ANY other use.

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

*If you’re a Cigna provider, please log in to the Cigna for Health Care Professionals website and search for specific patients to view their covered medications.*
## FDA Approved Indications

### FDA Approved Indication

<table>
<thead>
<tr>
<th>Product</th>
<th>FDA Approved Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exjade (deferasirox)</td>
<td>Treatment of Chronic Iron Overload Due to Blood Transfusions (Transfusional Iron Overload)</td>
</tr>
<tr>
<td></td>
<td>Exjade is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older.</td>
</tr>
<tr>
<td></td>
<td>Treatment of Chronic Iron Overload in Non-Transfusion-Dependent Thalassemia Syndromes</td>
</tr>
<tr>
<td></td>
<td>Exjade is indicated for the treatment of chronic iron overload in patients 10 years of age and older 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 greater than 300 mcg/L. This indication is based on achievement of an LIC less than 5 mg Fe/g dw. An improvement in survival or disease-related symptoms has not been established.</td>
</tr>
<tr>
<td></td>
<td>Limitations of Use</td>
</tr>
<tr>
<td></td>
<td>Controlled clinical trials of Exjade with myelodysplastic syndromes (MDS) and chronic iron overload due to blood transfusions have not been performed.</td>
</tr>
<tr>
<td></td>
<td>The safety and efficacy of Exjade when administered with other iron chelation therapy have not been established.</td>
</tr>
<tr>
<td>Ferriprox (deferiprone)</td>
<td>Ferriprox (deferiprone) is indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.</td>
</tr>
<tr>
<td></td>
<td>Approval is based on a reduction in serum ferritin levels. There are no controlled trials demonstrating a direct treatment benefit, such as improvement in disease-related symptoms, functioning, or increased survival.</td>
</tr>
<tr>
<td></td>
<td>Limitation of Use</td>
</tr>
<tr>
<td></td>
<td>Safety and effectiveness have not been established for the treatment of transfusional iron overload in patients with other chronic anemias.</td>
</tr>
<tr>
<td>Jadenu (deferasirox)</td>
<td>Treatment of Chronic Iron Overload Due to Blood Transfusions (Transfusional Iron Overload)</td>
</tr>
<tr>
<td></td>
<td>Jadenu is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older.</td>
</tr>
<tr>
<td></td>
<td>Treatment of Chronic Iron Overload in Non-Transfusion-Dependent Thalassemia Syndromes</td>
</tr>
<tr>
<td></td>
<td>Jadenu is indicated for the treatment of chronic iron overload in patients 10 years of age and older 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 greater than 300 mcg/L. This indication is approved under accelerated approval based on a reduction of liver iron concentrations (to less than 5 mg Fe/g dw) and serum ferritin levels. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.</td>
</tr>
<tr>
<td></td>
<td>Limitations of Use</td>
</tr>
<tr>
<td></td>
<td>Controlled clinical trials of Jadenu with myelodysplastic syndromes (MDS) and chronic iron overload due to blood transfusions have not been performed.</td>
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<tr>
<td></td>
<td>The safety and efficacy of Jadenu when administered with other iron chelation therapy have not been established.</td>
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</tbody>
</table>
## FDA Recommended Dosing

<table>
<thead>
<tr>
<th>Product</th>
<th>Transfusional Iron Overload</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exjade (deferasirox)</td>
<td>Exjade therapy should only be considered when a patient has evidence of chronic transfusional iron overload. The evidence should include the transfusion of at least 100 mL/kg of packed red blood cells (e.g., at least 20 units of packed red blood cells for a 40 kg person or more in individuals weighing more than 40 kg), and a serum ferritin consistently greater than 1000 mcg/L.</td>
</tr>
</tbody>
</table>

Prior to starting therapy or increasing dose, evaluate:

- Serum ferritin level
- Baseline renal function:
  - Obtain serum creatinine in duplicate (due to variations in measurements) to establish accurate baseline
  - Calculate the estimated glomerular filtration rate (eGFR). Use a prediction equation appropriate for adult patients (e.g., CKD-EPI, MDRD method) and in pediatric patients (e.g., Schwartz equations).
  - Obtain urinalyses and serum electrolytes to evaluate renal tubular function [see Dosage and Administration (2.4), Warnings and Precautions (5.1)].
  - Serum transaminases and bilirubin [see Dosage and Administration (2.4), Warnings and Precautions (5.2)]
  - Baseline auditory and ophthalmic examinations [see Warnings and Precautions (5.10)]

Initiating Therapy: The recommended initial dose of Exjade for patients 2 years of age and older with eGFR greater than 60 mL/min/1.73 m² is 20 mg per kg body weight orally, once daily. Calculate doses (mg per kg per day) to the nearest whole tablet.

During Therapy:

- Monitor serum ferritin monthly and adjust the dose of Exjade, if necessary, every 3-6 months based on serum ferritin trends.
- Use the minimum effective dose to achieve a trend of decreasing ferritin.
- Make dose adjustments in steps of 5 or 10 mg per kg and tailor adjustments to the individual patient's response and therapeutic goals.
- In patients not adequately controlled with doses of 30 mg per kg (e.g., serum ferritin levels persistently above 2,500 mcg/L and not showing a decreasing trend over time), doses of up to 40 mg per kg may be considered. Doses above 40 mg per kg are not recommended [see Warnings and Precautions (5.6)].
- Adjust dose based on serum ferritin levels
  - If the serum ferritin falls below 1000 mcg/L at 2 consecutive visits, consider dose reduction, especially if the dose is greater than 25 mg/kg/day [see Adverse Reactions (6.1)].
  - If the serum ferritin falls below 500 mcg/L, interrupt Exjade and continue monthly monitoring.
  - Evaluate the need for ongoing chelation therapy for patients whose conditions no longer require regular blood transfusions.
  - Use the minimum effective dose to maintain iron burden in the target range [see Warnings and Precautions (5.6)].
<table>
<thead>
<tr>
<th>Product</th>
<th>FDA Recommended Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Monitor blood counts, liver function, renal function and ferritin monthly [see Warnings and Precautions (5.1, 5.2, 5.4)].</td>
</tr>
<tr>
<td></td>
<td>• Interrupt Exjade for pediatric patients who have acute illnesses which can cause volume depletion, such as vomiting, diarrhea, or prolonged decreased oral intake, and monitor more frequently. Resume therapy as appropriate, based on assessments of renal function, when oral intake and volume status are normal [see Dosage and Administration (2.4, 2.5), Warnings and Precautions (5.1), Use in Specific Populations (8.4), Clinical Pharmacology (12.3)].</td>
</tr>
</tbody>
</table>

Iron Overload in Non-Transfusion-Dependent Thalassemia Syndromes

Exjade therapy should only be considered when a patient with NTDT syndrome has an LIC of at least 5 mg Fe/g dw and a serum ferritin greater than 300 mcg/L. Prior to starting therapy, obtain:

- LIC by liver biopsy or by an FDA-cleared or approved method for identifying patients for treatment with deferasirox therapy
- Serum ferritin level on at least 2 measurements 1-month apart [see Clinical Studies (14)]
- Baseline renal function:
  - Obtain serum creatinine in duplicate (due to variations in measurements) to establish accurate baseline
  - Calculate eGFR. Use a prediction equation appropriate for adult patients (e.g., CKD-EPI, MDRD method) and in pediatric patients (e.g., Schwartz equations).
  - Obtain urinalyses and serum electrolytes to evaluate renal tubular function [see Dosage and Administration (2.4), Warnings and Precautions (5.1)]
- Serum transaminases and bilirubin [see Dosage and Administration (2.4), Warnings and Precautions (5.2)]
- Baseline auditory and ophthalmic examinations [see Warnings and Precautions (5.10)]

Initiating Therapy: The recommended initial dose of Exjade for patients with eGFR greater than 60 mL/min/1.73 m² is 10 mg per kg body weight orally once daily. Calculate doses (mg per kg per day) to the nearest whole tablet.

- If the baseline LIC is greater than 15 mg Fe/g dw, consider increasing the dose to 20 mg/kg/day after 4 weeks.

During Therapy: Monitor serum ferritin monthly. Interrupt treatment when serum ferritin is less than 300 mcg/L and obtain an LIC to determine whether the LIC has fallen to less than 3 mg Fe/g dw.

- Use the minimum effective dose to achieve a trend of decreasing ferritin.
- Monitor LIC every 6 months.
- After 6 months of therapy, if the LIC remains greater than 7 mg Fe/g dw, increase the dose of deferasirox to a maximum of 20 mg/kg/day. Do not exceed a maximum of 20 mg/kg/day.
- If after 6 months of therapy, the LIC is 3–7 mg Fe/g dw, continue treatment with deferasirox at no more than 10 mg/kg/day.
- When the LIC is less than 3 mg Fe/g dw, interrupt treatment with deferasirox and continue to monitor the LIC.
- Monitor blood counts, liver function, renal function and ferritin monthly [see Warnings and Precautions (5.1, 5.2, 5.4)].
**Pharmacy Benefit Clinical Criteria: P0090**

**Ferriprox (deferiprone)**

The recommended initial dose of Ferriprox is 25 mg/kg, orally, three times per day for a total of 75 mg/kg/day. The maximum dose is 33 mg/kg, three times per day for a total of 99 mg/kg/day.

Dose adjustments up to 33 mg/kg, orally, three times per day should be tailored to the individual patient’s response and therapeutic goals (maintenance or reduction of body iron burden). The maximum recommended total daily dose is 99 mg/kg per day. The dose should be rounded by the prescriber to the nearest 250 mg (half-tablet).

### Table: Tablet requirement to achieve a 25 mg/kg (rounded to the nearest half-tablet) dose level for administration three times a day.

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Dose (mg)</th>
<th>Number of tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>500</td>
<td>1</td>
</tr>
<tr>
<td>30</td>
<td>750</td>
<td>1.5</td>
</tr>
<tr>
<td>40</td>
<td>1000</td>
<td>2</td>
</tr>
<tr>
<td>50</td>
<td>1250</td>
<td>2.5</td>
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<tr>
<td>60</td>
<td>1500</td>
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<tr>
<td>70</td>
<td>1750</td>
<td>3.5</td>
</tr>
<tr>
<td>80</td>
<td>2000</td>
<td>4</td>
</tr>
<tr>
<td>90</td>
<td>2250</td>
<td>4.5</td>
</tr>
</tbody>
</table>

**Jadenu (deferasirox)**

Transfusional Iron Overload

Jadenu therapy should only be considered when a patient has evidence of chronic transfusional iron overload. The evidence should include the transfusion of at least 100 mL/kg of packed red blood cells (e.g., at least 20 units of packed red blood cells for a 40 kg person or more in individuals weighing more than 40 kg), and a serum ferritin consistently greater than 1000 mcg/L.

Prior to starting therapy, or increasing dose, evaluate:

- Serum ferritin level
- Baseline renal function:
  - Obtain serum creatinine in duplicate (due to variations in measurements)
  - Calculate the estimated glomerular filtration rate (eGFR). Use a prediction equation appropriate for adult patients (e.g., CKD-EPI, MDRD method) and in pediatric patients (e.g., Schwartz equations).
  - Obtain urinalyses and serum electrolytes to evaluate renal tubular function [see Dosage and Administration (2.4), Warnings and Precautions (5.1)].
- Serum transaminases and bilirubin [see Dosage and Administration (2.4), Warnings and Precautions (5.2)]
- Baseline auditory and ophthalmic examinations [see Warnings and Precautions (5.10)]
Initiating Therapy: The recommended initial dose of Jadenu for patients 2 years of age and older with eGFR greater than 60 mL/min/1.73 m² is 14 mg per kg body weight orally, once daily. Calculate doses (mg per kg per day) to the nearest whole tablet or nearest whole sachet content for granules. Changes in weight of pediatric patients over time must be taken into account when calculating the dose.

During Therapy:
- Monitor serum ferritin monthly and adjust the dose of Jadenu, if necessary, every 3 to 6 months based on serum ferritin trends.
- Use the minimum effective dose to achieve a trend of decreasing ferritin
- Make dose adjustments in steps of 3.5 or 7 mg per kg and tailor adjustments to the individual patient's response and therapeutic goals.
- In patients not adequately controlled with doses of 21 mg per kg (e.g., serum ferritin levels persistently above 2500 mcg/L and not showing a decreasing trend over time), doses of up to 28 mg per kg may be considered. Doses above 28 mg per kg are not recommended [see Warnings and Precautions (5.6)].
- Adjust dose based on serum ferritin levels
  - If the serum ferritin falls below 1000 mcg/L at 2 consecutive visits, consider dose reduction, especially if the Jadenu dose is greater than 17.5 mg/kg/day [see Adverse Reactions (6.1)].
  - If the serum ferritin falls below 500 mcg/L, interrupt Jadenu therapy and continue monthly monitoring.
  - Evaluate the need for ongoing chelation therapy for patients whose conditions no longer require regular blood transfusions.
  - Use the minimum effective dose to maintain iron burden in the target range [see Warnings and Precautions (5.6)].
- Monitor blood counts, liver function, renal function and ferritin monthly [see Warnings and Precautions (5.1, 5.2, 5.4)].
- Interrupt Jadenu for pediatric patients who have acute illnesses, which can cause volume depletion, such as vomiting, diarrhea, or prolonged decreased oral intake, and monitor more frequently. Resume therapy as appropriate, based on assessments of renal function, when oral intake and volume status are normal [see Dosage and Administration (2.4, 2.5), Warnings and Precautions (5.1), Use in Specific Populations (8.4), Clinical Pharmacology (12.3)].

Iron Overload in Non-Transfusion-Dependent Thalassemia Syndromes
Jadenu therapy should only be considered when a patient with NTDT syndrome has an LIC of at least 5 mg Fe/g dw and a serum ferritin greater than 300 mcg/L.

Prior to starting therapy, obtain:
- LIC by liver biopsy or by an FDA-cleared or approved method for identifying patients for treatment with deferasirox therapy
- Serum ferritin level on at least 2 measurements 1-month apart [see Clinical Studies (14)]
- Baseline renal function:
  - Obtain serum creatinine in duplicate (due to variations in measurements)
  - Calculate the estimated glomerular filtration rate (eGFR). Use a prediction equation appropriate for adult patients (e.g., CKD-EPI, MDRD method) and in pediatric patients (e.g., Schwartz equations).
  - Obtain urinalyses and serum electrolytes to evaluate renal tubular function [see Dosage and Administration (2.4), Warnings and Precautions (5.1)].
- Serum transaminases and bilirubin [see Dosage and Administration (2.4), Warnings and Precautions (5.2)]
Pharmacy Benefit Clinical Criteria: P0090

<table>
<thead>
<tr>
<th>Product</th>
<th>FDA Recommended Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline auditory and ophthalmic examinations [see Warnings and Precautions (5.10)]</td>
</tr>
</tbody>
</table>

Initiating Therapy:
The recommended initial dose of Jadenu for patients with eGFR greater than 60 mL/min/1.73 m² is 7 mg per kg body weight orally once daily. Calculate doses (mg per kg per day) to the nearest whole tablet or nearest whole sachet content for granules.
- If the baseline LIC is greater than 15 mg Fe/g dw, consider increasing the dose to 14 mg/kg/day after 4 weeks.

During Therapy:
Monitor serum ferritin monthly. Interrupt treatment when serum ferritin is less than 300 mcg/L and obtain an LIC to determine whether the LIC has fallen to less than 3 mg Fe/g dw.
- Use the minimum effective dose to achieve a trend of decreasing ferritin.
- Monitor LIC every 6 months.
- After 6 months of therapy, if the LIC remains greater than 7 mg Fe/g dw, increase the dose of deferasirox to a maximum of 14 mg/kg/day. Do not exceed a maximum of 14 mg/kg/day.
- If after 6 months of therapy, the LIC is 3 to 7 mg Fe/g dw, continue treatment with deferasirox at no more than 7 mg/kg/day.
- When the LIC is less than 3 mg Fe/g dw, interrupt treatment with deferasirox and continue to monitor the LIC.
- Monitor blood counts, liver function, renal function and ferritin monthly [see Warnings and Precautions (5.1, 5.2, 5.4)].
- Increase monitoring frequency for pediatric patients who have acute illness which can cause volume depletion, such as vomiting, diarrhea, or prolonged decreased oral intake. Consider dose interruption until oral intake and volume status are normal [see Dosage and Administration (2.4, 2.5), Warnings and Precautions (5.1), Use in Specific Populations (8.4), Clinical Pharmacology (12.3)].

Restart treatment when the LIC rises again to more than 5 mg Fe/g dw.

See package insert for additional dosage and administration information.

<table>
<thead>
<tr>
<th>Drug Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product</strong></td>
</tr>
<tr>
<td>Exjade (deferasirox)</td>
</tr>
<tr>
<td>Ferriprox (deferiprone)</td>
</tr>
<tr>
<td>Jadenu (deferasirox)</td>
</tr>
</tbody>
</table>

**Background**

**Disease Overview**
Iron chelating therapy should be considered in all patients who require long-term blood transfusions. (Algren, 2018)
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. 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. (Chalmers, 2017)

Serum ferritin level measurements are the laboratory parameter most often used to assess the iron burden and response to chelation therapy. (Algren, 2018) 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. (Brittenham, 2011) 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.

Ferriprox is indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. In pooled analysis of patients from several studies, the main criterion for chelation failure was serum ferritin > 2,500 mcg/L before treatment with Ferriprox. Treatment with Ferriprox was considered successful in patients who experienced a ≥ 20% decline in serum ferritin levels within 1 year of starting therapy. (Ferriprox Prescribing Information, 2015)

Exjade and Jadenu (granules or tablets) are indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients ≥ 2 years of age. (Exjade Prescribing Information 2018; Jadenu Prescribing Information, 2018) These pivotal studies included patients with β-thalassemia, chronic anemias, myelodysplastic syndromes, sickle cell disease, Diamond-Blackfan syndrome and other congenital or acquired anemias. 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%). 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. (NCCN, 2018)

Exjade and Jadenu (granules or tablets) are indicated for the treatment of chronic iron overload in patients ≥ 10 years of age and older with non-transfusion-dependent thalassemia syndromes. (Exjade Prescribing Information 2018; Jadenu Prescribing Information, 2018) It’s specifically indicated in patients with liver iron concentration (LIC) of at least 5 mg of iron/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.

**Therapeutic Alternatives**
Deferasirox has an FDA approved generic therapeutic equivalent.

**Professional Societies/Organizations**
**American Heart Association**
The American Heart Association published a consensus statement on cardiovascular function and treatment in β-thalassemia major. (Pennell, 2013) 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.

National Comprehensive Cancer Network (NCCN)
The National Comprehensive Cancer Network (NCCN) guidelines for myelodysplastic syndromes (MDS) (version 2.2018) has the following recommendations under supportive care, for the management of iron overload. (NCCN, 2018) 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 low- or intermediate-1 risk patients who have received or anticipated to receive > 20 transfusions; or patients for whom ongoing transfusions are anticipated; and patients with serum ferritin levels > 2,500 ng/mL. The NCCN recommendations do not specifically address the use of Ferriprox for MDS. It just notes that a third oral chelating agent is available and it was approved based on retrospective analysis of pooled efficacy and safety studies of Ferriprox use 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.

Off Label Uses
Ferriprox
Iron Overload, Chronic – Transfusion – Related Due to Sickle Cell Disease
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. (Calvaruso, 2015) Patients (n = 60) were > 13 years of age and had serum ferritin concentration between 500 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. (Marsela, 2014)

Iron Overload, Chronic – Non-Transfusion-Dependent Thalassemia Syndromes.
Iron overload in thalassemia intermedia is mainly due to increased intestinal absorption of iron due to chronic anemia. (Calvaruso, 2015) 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. (Kontoghiorghe, 2016)

AHFS Drug Information 2019 Edition does not support any off-label uses of iron chelating agents.

Generics
The FDA’s generic drug approval process does not require the drug sponsor to repeat costly animal and clinical research on ingredients or dosage forms already approved for safety and effectiveness. Generic drugs must establish the following for approval:
• contain the same active ingredients as the innovator drug(inactive ingredients may vary)
• be identical in strength, dosage form, and route of administration
• have the same use indications
• be bioequivalent
• meet the same batch requirements for identity, strength, purity, and quality
• be manufactured under the same strict standards of FDA’s good manufacturing practice regulations required for innovator products

A generic drug is the same as a brand-name drug in dosage, safety, strength, quality, the way it works, the way it is taken and the way it should be used. FDA requires generic drugs have the same high quality, strength, purity
and stability as brand-name drugs. Not every brand-name drug has a generic drug. When new drugs are first made they have drug patents. Most drug patents are protected for 20 years. The patent, which protects the company that made the drug first, doesn't allow anyone else to make and sell the drug. When the patent expires, other drug companies can start selling a generic version of the drug. But, first, they must test the drug and the FDA must approve it.

References

1. AHFS Drug Information 2019
9. Exjade® tablets for suspension [prescribing information]. East Hanover, NJ: Novartis; February 2018

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