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

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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)

*Medical Necessity Plans

Monoferic is not medically necessary for the treatment of any diagnosis addressed within this policy (for Medicare reviews, refer to the CMS section**).

Published clinical evidence does not demonstrate superiority in the efficacy and safety of this product to other available intravenous iron replacement products.

Feraheme (ferumoxytol), Injectafer (ferric carboxymaltose), and Monoferic (ferric derisomaltose) 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
Intravenous Iron Replacement Therapy (Feraheme™, Injectafer™, & Monoferric™)

Patient does not have CKD; and
- History of failure, contraindication, or intolerance, to oral iron therapy; and
- One of the following: (For Medicare reviews, refer to the CMS section.* )
  - 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)
    - 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
  - 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)
    - 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
- One of the following:
  - Feraheme dose does not exceed 510 mg elemental iron per dose and 2.04g elemental iron per course; or
  - Injectafer dose does not exceed 750 mg elemental iron per dose and 1500mg elemental iron per course

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 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; or
  - Injectafer dose does not exceed 750 mg elemental iron per dose and 1500mg elemental iron per course

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
  - 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
  - One of the following: (for Medicare reviews, refer to the CMS section** )
    - 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; or
    - 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 of 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; or
  - 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.

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: Serum ferritin <30 ng/mL or transferrin saturation (TSAT) <20% or an absence of stainable iron in bone marrow. \(^3,4,7,11,18\)
- 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 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.
### 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.

### Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.
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 Franceschi 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

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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 mg/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 mg/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 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 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.

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.
Centers for Medicare and Medicaid Services (CMS)

Medicare does not have a National Coverage Determination (NCD) for Feraheme® (Ferumoxytol), Injectafer® (ferric carboxymaltose), or Monoferric® (ferric derisomaltose). Local Coverage Articles (LCAs) exist; refer to the LCAs for Parenteral Iron Administration Coverage in Non-Dialysis Usage.

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 October 30, 2020)

*Preferred therapy criteria is not applicable for Medicare Advantage members.

References

Policy History/Revision Information

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<tr>
<th>Date</th>
<th>Summary of Changes</th>
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<tr>
<td>07/01/2021</td>
<td>Template Update</td>
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<tr>
<td></td>
<td>Replaced reference to “MCG™ Care Guidelines” with “InterQual® criteria” in Instructions for Use</td>
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<tr>
<td></td>
<td>Coverage Rationale</td>
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<td>Added language to indicate 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</td>
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<tr>
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<td>Removed language indicating Monoferric is medically necessary for the treatment of:</td>
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<td>o Iron Deficiency Anemia (IDA) Without Chronic Kidney Disease (CKD)</td>
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<td>o Iron Deficiency Anemia (IDA) Associated With Chronic Kidney Disease (CKD), Without End Stage Renal Disease (ESRD)</td>
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<td>Revised medical necessity criteria; removed criterion requiring:</td>
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<td>o Physician attests that in their clinical opinion, the clinical response would be expected to be superior with Monoferric than experienced with the other products</td>
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<td>Removed language pertaining to Monoferric dosing requirements</td>
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Supporting Information

- Archived previous policy version 2021D0088E

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard 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 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.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. 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.