IRON CHELATING AGENTS: EXJADE® (deferasirox) tablet for oral suspension, FERRIPROX® (deferiprone) tablet for oral use and oral solution, & JADENU™ (deferasirox) tablet for oral use

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member’s specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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Description:

Exjade (deferasirox) tablet for oral suspension & Jadenu (deferasirox) oral tablets are indicated for the treatment of chronic iron (Fe) overload in patients 2 years of age and older whose iron overload is due to blood transfusions (transfusional hemosiderosis) with at least 100 mL/kg of packed red blood cells and have a serum ferritin that is consistently greater than 1,000 mcg/L. Both are also indicated for the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion-dependent thalassemia (NTDT) syndromes with 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.

Ferriprox (deferiprone), tablet and solution, is another oral iron chelating agent indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. The safety and effectiveness have not been established for the treatment of transfusional iron overload in patients with other chronic anemias.
An injectable iron chelating agent, deferoxamine (Desferal and generics), is available and is administered intramuscularly, subcutaneously, or intravenously. It is indicated for the treatment of acute iron intoxication and of chronic iron overload due to transfusion-dependent anemias.

All body cells need iron. It is crucial for oxygen transport, energy production, and cellular growth and proliferation. The human body contains an average of 3.5 g of iron (males 4 g, females 3 g). Iron is bound and transported in the body by the glycoprotein carrier protein transferrin and it is stored in ferritin molecules. Ferritin is particularly abundant in the liver and heart. When there is an excess of iron, the body responds by producing more ferritin to facilitate iron storage. When iron concentrations exceed the storage capacity of ferritin molecules, unbound iron deposits in many organs and causes free-radical formation in cells, resulting in membrane lipid peroxidation, cellular injury, and organ dysfunction. Iron overload may result from either inherited or acquired disorders such as transfusion dependent anemia, various liver diseases, hemolytic anemia, thalassemia, sickle cell anemia and excessive iron ingestion.

Determination of iron status can be accomplished by several methods. Serial measurement of serum ferritin is a reliable and the easiest method to evaluate iron overload. Determination of liver iron concentration can be done via a liver biopsy but it is an invasive procedure with the possibility of complications. Recently, nuclear magnetic resonance imaging techniques for assessing total body iron has become available. R2 and T2* parameters have been validated for liver iron concentration.

Myelodysplastic syndrome (MDS) refers to a heterogeneous group of clonal hematopoietic disorders with the potential to transform into acute myelocytic leukemia (AML). The International Prognostic Scoring System (IPSS) and a revised IPSS (IPSS-R) use cytogenetic, morphologic, and clinical data to define MDS risk groups. IPSS for MDS stratifies patients into four distinctive risk groups in terms of both survival and AML evolution. The IPSS-R defines five risk groups. The IPSS-R has been validated in a number of studies.

Exjade (deferasirox) is a soluble oral tablet for suspension in solution available in 125 mg, 250 mg, and 500 mg strengths, it should not be chewed or swallowed whole; Jadenu (deferasirox) is an oral tablet in 90 mg, 180 mg, and 360 mg strengths. Ferriprox (deferiprone) is an oral tablet available as 500 mg strength, it is also available as a 100 mg/mL oral solution. Both Exjade and Jadenu have boxed warnings related to the risk of causing renal impairment and failure, hepatic impairment and failure, and gastrointestinal hemorrhage. Ferriprox has a boxed warning regarding the risk of agranulocytosis/neutropenia that may lead to serious infections and death. The safety and efficacy of combining oral chelating therapy have not been established. Controlled clinical trials of Exjade & Jadenu with MDS and chronic iron overload due to blood transfusions have not been performed.

Definitions:

The Child-Pugh classification system:

The Child-Pugh classification is a scoring system used to determine the prognosis of individuals with cirrhosis. Scoring is based upon several factors: albumin, ascites, total bilirubin, prothrombin time, and encephalopathy, as follows:
Iron Chelating Agents (cont.)

<table>
<thead>
<tr>
<th></th>
<th>Score: 1 point</th>
<th>Score: 2 points</th>
<th>Score: 3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Albumin (g/dL)</td>
<td>&gt;3.5</td>
<td>3.0 - 3.5</td>
<td>&lt;3.0</td>
</tr>
<tr>
<td>Serum Bilirubin (mg/dL)</td>
<td>&lt;2.0</td>
<td>2.0 - 3.0</td>
<td>&gt;3.0</td>
</tr>
<tr>
<td>Prothrombin time (seconds)</td>
<td>1 - 4</td>
<td>4 - 6</td>
<td>&gt;6</td>
</tr>
<tr>
<td>Ascites</td>
<td>none</td>
<td>moderate</td>
<td>severe</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>none</td>
<td>mild</td>
<td>severe</td>
</tr>
</tbody>
</table>

The three classes and their scores are:
- **Class A** is score 5 – 6: Well compensated
- **Class B** is score 7 – 9: Significant functional compromise
- **Class C** is score >9: Decompensated disease

Methods for measuring iron overload:
- Liver iron concentration (LIC) by biopsy
- Magnetic resonance imaging with R2* or T2*
- R2 technique

Thalassemia syndromes:
- Alpha-thalassemia silent carrier
- Alpha-thalassemia trait (minor)
- Hemoglobin H disease
- Hemoglobin Bart’s Hydrops fetalis syndrome
- Beta-thalassemia trait (minor)
- Thalassemia intermedia
- Beta-thalassemia major (Cooley’s anemia)
- Beta-thalassemia minor
- Hemoglobin E (Hb-E) thalassemia

Mild Hb-E / Beta-thalassemia
Moderately severe Hb-E / Beta-thalassemia
Severe Hb-E / Beta-thalassemia
Delta-thalassemia
Hemoglobin S thalassemia
Hemoglobin C thalassemia
Hemoglobin D thalassemia
Delta-thalassemia
Hereditary persistence of fetal hemoglobin (HPFH)

Myelodysplastic syndrome (MDS):
A heterogeneous group of clonal hematopoietic disorders with the potential to transform into acute myelocytic leukemia (AML). MDS include, but are not limited to:
- del 5q syndrome
- Refractory anemia
- Refractory anemia with:
  - Ringed sideroblasts
  - Excess blasts 1 and 2
- Refractory cytopenia with multilineage dysplasia or ring sideroblasts
International Prognostic Scoring System for MDS: (IPSS & IPSS-R)

### International Prognostic Scoring System (IPSS)

<table>
<thead>
<tr>
<th>Survival and AML evolution</th>
<th>Score value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic variable</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Bone marrow blasts (%)</td>
<td>&lt; 5</td>
</tr>
<tr>
<td></td>
<td>5-10</td>
</tr>
<tr>
<td>Karyotype</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0/1</td>
</tr>
<tr>
<td></td>
<td>2/3</td>
</tr>
</tbody>
</table>

### Prognosis

<table>
<thead>
<tr>
<th>Overall Score</th>
<th>IPSS Group</th>
<th>Median survival (y)</th>
<th>25% AML progression (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>5.7</td>
<td>9.4</td>
</tr>
<tr>
<td>0.5-1</td>
<td>Intermediate-1</td>
<td>3.5</td>
<td>3.3</td>
</tr>
<tr>
<td>1.5-2</td>
<td>Intermediate-2</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>&gt; 2.5</td>
<td>High</td>
<td>0.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Patients with 20-30% blasts may be considered to have MDS (FAB) or AML (WHO)

Cytogenetics: **Good** = normal, -Y alone, del(5q) alone, or del(20q) alone; **Poor** = complex (> 3 abnormalities) or chromosome 7 anomalies; **Intermediate** = other abnormalities. [This excludes karyotypes t(8;21), inv16, and t(15;17) which are considered to be AML and not MDS]

Cytopenias: neutrophil count < 1,800/mcL, platelets < 100,000 mcL, Hb < 10 g/dL

### Revised International Prognostic Scoring System (IPSS-R)

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow blasts (%)</td>
<td>≤ 2</td>
<td>-</td>
<td></td>
<td>&gt; 2-&lt;5</td>
<td>-</td>
<td>5-10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&gt; 10</td>
<td>-</td>
<td></td>
<td>8-&lt;10</td>
<td>&lt;8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Platelets</td>
<td>&gt; 100</td>
<td>50-&lt;100</td>
<td>&lt;50</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ANC</td>
<td>&gt; 0.8</td>
<td>&lt;0.8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Prognosis

<table>
<thead>
<tr>
<th>Overall Score</th>
<th>IPSS-R Group</th>
<th>Median survival (y)</th>
<th>25% AML progression (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.5</td>
<td>Very low</td>
<td>8.8</td>
<td>Not reached</td>
</tr>
<tr>
<td>&gt; 1.5-&lt;3</td>
<td>Low</td>
<td>5.3</td>
<td>10.8</td>
</tr>
<tr>
<td>&gt; 3-&lt;4.5</td>
<td>Intermediate</td>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td>&gt; 4.5-&lt;6</td>
<td>High</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>&gt; 6</td>
<td>Very high</td>
<td>0.8</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Cyogenetic risks: **Very good** = -Y, del(11q); **Good** = normal del(5q), del(12p), del(20q), double including del(5q); **Intermediate** = del(7q), +8, +19, i(17q), any single or double independent clones; **Poor** = -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities; **Very poor** = complex: 3 abnormalities.
Performance scores:

<table>
<thead>
<tr>
<th>ECOG Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Asymptomatic, fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Symptomatic, fully ambulatory, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example light house work or office work</td>
</tr>
<tr>
<td>2</td>
<td>Symptomatic, in bed less than 50% of the day, ambulatory and capable of all self-care but unable to carry out any work activities</td>
</tr>
<tr>
<td>3</td>
<td>Symptomatic, confined to bed or chair more than 50% of the day but not bedridden, capable of only limited self-care</td>
</tr>
<tr>
<td>4</td>
<td>Bedridden, cannot perform any self-care, completely disabled</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Karnofsky Performance Score:

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Able to carry on normal activity, no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity, minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort, some signs and symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self, unable to carry on normal activity or to work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance from others but able to care for most needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance from others and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled, requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled, hospitalization indicated, though death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick, hospitalization indicated, active support treatment necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Lansky Play Score (Also known as Lansky Play - Performance Scale):

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Fully active, normal</td>
</tr>
<tr>
<td>90</td>
<td>Minor restrictions in physically strenuous activity</td>
</tr>
<tr>
<td>80</td>
<td>Active, but tires more quickly</td>
</tr>
<tr>
<td>70</td>
<td>Both greater restriction of and less time spent in play activity</td>
</tr>
<tr>
<td>60</td>
<td>Up and around, but minimal active play; keeps busy with quieter activities</td>
</tr>
<tr>
<td>50</td>
<td>Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities</td>
</tr>
<tr>
<td>40</td>
<td>Mostly in bed; participates in quiet activities</td>
</tr>
<tr>
<td>30</td>
<td>In bed; needs assistance even for quiet play</td>
</tr>
<tr>
<td>20</td>
<td>Often sleeping; play entirely limited to very passive activities</td>
</tr>
<tr>
<td>10</td>
<td>No play; does not get out of bed</td>
</tr>
<tr>
<td>0</td>
<td>Unresponsive</td>
</tr>
</tbody>
</table>

Drug related events:

**Ineffective / failure**

Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of...
individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

**Adverse Drug Event:** Allergic reaction / Hypersensitivity / Intolerance

Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual's outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals’ body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

*Allergic reaction / hypersensitivity* – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline.

*Intolerance* – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record.

**Contraindication**

Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled recommendation and is considered investigational or experimental

**Non-adherence**

Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record

**Precertification:**

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

This Pharmacy Coverage Guideline does not apply to FEP or other states’ Blues Plans.

Information about medications that require precertification is available at [www.azblue.com/pharmacy](http://www.azblue.com/pharmacy).
Iron Chelating Agents (cont.)

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Criteria:

See “Resources” section for FDA-approved dosage.

- Precertification for Exjade, Jadenu, and Ferriprox requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. Incomplete forms will be returned.

Criteria for Exjade and Jadenu:

- FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Exjade or Jadenu is considered medically necessary with medical record documentation of ALL of the following:

  1. Individual is 2 years of age or older

  2. Medical record documentation of chronic iron overload due to blood transfusions (transfusional hemosiderosis) with ALL of the following:
      - Receives blood transfusions on a regular basis or is participating in blood transfusion program
      - Transfused with at least 100 mL/kg of packed red blood cells (PRBC) (at least 20 units of PRBC for a 40-kg person) OR a history of frequent blood transfusions that have resulted in chronic iron overload
      - Serum ferritin are consistently > 1,000 mcg/L

  3. ALL of the following baseline tests have been obtained before initiation of therapy:
      - Serum ferritin
      - Serum creatinine and creatinine clearance
      - Serum transaminase and bilirubin
      - Auditory examination
      - Ophthalmic examination including slit lamp examination and dilated fundoscopy
      - Complete blood count
      - When used in myelodysplastic syndrome (MDS), ALL of the following:
          - IPSS or IPSS-R score (score must be submitted with request)
          - Performance status (score must be submitted with request) using ONE of the following:
              - ECOG or Karnofsky score
              - For age 10 or under a Lansky Plat score

  4. Absence of ALL of the following contraindications:
IRON CHELATING AGENTS (cont.)

- Serum creatinine greater than 2 times the age-appropriate upper limit of normal OR creatinine clearance of less than 40 mL/min
- Individual with a platelet count of less than 50 x 10^9/L
- Individuals with advanced malignancies
- High-risk MDS defined by either IPSS or IPSS-R
- Poor performance status defined by ONE of the following:
  - ECOG score of greater than or equal to 3 OR a Karnofsky score of less than 70%
  - For age 10 or under a Lansky Play score of less than 70%

5. Absence of ALL of the following exclusions:
- Serum ferritin consistently < 500 mcg/L
- Severe hepatic impairment (Child-Pugh Class C)
- When applicable, drugs that interact significantly with Exjade or Jadenu have been discontinued or doses adjusted, if clinically safe to do so
- Woman of reproductive potential who is pregnant or likely to become pregnant, unless using effective contraception
- Woman who is breast feeding an infant or child

- FDA-approved dosage of Exjade or Jadenu is considered **medically necessary** with ALL of the following:
  1. Individual is 10 years of age or older
  2. Medical record documentation of chronic iron overload due to non-transfusional thalassemia (NTDT) syndromes with ALL of the following:
     - Serum ferritin are consistently > 300 mcg/L on at least 2 measurements at least one month apart
     - Liver iron concentration (LIC) is ≥ 5 mg Fe/g dw by biopsy or by an FDA-approved method
  3. ALL of the following baseline tests have been obtained before initiation of therapy:
     - Liver iron concentration by liver biopsy OR by an FDA-cleared OR approved method
     - Serum ferritin
     - Serum creatinine and creatinine clearance
     - Serum transaminase and bilirubin
     - Auditory examination
     - Ophthalmic examination including slit lamp examination and dilated fundoscopy
     - Complete blood count
  4. Absence of ALL of the following contraindications:
     - Serum creatinine greater than 2 times the age-appropriate upper limit of normal OR creatinine clearance of less than 40 mL/min
     - Individual with a platelet count of less than 50 x 10^9/L
     - Individuals with advanced malignancies
     - High-risk MDS defined by either IPSS or IPSS-R
     - Poor performance status defined by ONE of the following:
       - ECOG score of greater than or equal to 3 OR a Karnofsky score of less than 70%
       - For age 10, a Lansky Play score of less than 70%
IRON CHELATING AGENTS (cont.)

5. Absence of ALL of the following exclusions:
   - Serum ferritin consistently < 300 mcg/L
   - Severe hepatic impairment (Child-Pugh Class C)
   - LIC less than or equal to 3 mg Fe/g dw by biopsy or by an FDA-approved method
   - When applicable, drugs that interact significantly with Exjade or Jadenu have been discontinued or doses adjusted, if clinically safe to do so
   - Woman of reproductive potential who is pregnant or likely to become pregnant, unless using effective contraception
   - Woman who is breast feeding an infant or child

Criteria for Ferriprox:

- FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Ferriprox is considered **medically necessary** with medical record documentation of iron overload that satisfies **ALL** of the following:
  1. Individual is 18 years of age or older
  2. Medical record diagnosis of transfusional iron overload due to thalassemia syndrome
  3. Current chelation therapy with Exjade or Jadenu resulted in an inadequate response, or significant intolerance, or are contraindicated
  4. Serum ferritin are consistently > 1,000 mcg/L
  5. **All** of the following baseline tests have been obtained before initiation of therapy:
     - Serum ferritin
     - Complete blood count with differential
     - Pregnancy test in a woman of child bearing age, unless using effective contraception
     - Liver enzymes
  6. Absence of **ALL** of the following exclusions:
     - Serum ferritin consistently < 500 mcg/L
     - Agranulocytosis / neutropenia
     - Absolute neutrophil count < 1.5 x 10⁹/L
     - Acute or chronic infection
     - Severe hepatic impairment (Child-Pugh Class C)
     - Woman of child bearing age who is pregnant
     - Woman who is breast feeding an infant or child
     - When applicable, drugs that interact significantly with Ferriprox have been discontinued or doses adjusted, if clinically safe to do so

- Exjade, Jadenu and Ferriprox for all other indications not previously listed is considered **experimental or investigational** based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
IRON CHELATING AGENTS (cont.)

3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to the following:
- Combination oral iron chelation therapy
- Ferriprox use in other chronic anemia than listed above

Resources:


Hoffbrand AV, Taher A, Cappellini MD. How I treat transfusional iron overload. Blood 2012 Nov; 120(18): 3657-3669


FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
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</table>
| EXJADE is an iron chelator indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. This indication is based on reduction in serum ferritin and liver iron concentration (LIC). An improvement in survival or disease-related symptoms has not been established. 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 (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight and a serum ferritin greater than 300 mcg/L. This indication is based on achievement of an LIC less than 5 mg | • Transfusional iron overload: Initial dose 20 mg/kg (calculated to nearest whole tablet) once daily, as an oral suspension.  
  • NTDT syndromes: Initial dose 10 mg/kg (calculated to nearest whole tablet) once daily, as an oral suspension.  
  • Monitor serum ferritin monthly and adjust dose accordingly.  
  • Monitor LIC every 6 months and adjust dose accordingly. |
**IRON CHELATING AGENTS (cont.)**

<table>
<thead>
<tr>
<th><strong>JADENU</strong></th>
<th><strong>Transfusional iron overload:</strong> Initial dose 14 mg/kg (calculated to nearest whole tablet) once daily.</th>
</tr>
</thead>
</table>
| **FERRIPROX (deferiprone)** | - Transfusional iron overload: Initial dose 14 mg/kg (calculated to nearest whole tablet) once daily.  
| | - NTDT syndromes: Initial dose 7 mg/kg (calculated to nearest whole tablet) once daily.  
| | - Monitor serum ferritin monthly and adjust dose accordingly.  
| | - Monitor LIC every 6 months and adjust dose accordingly.  
| | - Take on an empty stomach or with a low-fat meal.  
| | - Reduce dose for moderate (Child-Pugh B) hepatic impairment by 50%. Avoid in patients with severe (Child-Pugh C) hepatic impairment.  
| | - Reduce dose by 50% in patients with renal impairment (CICr 40–60 mL/min).  

**Fe/g dw.** An improvement in survival or disease-related symptoms has not been established.

**Limitation of Use**  
Controlled clinical trials of Exjade in patients with myelodysplastic syndromes (MDS) and chronic iron overload due to blood transfusion have not been performed.

The safety and efficacy of Exjade when administered with other iron chelation therapy have not been established.

**JADENU** is an iron chelator indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. This indication is approved under accelerated approval based on a reduction of liver iron concentrations and serum ferritin levels. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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 (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight (Fe/g dw) and a serum ferritin greater than 30 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.

**Limitation of Use**  
Controlled clinical trials of Jadenu in patients with myelodysplastic syndromes (MDS) and chronic iron overload due to blood transfusion have not been performed.

The safety and efficacy of Jadenu when administered with other iron chelation therapy have not been established.

**FERRIPROX (deferiprone)** is indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.

**Limitation of Use**  
Safety and effectiveness have not been established for the treatment of transfusional iron overload in patients with other chronic anemias.

<table>
<thead>
<tr>
<th><strong>Fe/g dw.</strong></th>
<th><strong>Take on an empty stomach at least 30 minutes before food. Disperse tablets by stirring in an appropriate amount of water, orange juice, or apple juice.</strong></th>
</tr>
</thead>
</table>
| | - Reduce starting dose for moderate (Child-Pugh B) hepatic impairment by 50%. Avoid in patients with severe (Child-Pugh C) hepatic impairment.  
| | - Reduce starting dose by 50% in patients with renal impairment (CICr 40–60 mL/min).  

| | **Monitor LIC every 6 months and adjust dose accordingly.** |
| | **Take on an empty stomach or with a low-fat meal.** |
| | **Reduce dose for moderate (Child-Pugh B) hepatic impairment by 50%. Avoid in patients with severe (Child-Pugh C) hepatic impairment.** |
| | **Reduce dose by 50% in patients with renal impairment (CICr 40–60 mL/min).** |
The safety and efficacy of Ferriprox when administered with other iron chelation therapy have not been established.

The safety and effectiveness of Ferriprox tablets for oral use in pediatric patients have not been established.

- 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).
- Monitor serum ferritin concentration every two to three months to assess the effects of Ferriprox on body iron stores.
- Dose adjustments should be tailored to the individual patient’s response and therapeutic goals (maintenance or reduction of body iron burden).