INTRAVENOUS IRON REPLACEMENT THERAPY (FERAHEME & INJECTAFER)

Policy Number: CS2020D0088A **Effective Date: TBD**

Instructions for Use

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Commercial Policy

- **Intravenous Iron Replacement Therapy (Feraheme & Injectafer)**

COVERAGE RATIONALE

This policy refers to the following intravenous iron replacements:
- **Feraheme® (ferumoxytol)**
- **Injectafer® (ferric carboxymaltose)**

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) and Injectafer (ferric carboxymaltose) are proven for the following indications:

- **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**
    - **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 or 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 Feraheme or Injectafer, 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;**

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

- **For continuation therapy, all of the following:**
  - **Coverage has previously been provided by UnitedHealthcare for Feraheme or Injectafer for the treatment of IDA; and**
  - **Submission of recent laboratory results (within the past 4 weeks) since the last Feraheme or Injectafer 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;**

    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 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**
    - **If CKD does not require hemodialysis or peritoneal dialysis - 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 or 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 Feraheme or Injectafer, 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;**

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

- **For continuation therapy, all of the following:**
  - **Coverage has previously been provided by UnitedHealthcare for Feraheme or Injectafer for the treatment of IDA with CKD; and**
  - **Patient does not have ESRD; and**
  - **Submission of recent laboratory results (within the past 4 weeks) since the last Feraheme or Injectafer 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;**

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

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 Coverage Determination Guidelines may apply.

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

ICD-10 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
N18.1	Chronic kidney disease, stage 1
N18.2	Chronic kidney disease, stage 2 (mild)

ICD-10 Diagnosis Code	Description
N18.3	Chronic kidney disease, stage 3 (moderate)
N18.4	Chronic kidney disease, stage 4 (severe)
N18.5	Chronic kidney disease, stage 5
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

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 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 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 regards 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 regards 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 2011, the British Society of Gastroenterology published their guidelines for the management of iron deficiency anemia. In regards 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 patients who have intolerance to oral iron or have had unsatisfactory response to oral iron or who have non-dialysis dependent CKD.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for Feraheme® (ferumoxytol) or for Injectafer® (ferric carboxymaltose). Local Coverage Determinations (LCDs) do exist; refer to the LCDs for Chemotherapy and Biologicals.

In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals.
(Accessed November 13, 2019)

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
TBD	• New Medical Benefit Drug Policy

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 MCG™ Care Guidelines, 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.