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

Policy Number: IEXD0088.15
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Ü Instructions for Use

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Related Policies
None

Applicable States

This Medical Benefit Drug Policy applies to Individual Exchange benefit plans in all states except for Massachusetts, Nevada, and New York.

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)

***Monoferric is not medically necessary for the treatment of any diagnosis addressed within this policy.**
Published clinical evidence does not demonstrate superiority in the efficacy and safety of this product to other available intravenous iron replacement products.

Iron Deficiency Anemia (IDA) Without Chronic Kidney Disease (CKD)

Feraheme and Injectafer 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; **or**

- Patient has impaired absorption due to prior gastric surgery or disorder of the gastrointestinal tract (e.g., celiac disease, inflammatory bowel disease); **or**
- 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 to at least two of the following intravenous iron therapies (Note: Laboratory values should be obtained within 4 to 12 weeks following the last dose of intravenous iron in a treatment course):
      - Ferrlecit® (sodium ferric gluconate complex)
      - Infed® (iron dextran)
      - Venofer® (iron sucrose)

      and
    - Prescriber attests that the clinical response with Feraheme or Injectafer would be expected to be superior to the clinical response experienced with the preferred intravenous iron 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:
      - Ferrlecit® (sodium ferric gluconate complex)
      - Infed® (iron dextran)
      - Venofer® (iron sucrose)

      and
    - Prescriber attests that the same intolerance, contraindication, or severe adverse event experienced with the preferred intravenous iron products would not be expected to occur with Feraheme or Injectafer

  and
- Feraheme or Injectafer dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Initial authorization will be for no longer than 12 months

- For **continuation of therapy**, **all** of the following:
  - Coverage has previously been provided by UnitedHealthcare for Feraheme or Injectafer 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 to 12 weeks) since the last Feraheme or Injectafer administration to demonstrate need for additional therapy; **and**
  - Patient does **not** have CKD; **and**
  - Feraheme or Injectafer dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
  - Continuation authorization will be for no longer than 12 months

Iron Deficiency Anemia (IDA) Associated With Chronic Kidney Disease (CKD), Without End Stage Renal Disease (ESRD)

Feraheme and Injectafer 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 to **at least two** of the following intravenous iron therapies (Note: Laboratory values should be obtained within one to 4 to 12 weeks following the last dose of intravenous iron in a treatment course):
  - Ferrlecit® (sodium ferric gluconate complex)
  - Infed® (iron dextran)
  - Venofer® (iron sucrose)

  and
- Prescriber attests that the clinical response with Feraheme or Injectafer would be expected to be superior to the clinical response experienced with the preferred intravenous iron 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:
  - Ferrlecit® (sodium ferric gluconate complex)
  - Infed® (iron dextran)
  - Venofer® (iron sucrose)

  and
- Prescriber attests that the same intolerance, contraindication, or severe adverse event experience with the preferred intravenous iron products would not be expected to occur with Feraheme or Injectafer

and

o Feraheme or Injectafer dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**

o Initial authorization will be for no longer than 12 months

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

o Coverage has previously been provided by UnitedHealthcare for Feraheme or Injectafer 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

o Patient does not have ESRD; **and**

o Submission of recent laboratory results (within the past 4 to 12 weeks) since the last Feraheme or Injectafer administration to demonstrate need for additional therapy; **and**

o Feraheme or Injectafer dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**

o Continuation authorization will be for no longer than 12 months

Iron Deficiency Anemia (IDA) Associated With Chronic Kidney Disease (CKD), With End Stage Renal Disease (ESRD)

Feraheme is medically necessary when the following criteria are met:

- For **initial therapy**, **all** of the following:
  - o Diagnosis of Iron Deficiency Anemia (IDA) and Chronic Kidney Disease (CKD); **and**
  - o Submission of medical records (e.g., lab values, chart notes, etc.) supporting the diagnosis of IDA; **and**
  - o Patient has End Stage Renal Disease (ESRD); **and**
  - o Patient's CKD requires hemodialysis or peritoneal dialysis treatment; **and**
  - o **One** of the following:
    - § **Both** of the following:
      - Submission of laboratory values demonstrating treatment failure to **both** of the following intravenous iron therapies (Note: Laboratory values should be obtained within 4 to 12 weeks following the last dose of intravenous iron in a treatment course):
        - Ferrlecit® (sodium ferric gluconate complex)
        - Venofer® (iron sucrose)

        and
      - Prescriber attests that the clinical response with Feraheme would be expected to be superior to the clinical response experienced with the preferred intravenous iron products

      or

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

- Venofer® (iron sucrose)

and

- Prescriber attests that the same intolerance, contraindication, or severe adverse event experience with the preferred intravenous iron products would not be expected to occur with Feraheme

and

- Feraheme dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Feraheme dose does not exceed 510 mg elemental iron per dose and 2.04 g elemental iron per course; **and**
- Initial authorization will be for no longer than 12 months

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

    and
  - Patient has ESRD; **and**
  - Submission of recent laboratory results (within the past 4 to 12 weeks) since the last Feraheme administration to demonstrate need for additional therapy; **and**
  - Feraheme or Injectafer dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
  - Continuation authorization will be for no longer than 12 months

Iron Deficiency With Heart Failure

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 to at least two of the following intravenous iron therapies (**Note**: Laboratory values should be obtained within 4 to 12 weeks following the last dose of intravenous iron in a treatment course):
        - Ferrlecit® (sodium ferric gluconate complex)
        - Infed® (iron dextran)
        - Venofer® (iron sucrose)

        and
      - Prescriber attests that the clinical response with Injectafer would be expected to be superior to the clinical response experienced with the preferred intravenous iron 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:
        - Ferrlecit® (sodium ferric gluconate complex)
        - Infed® (iron dextran)
        - Venofer® (iron sucrose)

        and

- Prescriber attests that the same intolerance, contraindication, or severe adverse event experienced with the preferred intravenous iron products would not be expected to occur with Injectafer

and

- Injectafer dosing is in accordance with the United States Food and Drug Administration approved labeling for iron deficiency in heart failure; **and**
- Initial authorization will be for no longer than 12 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 to 12 weeks) since the last Injectafer administration to demonstrate need for additional therapy; **and**
  - Injectafer dosing is in accordance with the United States Food and Drug Administration approved labeling for iron deficiency in heart failure; **and**
  - Continuation authorization will be for no longer than 12 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
  - **Pediatric Patients < 12 years**: Hemoglobin concentration below the cutoffs to define anemia in children and adolescents (Table 1) and one of the following:
    - Serum ferritin ≤ 15 ug/L
    - Reticulocyte hemoglobin content (CHr) or reticulocyte hemoglobin equivalent (RET-He) supports a diagnosis of IDA

Table 1: Hemoglobin Cutoffs to Define Anemia in Children and Adolescents**

Population	Hemoglobin concentration (g/dL)
Children, 6–59 months	11.0
Children, 5–11 years	11.5

**Hemoglobin assessments for patients less than 6 months of age are not necessary due to a lack of data to support precise cutoffs for this population

- **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

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 the member specific benefit plan document 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, 10mg
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 (ESRD on dialysis)

Diagnosis Code	Description
D50.0	Iron deficiency anemia secondary to blood loss (chronic)

Diagnosis Code	Description
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
I13.11	Hypertensive heart and chronic kidney disease without heart failure, with stage 5 chronic kidney disease, or end stage renal disease
I13.2	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease
I20.0	Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal 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
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
N18.6	End stage renal disease

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).

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 iron deficiency (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 four weeks 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 erythropoiesis-stimulating agents (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 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, the European Society of Cardiology (ESC) published a focused updated of their 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Based on trials and recent meta-analysis, the following new recommendations were given in regard to iron deficiency and/or iron supplementation in patients with heart failure:

- Intravenous iron supplementation is recommended in symptomatic patients with heart failure with reduced ejection fraction (HFrEF) and heart failure with mildly reduced ejection fraction (HFmrEF), and iron deficiency, to alleviate HF symptoms and improve quality of life.
- Intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose should be considered in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to reduce the risk of HF hospitalization.

In 2023, recommendations from the International Consensus Conference on Anemia Management in Surgical Patients were published. 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. 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. 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 its 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 1,000 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. With 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 100 mg elemental iron per day is recommended in patients with IBD.
- Patients with IBD should be monitored for recurrent iron deficiency every three months for at least a year after correction, and between six 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.
With 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 one-to-three-month trial of oral iron therapy) if (2C):
    - An increase in Hb concentration without starting ESA treatment is desired.
    - 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 one-to-three-month trial of oral iron therapy) if (2C):
    - An increase in Hb concentration or a decrease in ESA dose is desired.
    - 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 three 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 non-dextran 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 C-reactive protein (CRP) levels, or reticulocyte Hgb concentration (CHr).

In 2011, the British Society of Gastroenterology published its guidelines for the management of iron deficiency anemia. With 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.

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Policy History/Revision Information

Date	Summary of Changes
03/01/2025	**Coverage Rationale** • Removed specific dosage requirements for the use of Feraheme (ferumoxytol) and Injectafer (ferric carboxymaltose); refer to the applicable U.S. FDA approved labeling • Revised coverage criteria: ***Initial Therapy*** o Replaced criterion requiring: § "Submission of laboratory values demonstrating treatment failure *after at least 3 weeks of therapy*, to at least two of the [listed] intravenous iron therapies *each* (laboratory values should be obtained within ***1*** to ***3*** weeks following the last dose of intravenous iron in a treatment course)" with "submission of laboratory values demonstrating treatment failure to at least two of the [listed] intravenous iron therapies (laboratory values should be obtained within ***4*** to ***12*** weeks following the last dose of intravenous iron in a treatment course)" § "*Physician* attests that *in their clinical opinion*, the clinical response would be expected to be superior with Feraheme or Injectafer than experienced with the other products" with "*prescriber* attests that the clinical response with Feraheme or Injectafer would be expected to be superior *to the clinical response* experienced with *the preferred intravenous iron products*"

Date	Summary of Changes
	§ "*Physician* attests *that in their clinical opinion*, the same intolerance, contraindication, or severe adverse event would not be expected to occur with Feraheme or Injectafer than experienced with the other [listed] products" with "prescriber attests that the same intolerance, contraindication, or severe adverse event experienced with the *preferred intravenous iron products* would not be expected to occur with Feraheme or Injectafer" ***Continuation of Therapy*** o Replaced criterion requiring "submission of recent laboratory results (within the past 4 weeks) since the last Feraheme or Injectafer administration to demonstrate need for additional therapy" with "submission of recent laboratory results (within the past 4 *to* ***12*** weeks) since the last Feraheme or Injectafer administration to demonstrate need for additional therapy" **Definitions** • Updated definition of "Iron Deficiency Anemia (IDA) Without Chronic Kidney Disease (CKD) or Acute or Chronic Inflammatory Conditions" **Supporting Information** • Updated *References* section to reflect the most current information • Archived previous policy version IEXD0088.14

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. 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.

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