Intravenous Iron Replacement Therapy (Feraheme®, Injectafer®, & Monoferric®) (for Louisiana Only)

Policy Number: ~~CSLA2024D0088G~~CSLA2024D0088H
Effective Date: TBD

Instructions for Use

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Application

This Medical Benefit Drug Policy only applies to the state of Louisiana.

Coverage Rationale

This policy refers to the following intravenous iron replacements:

- Feraheme® (ferumoxytol)
- Injectafer® (ferric carboxymaltose)
- Monoferric® (ferric derisomaltose)

The following intravenous iron replacements are not subject to the coverage criteria in this section:

- Ferrlecit® (sodium ferric gluconate complex)
- Infed® (iron dextran)
- Venofer® (iron sucrose)

Feraheme (ferumoxytol), Injectafer (ferric carboxymaltose), and Monoferric (ferric derisomaltose) are proven for the following indications:

- **Iron Deficiency Anemia (IDA) without Chronic Kidney Disease (CKD)**
  Feraheme, Injectafer, and Monoferric are medically necessary when the following criteria are met:
  - For **initial therapy**, **all** of the following:
    - Submission of medical records (e.g., lab values, chart notes, etc.) supporting the diagnosis of IDA; **and**
    - Patient does not have CKD; **and**
    - **One** of the following:
      - History of failure, contraindication, or intolerance, to **oral** iron therapy; or
      - **One** of the following:

- Patient has severe iron deficiency in late stage pregnancy
- Patient has impaired absorption due to prior gastric surgery or disorder of the gastrointestinal tract (e.g., celiac disease, inflammatory bowel disease)
- Blood loss exceeds the ability to replete iron orally;

and

- **One** of the following:
  - **Both** of the following:
    - Submission of laboratory values demonstrating treatment failure after at least 3 weeks of therapy, to at least **two** of the following intravenous iron therapies each (**Note**: Laboratory values should be obtained within 1 to 3 weeks following the last dose of intravenous iron in a treatment course):
      - Infed® (iron dextran)
      - Ferrlecit® (sodium ferric gluconate complex)
      - Venofer® (iron sucrose);

      and
    - Physician attests that in their clinical opinion, the clinical response would be expected to be superior with Feraheme, Injectafer, or Monoferric than experienced with the other products;

    or
  - **Both** of the following:
    - History of intolerance, contraindication, or severe adverse event, to **all** of the following intravenous iron therapies not previously tried and experienced treatment failure:
      - Infed® (iron dextran)
      - Ferrlecit® (sodium ferric gluconate complex)
      - Venofer® (iron sucrose);

      and
    - Physician attests that in their clinical opinion, the same intolerance, contraindication, or severe adverse event would not be expected to occur with Feraheme, Injectafer, or Monoferric than experienced with the other products;

  and
- **One** of the following:
  - Feraheme dose does not exceed 510 mg elemental iron per dose and 2.04g elemental iron per course
  - Injectafer dose does not exceed 750 mg elemental iron per dose and 1500mg elemental iron per course
  - Monoferric dose does not exceed 1000 mg elemental iron per dose/course;

  and
- Initial authorization will be for no longer than 3 months

o For **continuation of therapy**, **all** of the following:

- Coverage has previously been provided by UnitedHealthcare for Feraheme, Injectafer, or Monoferric for the treatment of IDA based on documented history of **one** of the following:
  - Intolerance, contraindication, or severe adverse event to all three preferred intravenous iron products; or
  - Treatment failure of at least two of the three preferred intravenous iron products

  and
- Submission of recent laboratory results (within the past 4 weeks) since the last Feraheme, Injectafer, or Monoferric administration to demonstrate need for additional therapy; **and**
- Patient does not have CKD; **and**
- **One** of the following:
  - Feraheme dose does not exceed 510 mg elemental iron per dose and 2.04g elemental iron per course

- Injectafer dose does not exceed 750 mg elemental iron per dose and 1500mg elemental iron per course
- Monoferric dose does not exceed 1000 mg elemental iron per dose/course;

and

- Continuation authorization will be for no longer than 3 months

- **Iron Deficiency Anemia (IDA) associated with Chronic Kidney Disease (CKD), without end stage renal disease (ESRD)**
  Feraheme, Injectafer, and Monoferric are medically necessary when the following criteria are met:
  - For **initial therapy**, **all** of the following:
    - Diagnosis of IDA and CKD; **and**
    - Submission of medical records (e.g., lab values, chart notes, etc.) supporting the diagnosis of IDA; **and**
    - Patient does **not** have ESRD; **and**
    - **One** of the following:
      - Patient's CKD requires hemodialysis or peritoneal dialysis treatment; **or**
      - **Both** of the following:
        - Patient's CKD does **not** require hemodialysis or peritoneal dialysis treatment; **and**
        - History of failure, contraindication, or intolerance, to **oral** iron therapy;

      and
    - **One** of the following:
      - **Both** of the following:
        - Submission of laboratory values demonstrating treatment failure after at least 3 weeks of therapy, to at least two of the following intravenous iron therapies each (**Note**: Laboratory values should be obtained within 1 to 3 weeks following the last dose of intravenous iron in a treatment course):
          - Infed® (iron dextran)
          - Ferrlecit® (sodium ferric gluconate complex)
          - Venofer® (iron sucrose);

          and
        - Physician attests that in their clinical opinion, the clinical response would be expected to be superior with Feraheme, Injectafer, or Monoferric than experienced with the other products;

        or
      - **Both** of the following:
        - History of intolerance, contraindication, or severe adverse event, to **all** of the following intravenous iron therapies not previously tried and experienced treatment failure:
          - Infed® (iron dextran)
          - Ferrlecit® (sodium ferric gluconate complex)
          - Venofer® (iron sucrose);

          and
        - Physician attests that in their clinical opinion, the same intolerance, contraindication, or severe adverse event would not be expected to occur with Feraheme, Injectafer, or Monoferric than experienced with the other products;

      and
    - **One** of the following:
      - Feraheme dose does not exceed 510 mg elemental iron per dose and 2.04g elemental iron per course
      - Injectafer dose does not exceed 750 mg elemental iron per dose and 1500mg elemental iron per course
      - Monoferric dose does not exceed 1000 mg elemental iron per dose/course;

      and
    - Initial authorization will be for no longer than 3 months

- For **continuation of therapy**, **all** of the following:
  - Coverage has previously been provided by UnitedHealthcare for Feraheme, Injectafer, or Monoferric for the treatment of IDA with CKD based on documented history of **one** of the following:
    - Intolerance, contraindication, or severe adverse event to all three preferred intravenous iron products; or
    - Treatment failure of at least two of the three preferred intravenous iron products

    and
  - Patient does **not** have ESRD; **and**
  - Submission of recent laboratory results (within the past 4 weeks) since the last Feraheme, Injectafer, or Monoferric administration to demonstrate need for additional therapy; **and**
  - **One** of the following:
    - Feraheme dose does not exceed 510 mg elemental iron per dose and 2.04g elemental iron per course
    - Injectafer dose does not exceed 750 mg elemental iron per dose and 1500mg elemental iron per course
    - Monoferric dose does not exceed 1000 mg elemental iron per dose/course;

    and
  - Continuation authorization will be for no longer than 3 months

Injectafer is medically necessary for the treatment of iron deficiency in adult patients with heart failure and New York Heart Association class II/III to improve exercise capacity in patients who meet all of the following criteria:

- For **initial therapy**, **all** of the following:
  - Submission of medical records (e.g., lab values, chart notes, etc.) supporting the diagnosis of iron deficiency including **one** of the following:
    - Serum ferritin < 100 ng/mL

    or
    - Both of the following:
      - Serum ferritin is 100 to 300 ng/mL
      - Transferrin saturation (TSAT) < 20%

    and
  - Heart failure is classified as **one** of the following:
    - New York Heart Association (NYHA) class II heart failure
    - New York Heart Association (NYHA) class III heart failure

    and
  - Patient has a left ventricular ejection fraction less than 45%; **and**
  - Patient has hemoglobin (Hb) <15 g/dl; **and**
  - **One** of the following:
    - **Both** of the following:
      - Submission of laboratory values demonstrating treatment failure after at least 3 weeks of therapy, to at least **two** of the following intravenous iron therapies each (**Note**: Laboratory values should be obtained within 1 to 3 weeks following the last dose of intravenous iron in a treatment course):
        - Infed® (iron dextran)
        - Ferrlecit® (sodium ferric gluconate complex)
        - Venofer® (iron sucrose)

        and
      - Physician attests that in their clinical opinion, the clinical response would be expected to be superior with Injectafer than experienced with the other products

      or
    - **Both** of the following:
      - History of intolerance, contraindication, or severe adverse event, to all of the following intravenous iron therapies not previously tried and experienced treatment failure:

- Infed® (iron dextran)
- Ferrlecit® (sodium ferric gluconate complex)
- Venofer® (iron sucrose)

and

- Physician attests that in their clinical opinion, the same intolerance, contraindication, or severe adverse event would not be expected to occur with Injectafer than experienced with the other products

- Injectafer dose does not exceed 1,000 mg elemental iron per dose
  and
- Initial authorization will be for no longer than 6 months.

- For **continuation of therapy**, **all** of the following:
  - Coverage has previously been provided by UnitedHealthcare for Injectafer for the treatment of iron deficiency based on documented history of **one** of the following:
    - Intolerance, contraindication, or severe adverse event to all three preferred intravenous iron products; or
    - Treatment failure of at least two of the three preferred intravenous iron products

    and
  - Submission of recent laboratory results (within the past 4 weeks) since the last Injectafer administration to demonstrate need for additional therapy; **and**
  - Injectafer dose dose does not exceed 1,000 mg elemental iron per dose; **and**
  - Continuation authorization will be for no longer than 6 months.

Definitions

For the purposes of this policy, iron deficiency anemia is defined as:

Iron Deficiency Anemia (IDA) without Chronic Kidney Disease (CKD) or Acute or Chronic Inflammatory Conditions:

- **Adults and pediatric patients > 12 years:** Serum ferritin < 30 ng/mL or transferrin saturation (TSAT) < 20% or an absence of stainable iron in bone marrow. [3,4,7,11,18]
- **Pediatric patients ≤ 12 years:** Hemoglobin concentration 2 standard deviations (SD) below the mean for age and gender (Table 1) and one of the following: [6, 20]
  - Serum ferritin ≤ 10 ug/L and C-reactive protein (CRP) within normal limits
  - Reticulocyte hemoglobin content (CHr) < 26 pg.[21, 22]

Table 1. Age-Based Hemoglobin Levels in Children and Adolescents

Age	Mean Hgb (g/dL)	-2 SD (g/dL)
Birth (term infant)	16.5	13.5
1 month	13.9	10.7
2 months	11.2	9.4
3-6 months	11.5	9.5
> 6 months to 2 years	12	10.5
> 2 to 6 years	12.5	11.5
> 6 to 12 years	13.5	11.5

Iron Deficiency Anemia (IDA) with CKD or Acute or Chronic Inflammatory Conditions: Serum ferritin < 100 ng/mL or TSAT < 20%. If serum ferritin is 100-300 ng/mL, TSAT < 20% is required to confirm iron deficiency.[3,4,7,11,18]

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not

imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J1437	Injection, ferric derisomaltose, 10 mg
J1439	Injection, ferric carboxymaltose, 1 mg
Q0138	Injection, ferumoxytol, for treatment of iron deficiency anemia, 1 mg (non-ESRD use)
Q0139	Injection, ferumoxytol, for treatment of iron deficiency anemia, 1 mg (for ESRD on dialysis)

Diagnosis Code	Description
D50.0	Iron deficiency anemia secondary to blood loss (chronic)
D50.1	Sideropenic dysphagia
D50.8	Other iron deficiency anemias
D50.9	Iron deficiency anemia, unspecified
D63.1	Anemia in chronic kidney disease
I12.9	Hypertensive chronic kidney disease with stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease
I13.0	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease
I13.10	Hypertensive heart and chronic kidney disease without heart failure, with stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease
I50.1	Left ventricular failure, unspecified
I50.20	Unspecified systolic (congestive) heart failure
I50.21	Acute systolic (congestive) heart failure
I50.22	Chronic systolic (congestive) heart failure
I50.23	Acute on chronic systolic (congestive) heart failure
I50.30	Unspecified diastolic (congestive) heart failure
I50.31	Acute diastolic (congestive) heart failure
I50.32	Chronic diastolic (congestive) heart failure
I50.33	Acute on chronic diastolic (congestive) heart failure
I50.40	Unspecified combined systolic (congestive) and diastolic (congestive) heart failure
I50.41	Acute combined systolic (congestive) and diastolic (congestive) heart failure
I50.42	Chronic combined systolic (congestive) and diastolic (congestive) heart failure
I50.43	Acute on chronic combined systolic (congestive) and diastolic (congestive) heart failure
I50.810	Right heart failure, unspecified
I50.811	Acute right heart failure
I50.812	Chronic right heart failure
I50.813	Acute on chronic right heart failure
I50.814	Right heart failure due to left heart failure

Diagnosis Code	Description
I50.82	Biventricular heart failure
I50.83	High output heart failure
I50.84	End stage heart failure
I50.89	Other heart failure
I50.9	Heart failure, unspecified
N18.1	Chronic kidney disease, stage 1
N18.2	Chronic kidney disease, stage 2 (mild)
N18.30	Chronic kidney disease, stage 3 unspecified
N18.31	Chronic kidney disease, stage 3a
N18.32	Chronic kidney disease, stage 3b
N18.4	Chronic kidney disease, stage 4 (severe)
N18.5	Chronic kidney disease, stage 5

Background

The major causes of iron deficiency are decreased dietary intake, reduced iron absorption, and blood loss. In countries with abundant resources, such as the United States, the most common cause of iron deficiency is blood loss, either overt or occult bleeding. Iron replacement, either taken orally or parenterally, provides supplemental iron and thereby increasing iron and ferritin levels, increasing iron stores, and decreasing total iron binding capacity. Iron supplementation can usually result in higher hemoglobin and hematocrit values, and often can decrease the need for epoetin in patients with anemia and chronic kidney disease.

Clinical Evidence

Iron Deficiency Anemia

Ferric carboxymaltose, ferric derisomaltose, and ferumoxytol are indicated for the treatment of iron deficiency anemia in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron or who have chronic kidney disease (CKD).[1,2]

Technology Assessments

De Franceshi et al, published a systematic review on the advances in diagnosis and treatment in the clinical management of iron deficiency anemia in adults. The authors performed their systematic review using specific search strategy, carried out the review of PubMed database, Cochrane Database of systemic reviews and international guidelines on diagnosis and clinical management of ID from 2010 to 2016. International guidelines were limited to those with peer-review process and published in journal present in citation index database. The eligible studies show that serum ferritin and transferrin saturation are the key tests in early decision-making process to identify iron deficiency anemia (IDA). Of the over 7,000 titles screened, 195 articles were manually reviewed and 58 were selected as relevant to the analysis. For the treatment of IDA, the analysis observed the following outcomes:

- The choice on iron supplementation is based on Hgb levels, the tolerance to oral iron supplementation and the presence of concomitant disease, which might affect iron absorption.
- Intravenous iron administration is definitively more effective in correction of ID since it by-passes the iron absorption step. It offers advantages over oral iron such as:
  - Rapid repletion of iron stores

- Single dose sufficient for most of the new IV formulation with a reduction in hospital visits
- Follow-up schedule of iron-supplementation therapy is based on the evaluation of Hgb levels at 4weeks of treatment. Day 14 Hgb levels have been proposed in decision-making process to move patient from oral to IV administration in case of failure.
- In CKD, iron oral supplementation is recommended in patients with IDA not receiving ESAs and not on hemodialysis (HD).
- IV iron should be proposed to patients on ESAs treatment and/or on HD, based on the evidence that oral iron does not sufficiently support ESAs stimulated erythropoiesis.
- Iron supplementation should be always considered as part of clinical management of CHF patients.
- In iron restricted iron deficiency anemia (IRIDA) patients, oral iron administration usually does not solve the problem, whereas IV iron temporally ameliorates this condition. Ferritin levels could be reduced or normal after iron treatment.

Peyrin-Biroulet and colleagues performed a systematic review of guidelines on the diagnosis and treatment of iron deficiency across several indications. In this review 127 guidelines were identified in a search of PubMed, Cochrane, and EMBASE and in main professional society websites. Overall, 29 guidelines were selected that involved multiple professional societies internationally. A total of 22 and 27 guidelines provided recommendations on diagnosis and treatment of iron deficiency (ID), respectively. To define ID, all guidelines recommended a concentration for serum ferritin. One-half of them (10 of 22) proposed transferrin saturation (TSAT) as an alternative or complementary diagnostic test. To treat ID, most of the guidelines (18 of 27) recommended preferentially the oral route if possible, particularly in children and in women in the pre- or post-pregnancy period. Iron supplementation should be administered intravenously according to 13 of 27 guidelines, particularly in patients with chronic kidney disease (CKD) (n = 7) and chemotherapy-induced anemia (n = 5). Treatment targets for ID included an increase in hemoglobin concentrations to 10–12 g/dL or normalization (n = 8) and serum ferritin > 100 µg/L (n = 7) or 200 µg/L (n = 4). For the latter, in some situations, such as CKD, ferritin concentrations should not exceed 500 µg/L (n = 5) or 800 µg/L (n = 5). Only 9 guidelines recommended TSAT as a target, proposing various thresholds ranging from 20% to 50%. The authors conclude that for the diagnosis of ID, a cutoff of 100 µg/L for serum ferritin concentration should be considered in most conditions and 20% for TSAT, except in particular situations, including young healthy women with heavy menstrual flow. New indications of intravenous iron supplementation are emerging.

Professional Societies

In 2023, recommendations from the International Consensus Conference on Anemia Management in Surgical Patients were published.[36] A group of experts in patient blood management (PBM) selected a multidisciplinary panel to participate in the International Consensus Conference on Anemia Management in Surgical Patients (ICCAMS). The opinion of the panel was that the available data suggest that iron therapy as a treatment for preoperative anemia should be limited to patients with IDA. Consensus Statements were provided for Treatment of Preoperative Anemia and Preoperative Iron Therapy:

- The aim of treating preoperative anemia is to improve Hb concentration and this may decrease RBC transfusion.
- Therapy should be tailored to the etiology of anemia.
- Iron therapy should be administered as treatment for preoperative IDA, except when it is contraindicated.
- IV iron is preferable to oral iron in preoperative IDA.
- Preoperative oral iron therapy should be started as early as possible.
- Preoperative IV iron therapy should be started as early as possible.
- Administration of IV iron is generally well tolerated and does not increase the patient’s risk of infection.

In 2022, the American Heart Association (AHA), American College of Cardiology (ACC), and Heart Failure Society of America (HFSA) published their clinical practice guidelines for the management of heart failure.[28] Recommendations are provided for select patients with heart failure (HF) and iron deficiency and anemia. The guidelines state:

- Iron deficiency is usually defined as ferritin level <100 μg /L or 100 to 300 μg/L, if the transferrin saturation is <20%.
- Intravenous repletion of iron has been shown to improve exercise capacity and QOL.
- Oral iron is not adequate to treat iron deficiency anemia in patients with HF.

In 2021, the European Society of Cardiology (ESC) published their clinical practice guidelines for the diagnosis and treatment of acute and chronic heart failure.[35] In regard to the treatment of iron deficiency anemia in heart failure, the guidelines state:

- Iron supplementation with i.v. ferric carboxymaltose should be considered for the improvement of symptoms, exercise capacity, and QOL in patients with HF and LVEF <45%.
- Iron supplementation with i.v. ferric carboxymaltose should also be considered for the reduction of HF rehospitalizations in patients with LVEF <50% recently hospitalized for worsening HF.
- Oral iron therapy is not effective in iron repletion and did not improve exercise capacity in patients with HFrEF and iron deficiency and therefore is not recommended for the treatment of iron deficiency in patients with HF.

In 2018, the European Society for Medical Oncology (ESMO) published their clinical practice guidelines for the management of anemia and iron deficiency in patients with cancer. In regard to the diagnosis and treatment of iron deficiency anemia, the guidelines state:

- Patients receiving ongoing chemotherapy who present with anemia (Hgb ≤ 11 g/dL or Hgb decrease ≥ 2 g/dL from a baseline level ≤ 12 g/dL) and absolute iron deficiency (ID) (serum ferritin < 100 ng/mL) should receive iron treatment with an intravenous (IV) iron preparation to correct ID. If erythropoiesis-stimulating agent (ESA) treatment is considered, iron treatment should be given before the initiation of and/or during ESA therapy in the case of functional ID (TSAT < 20% and serum ferritin > 100 ng/mL).
- IV iron without additional anemia therapy may be considered in individual patients with functional ID (TSAT < 20% and serum ferritin > 100 ng/mL).
- Iron treatment should be limited to patients on chemotherapy. In patients receiving cardiotoxic chemotherapy, IV iron should either be given before or after (not on the same day) administration of chemotherapy or at the end of a treatment cycle.
- Patients with confirmed functional ID should receive a dose of 1000 mg iron given as single dose or multiple doses according to the label of available IV iron formulations. Patients with confirmed absolute ID should receive IV iron doses according to the approved labels of available products until correction of ID.

In 2015, the European Crohn's and Colitis Organization published European consensus guidelines for the diagnosis, treatment, and prevention of iron deficiency and iron deficiency anemia, as well as for non-iron deficiency anemia and associated conditions. In regard to iron deficiency anemia, the guidelines recommend:

- Diagnostic criteria for iron deficiency depend on the level of inflammation. In patients without clinical, endoscopic, or biochemical evidence of active disease, serum ferritin < 30 μg/L is an appropriate criterion. In the presence of inflammation, a serum ferritin up to 100 μg/L may still be consistent with iron deficiency.
- In the presence of biochemical or clinical evidence of inflammation, the diagnostic criteria for anemia of chronic disease (ACD) are a serum ferritin > 100 μg/L and TfS < 20%. If the serum ferritin level is between 30 and 100 μg/L, a combination of true iron deficiency and ACD is likely.
- Iron supplementation is recommended in all inflammatory bowel disease (IBD) patients when iron deficiency anemia (IDA) is present.
- The goal of iron supplementation is to normalize hemoglobin levels and iron stores.

- Intravenous iron should be considered as first line treatment in patients with clinically active IBD, with previous intolerance to oral iron, with hemoglobin below 10g/dL, and in patients who need erythropoiesis-stimulating agents (ESAs).
- Oral iron is effective in patients with IBD and may be used in patients with mild anemia, whose disease is clinically inactive, and who have not been previously intolerant to oral iron.
- No more than 100mg elemental iron per day is recommended in patients with IBD.
- Patients with IBD should be monitored for recurrent iron deficiency every 3 months for at least a year after correction, and between 6 and 12 months thereafter.
- After successful treatment of iron deficiency anemia with intravenous iron, re-treatment with intravenous iron should be initiated as soon as serum ferritin drops below 100 µg/L or hemoglobin below 12 or 13g/dL (according to gender).

In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for anemia in CKD was published. In regard to diagnosis and treatment, the guideline recommends:

- Diagnosis of anemia:
  - Diagnose anemia in adults and children > 15 years with CKD when the Hb concentration is < 13.0 g/dl (< 130 g/l) in males and < 12.0 g/dl (< 120 g/l) in females. (Not graded)
  - Diagnose anemia in children with CKD if Hb concentration is < 11.0 g/dl (< 110 g/l) in children 0.5–5 years, < 11.5 g/dl (115 g/l) in children 5–12 years, and < 12.0 g/dl (120 g/l) in children 12–15 years. (Not Graded)
- Investigation of anemia:
  - In patients with CKD and anemia (regardless of age and CKD stage), include the following tests in initial evaluation of the anemia (not graded):
    - Complete blood count (CBC), which should include Hb concentration, red cell indices, white blood cell count and differential, and platelet count
    - Absolute reticulocyte count
    - Serum ferritin level
    - Serum transferrin saturation (TSAT)
    - Serum vitamin B12 and folate levels
- Treatment with iron agents:
  - When prescribing iron therapy, balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the risks of harm in individual patients (e.g., anaphylactoid and other acute reactions, unknown long-term risks). (Not graded)
  - For adult CKD patients with anemia not on iron or ESA therapy we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (2C):
    - an increase in Hb concentration without starting ESA treatment is desired; and
    - TSAT is ≤ 30% and ferritin is ≤ 500 ng/ml (≤ 500 mg/l)
  - For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (2C):
    - an increase in Hb concentration or a decrease in ESA dose is desired; and
    - TSAT is ≤ 30% and ferritin is ≤ 500 ng/ml (≤ 500 mg/l)
  - For CKD ND patients who require iron supplementation, select the route of iron administration based on the severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or IV iron therapy, patient compliance, and cost. (Not graded)
  - Guide subsequent iron administration in CKD patients based on Hb responses to recent iron therapy, as well as ongoing blood losses, iron status tests (TSAT and ferritin), Hb concentration, ESA responsiveness and ESA dose in ESA treated patients, trends in each parameter, and the patient's clinical status. (Not graded)
  - For all pediatric CKD patients with anemia not on iron or ESA therapy, we recommend oral iron (or IV iron in CKD HD patients) administration when TSAT is ≤ 20% and ferritin is ≤ 100 ng/ml (≤ 100 lg/l). (1D)

- For all pediatric CKD patients on ESA therapy who are not receiving iron supplementation, we recommend oral iron (or IV iron in CKD HD patients) administration to maintain TSAT > 20% and ferritin > 100 ng/ml (> 100 lg/l). (1D)

- Iron status evaluation:
  - Evaluate iron status (TSAT and ferritin) at least every 3 months during ESA therapy, including the decision to start or continue iron therapy. (Not graded)
  - Test iron status (TSAT and ferritin) more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron, and in other circumstances where iron stores may become depleted. (Not graded)
- Cautions regarding iron therapy:
  - When the initial dose of IV iron dextran is administered, we recommend (1B) and when the initial dose of IV nondextran iron is administered, we suggest (2C) that patients be monitored for 60 minutes after the infusion, and that resuscitative facilities (including medications) and personnel trained to evaluate and treat serious adverse reactions be available.

In 2013, the American Academy of Pediatrics (AAP) published a clinical report for the diagnosis and prevention of Iron deficiency and Iron-Deficiency Anemia in Infants and Young Children (0-3 years of age). In regard to diagnosis, the AAP defines anemia as a hemoglobin (Hgb) concentration 2 standard deviations below the mean Hgb for a normal population of the same gender and age range, as defined by the World Health Organization, the United Nations Children's Fund, and the United Nations University. Additional screening tests for iron deficiency or iron deficiency anemia should include measurements of serum ferritin and CRP levels, or reticulocyte Hgb concentration (CHr).

In 2011, the British Society of Gastroenterology published their guidelines for the management of iron deficiency anemia. In regard to treatment, the guideline recommends:

- All patients should have iron supplementation both to correct anemia and replenish body stores (B).
- Parenteral iron can be used when oral preparations are not tolerated (C).
- Blood transfusions should be reserved for patients with or at risk of cardiovascular instability due to the degree of their anemia (C).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Feraheme (ferumoxytol) is an iron replacement product indicated for the treatment of iron deficiency anemia (IDA) in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron or who have chronic kidney disease (CKD).

Injectafer (ferric carboxymaltose) is an iron replacement product indicated for the treatment of IDA in adult and pediatric patients 1 year of age and older who have intolerance to oral iron or have had unsatisfactory response to oral iron; and adult patients who have non-dialysis dependent CKD. Injectafer is also indicated for the treatment of iron deficiency in adult patients with heart failure and New York Heart Association class II/III to improve exercise capacity.

Monoferric (ferric derisomaltose) is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron or who have non-hemodialysis dependent chronic kidney disease.

References

1. Feraheme [prescribing information]. Waltham, MA: AMAG Pharmaceuticals, Inc.; June 2022.
2. Injectafer [prescribing information]. Shirley, NY: American Regent, Inc.; May 2023.
3. KDIGO 2012 clinical practice guideline for evaluation and management of chronic kidney disease. Kidney International Supplements. January 2013; 3(1): 1-136.
4. KDIGO 2012 clinical practice guideline for anemia in chronic kidney disease. Kidney International Supplements. August 2012; 2(4): 279-331.
5. Camaschella C. Iron-Deficiency Anemia. N Engl J Med. 2015; 372: 1832-43.
6. Short MW, Domagalski JE. Iron Deficiency Anemia: Evaluation and Management. Am Fam Physician. 2013; 87(2): 98-104.
7. Macdougall IC, Bircher AJ, Eckardt KU, et al. Iron management in chronic kidney disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int. 2016 Jan;89(1):28-39.
8. Braunstein EM. Iron Deficiency Anemia. Porter RS, Ed. Merk Manual Merck & Co., Inc., Kenilworth, NJ. Accessed November 20, 2019.
9. Auerbach M. Causes and diagnosis of iron deficiency and iron deficiency anemia in adults. ~~Timauer~~ Tirnauer JS, ~~Kunins L~~Givens J, Eds. UptoDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com. Accessed ~~December 3, 2022~~November 30, 2023.
10. Auerbach M. Treatment of iron deficiency anemia in adults. TirnauerTimauer JS, Givens J~~Kunins L~~, Eds. UptoDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com. Accessed November 30, 2023~~December 3, 2022~~.
11. Bems JS. Diagnosis of iron deficiency in chronic kidney disease. ~~Motwani S~~Taylor EN, Ed. Waltham, MA: UpToDate Inc. https://www.uptodate.com. Accessed November 30, 2023~~December 3, 2022~~.
12. Breymann C, Honegger C, Hösli I, Surbek D. Diagnosis and Treatment of Iron-Deficiency Anaemia in Pregnancy and Postpartum. Arch Gynecol Obstet. December 2017; 296(6), 1229-1234; Dec 2017.
13. Peyrin-Biroulet L, Williet N, Cacoub P. Guidelines on the diagnosis and treatment of iron deficiency across indications: a systematic review. Am J Clin Nutr. 2015;102(6):1585–1594.
14. De Franceschi L, Iolascon A, Taher A, Cappellini MD. Clinical management of iron deficiency anemia in adults: Systemic review on advances in diagnosis and treatment. Eur J Intern Med. 2017;42:16–23.
15. Goddard AF, James MW, McIntyre AS, et al. Guidelines for the management of iron deficiency anaemia. Gut. October 2011. 60(10), 1309-16.
16. Dignass AU, Gasche C, Bettenworth D, et al. European Consensus on the Diagnosis and Management of Iron Deficiency and Anaemia in Inflammatory Bowel Diseases. J Crohns Colitis. March 2015; 9(3), 211-22.
17. Aapro M, Beguin Y, Bokemeyer C, et al. Management of anaemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2018;29(Suppl 4):iv96–iv110.
18. Dignass A, Farraq K, Stein J. Limitations of Serum Ferritin in Diagnosing Iron Deficiency in Inflammatory Conditions. Int J Chronic Dis. 2018 Mar 18; 2018:9394060.
19. Monoferric [prescribing information]. Morristown, NJ: Pharmacosmos A/S; February 2022.
20. Baker RD, Greer FR; Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). *Pediatrics*. 2010;126(5):1040-1050.
21. Brugnara C, Zurakowski D, DiCanzio J, Boyd T, Platt O. Reticulocyte hemoglobin content to diagnose iron deficiency in children. *JAMA*. 1999;281(23):2225-2230.

22. Fishbane S, Galgano C, Langley RC Jr, Canfield W, Maesaka JK. Reticulocyte hemoglobin content in the evaluation of iron status of hemodialysis patients. *Kidney Int.* 1997;52(1):217-222.

23. Ko CW, Siddique SM, Patel A, et al. AGA Clinical Practice Guidelines on the Gastrointestinal Evaluation of Iron Deficiency Anemia. *Gastroenterology*. 2020;159(3):1085-1094.

24. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. Anemia in Pregnancy: ACOG Practice Bulletin, Number 233. Obstet Gynecol. 2021;138(2):e55-e64.

25. Abdullah K, Birken CS, Maguire JL, et al. Re-Evaluation of Serum Ferritin Cut-Off Values for the Diagnosis of Iron Deficiency in Children Aged 12-36 Months. J Pediatr. 2017;188:287-290. doi:10.1016/j.jpeds.2017.03.028.

26. Mei Z, Addo OY, Jefferds ME, Sharma AJ, Flores-Ayala RC, Brittenham GM. Physiologically based serum ferritin thresholds for iron deficiency in children and non-pregnant women: a US National Health and Nutrition Examination Surveys (NHANES) serial cross-sectional study. Lancet Haematol. 2021;8(8):e572-e582. doi:10.1016/S2352-3026(21)00168-X.

27. WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations. Geneva: World Health Organization; 2020.

28. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in Circulation. 2022 May 3;145(18):e1033] [published correction appears in Circulation. 2022 Sep 27;146(13):e185] [published correction appears in Circulation. 2023 Apr 4;147(14):e674]. Circulation. 2022;145(18):e895-e1032. doi:10.1161/CIR.0000000000001063

29. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency.N Engl J Med. 2009; 361:2436–2448.

30. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiencydagger.Eur Heart J. 2015; 36:657–668.

31. Beck-da-Silva L, Piardi D, Soder S, et al. IRON-HF study: a randomized trial to assess the effects of iron in heart failure patients with anemia.Int J Cardiol. 2013; 168:3439–3442.

32. Anker SD, Kirwan BA, van Veldhuisen DJ, et al. Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis.Eur J Heart Fail. 2018; 20:125–133.

33. Kapoor M, Schleinitz MD, Gemignani A, et al. Outcomes of patients with chronic heart failure and iron deficiency treated with intravenous iron: a meta-analysis.Cardiovasc Hematol Disord Drug Targets. 2013; 13:35–44.

34. Ponikowski P, Kirwan BA, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial.Lancet. 2020; 396:1895–1904.

35. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [published correction appears in Eur Heart J. 2021 Oct 14;:]. Eur Heart J. 2021;42(36):3599-3726. doi:10.1093/eurheartj/ehab368

36. Shander A, Corwin HL, Meier J, et al. Recommendations From the International Consensus Conference on Anemia Management in Surgical Patients (ICCAMS). Ann Surg. 2023;277(4):581-590. doi:10.1097/SLA.0000000000005721

Policy History/Revision Information

Date	Summary of Changes
TBD	Annual review. Updated coverage criteria to add other gastrointestinal conditions that may lead to iron deficiency due to impaired absorption. Updated Clinical Evidence and references.

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Archived Policy Versions

Effective Date	Policy Number	Policy Title
12/01/2022 – 01/31/2023	CSLA2022D0088D	Intravenous Iron Replacement Therapy (Feraheme® & Injectafer®) (for Louisiana Only)
05/01/2022 – 11/30/2022	CSLA2022D0088C	Intravenous Iron Replacement Therapy (Feraheme® & Injectafer®) (for Louisiana Only)
02/01/2021 – 04/30/2022	CSLA2021D0088B	Intravenous Iron Replacement Therapy (Feraheme®, Injectafer®, & Monoferric®) (for Louisiana Only)
06/01/2020 – 01/31/2021	CSLA2020D0088A	Intravenous Iron Replacement Therapy (Feraheme® & Injectafer®) (for Louisiana Only)