Medical Policy

BlueCross BlueShield Kansas
An Independent licensee of the
Blue Cross Blue Shield Association

Title: Intravenous Iron Replacement Therapy

Professional / Institutional
Original Effective Date: June 20, 2022
Latest Review Date: August 8, 2023
Current Effective Date: June 20, 2022

DESCRIPTION

Iron replacement provides supplemental iron to treat iron deficiency. Iron replacement, either taken orally or parenterally, increases iron and ferritin levels, increases iron stores, and decreases total iron binding capacity. Iron supplementation usually results in higher hemoglobin and hematocrit values and can often decrease the need for epoetin in patients with anemia and chronic kidney disease. Parental iron therapy is indicated for some patients who fail oral iron.

OBJECTIVE

The objective of this medical policy is to determine whether the use of targeted intravenous iron replacement improves the net health outcome in patients with iron deficiency anemia, compared with other available iron therapy.

BACKGROUND

Iron deficiency anemia

Iron deficiency anemia is diminished red blood cell production due to low iron stores in the body. It is the most common nutritional disorder worldwide and accounts for approximately one-half of anemia cases. The diagnosis of iron deficiency anemia is confirmed by the findings of low iron stores and a hemoglobin level two standard deviations below normal for age and sex. Patients should be screened during pregnancy, and children screened at one year of age. Supplemental iron may be given initially, followed by further workup if the patient is not responsive to therapy. The underlying cause should be treated, and oral iron therapy can be initiated to replenish iron stores. Parenteral therapy may be used in patients who cannot tolerate or absorb oral preparations.

The Food and Drug Administration (FDA) has approved numerous intravenous iron replacement therapies. This policy addresses only selected intravenous replacements, sometimes known as novel therapeutic agents, including ferumoxytol (Feraheme®), ferric carboxymaltose (Injectafer®), and ferric derisomaltose (Monoferric®) for use in non-dialysis settings only.

Ferumoxytol (Feraheme®)

Ferumoxytol (Feraheme®) is an iron replacement product containing ferumoxytol for intravenous infusion. Ferumoxytol is a superparamagnetic iron oxide coated with polyglucose sorbitol carboxymethylether. Feraheme® has been FDA approved for patients who have:

- Intolerance to oral iron or have had unsatisfactory response to oral iron, or
- Chronic kidney disease.

Ferric carboxymaltose (Injectafer®)

Ferric carboxymaltose (Injectafer®) is a colloidal iron (III) hydroxide in complex with carboxymaltose, a carbohydrate polymer that releases iron. The drug is administered by intravenous push or by infusion. Injectafer® has been FDA approved 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
- Non-dialysis dependent chronic kidney disease.

Ferric derisomaltose (Monoferric®)

Ferric derisomaltose (Monoferric®) is an iron carbohydrate oligosaccharide that releases iron. The drug is administered by intravenous infusion. Monoferric® has been FDA approved 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
- Non-dialysis dependent chronic kidney disease.

REGULATORY STATUS

Intravenous iron replacement therapy is associated with serious and sometimes fatal hypersensitivity reactions including anaphylaxis. The FDA requires the prescribing information for ferumoxytol (Feraheme®) to include a black box warning. Other significant safety concerns associated with these drugs include hypotension, hypertension, hypophosphatemia and iron overload. Additionally, ferumoxytol (Feraheme®) may transiently affect the diagnostic ability of magnetic resonance imaging.

POLICY

This policy does NOT address intravenous iron replacement therapy for use in patients with chronic kidney disease (CKD)

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

TARGET AGENT(S)
Feraheme® (ferumoxytol)
Injectafer® (ferric carboxymaltose)
Monoferric (ferric derisomaltose)

A. **Target Agent(s)** maybe considered **medically necessary** when **ALL** of the following are met:
   1. The patient has **ONE** of the following:
      a. A diagnosis of iron deficiency anemia **AND ALL** of the following:
         I. **ONE** of the following:
            i. Serum ferritin <30 ng/mL
               OR
            ii. Transferrin saturation (TSAT) <20%
               OR
            iii. Absence of stainable iron in bone marrow
               AND
         II. **ONE** of the following:
            i. The patient has tried and had an inadequate response to oral iron therapy, documented by laboratory values 1 to 3 weeks following the last dose, used for at least 3 months
               OR
            ii. The patient has an intolerance to oral iron therapy that persists despite documented attempts to improve tolerance
               OR
            iii. The patient has a hypersensitivity to oral iron therapy
               OR
            iv. The patient has an FDA labeled contraindication to oral iron therapy
               OR
            v. Information has been provided supporting the use of the requested agent over oral iron therapy (medical records required)
            OR
      b. Co-existing condition that would prevent absorption of oral iron therapy

         AND

2. **ONE** of the following:
   a. The patient's age is within FDA labeling for the requested indication for the requested agent
      OR
   b. The prescriber has provided information in support of using the requested agent for the patient's age

      AND

3. **ONE** of the following:
   a. The patient has tried and had an inadequate response to **ALL** of the following:
      I. Ferrlecit (sodium ferric gluconate complex in sucrose)
         AND
      II. INFeD (iron dextran)
         AND
      III. Venofer (iron sucrose)
      OR
   b. The patient has an intolerance or hypersensitivity to Ferrlecit (sodium ferric gluconate complex in sucrose), INFeD (iron dextran) AND Venofer (iron sucrose) that is not expected to occur with the requested agent
      OR
   c. The patient has an FDA labeled contraindication to Ferrlecit (sodium ferric gluconate complex in sucrose), INFeD (iron dextran) AND Venofer (iron sucrose) that is not expected to occur with the requested agent

      AND

4. The patient does NOT have any FDA labeled contraindications to the requested agent

      AND

5. The requested quantity (dose) is within FDA labeled dosing or supported in compendia for the requested indication

B. Uses of ferumoxytol (Feraheme®) for iron deficiency anemia in patients not requiring dialysis are considered **Not Medically Necessary** when the above conditions area not met.

C. Uses of ferric carboxymaltose (Injectafer®) or ferric derisomaltose (Monoferric®) are considered **Not Medically Necessary** when the above conditions area not met.

D. All other uses of the target agents are considered **Experimental/ Investigational**.

CRITERIA FOR RENEWAL

A. Use of ferumoxytol, ferric carboxymaltose, or ferric derisomaltose may be considered **Medically Necessary** for retreatment in adult patients when **ALL** of the following criteria are met:
   1. Previously approved for the requested agent through the initial review process; **AND**
   2. Demonstrated positive clinical response to the requested agent (e.g., increased hemoglobin level); **AND**
   3. Recent laboratory results (within the past 4 weeks) since last administration of the requested agent demonstrating a need for additional therapy; **AND**
   4. No FDA labeled contraindications to the requested agent; **AND**
   5. Requested dose is within the FDA labeled dose for the indication

POLICY GUIDELINES

A. **Length of Approval**: 30 days/1 treatment cycle
B. **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	Indication(s)	Dosage
Feraheme® (ferumoxytol) Injection for intravenous use	Treatment of iron deficiency anemia (IDA) in adult patients who: • Have intolerance to oral iron or have had unsatisfactory response to oral iron • Have chronic kidney disease (CKD)	The recommended dose of Feraheme is an initial 510 mg IV followed by a second 510 mg dose IV 3 to 8 days later
Injectafer® (ferric carboxymaltose) Injection for intravenous use	Treatment of iron deficiency anemia in adult patients who: • Have intolerance to oral iron or have had unsatisfactory response to oral iron • Have non-dialysis dependent chronic kidney disease	**Patients weighing less than 50 kg:** Give Injectafer in two doses of 15mg/kg of body weight at least 7 days apart for a cumulative dose not to exceed 1500 mg of iron pe course **Patients weighing 50 kg or more:** Give Injectafer in two doses of 750 mg at least 7 days apart cumulative dose not to exceed 1500 mg iron per course

Agent(s)	Indication(s)	Dosage
Monoferric (ferric derisomaltose) Injection for intravenous use	Treatment of iron deficiency anemia in adult patients who: • Have intolerance to oral iron or have had unsatisfactory response to oral iron • Have non-hemodialysis dependent chronic kidney disease	**Patients weighing less than 50 kg:** 20 mg/kg actual body weight by IV infusion over at least 20 minutes as a single dose. Repeat dose if iron deficiency anemia reoccurs **Patients weighing 50 kg or more:** 1,000 mg by IV infusion over at least 20 minutes as a single dose. Repeat dose if iron deficiency anemia reoccurs

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

Iron deficiency anemia

The evaluation for iron deficiency anemia should begin with a thorough history and physical examination to help identify the cause of iron deficiency. The history should focus on potential etiologies and may include questions about diet, GI symptoms, history of pica or pagophagia, signs of blood loss, surgical history, and family history of GI malignancy.

Oral iron therapy should be used after iron deficiency anemia is diagnosed and underlying cause of iron deficiency anemia treatment (if applicable) is started. An increase in hemoglobin of 1 g/dL after one month of treatment shows an adequate response to treatment and confirms the diagnosis. In adults, therapy should be continued for three months after the anemia is corrected to allow iron stores to become replenished. Adherence to oral iron therapy can be a barrier to treatment because of GI adverse effects such as epigastric discomfort, nausea, diarrhea, and constipation. These effects may be reduced when iron is taken with meals, but absorption may decrease by 40%. Medications such as proton pump inhibitors and factors that induce gastric acid hyposecretion (e.g., chronic atrophic gastritis, recent gastrectomy, or vagotomy) as re-associated with reduced absorption of dietary iron and iron tablets.

Parenteral iron therapy may be used in patients who cannot tolerate or absorb oral preparations (e.g., patients who have undergone gastrectomy, gastrojejunostomy, bariatric surgery, or other small bowel surgeries). The most common indications for intravenous therapy include GI effects, worsening symptoms of inflammatory bowel disease, unresolved bleeding, renal failure, induced anemia treated with erythropoietin, and insufficient absorption in patients with celiac disease.

Safety

Feraheme contains a black box warning for risk of serious hypersensitivity/anaphylaxis reactions. Hypersensitivity reactions have occurred in patients in whom a previous Feraheme dose was tolerated.

- Feraheme (ferumoxytol) is contraindicated in patient with:
    - Known hypersensitivity to Feraheme or any of its components
    - History of allergic reaction to any intravenous iron product
- Injectafer (ferric carboxymaltose) is contraindicated in patients with:
    - Known hypersensitivity to Injectafer or any of its inactive components
- Monoferric (ferric derisomaltose) is contraindicated in patients with:
    - Serious hypersensitivity to Monoferric or any of its components

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
Q0138	Injection, Ferumoxytol, for treatment of iron deficiency anemia, 1 mg (non-esrd use)
J1439	Injection, Ferric Carboxymaltose, 1 mg
J1437	Injection, Ferric Derisomaltose, 10 mg

REVISIONS	
06-20-2022	Policy added to the bcbsks.com web site.
08-08-2023	Updated Coding Section ▪ Removed ICD-10 Diagnoses box

REFERENCES

1. Feraheme Prescribing Information. AMAG Pharmaceuticals, Inc. September 2020.
2. Injectafer Prescribing Information. American Regent, Inc. September 2020.
3. Monoferric Prescribing Information. Pharmacosmos A/S. September 2020.
4. Short MW, Domagalski JE. Iron deficiency Anemia: Evaluation and Management. Am Fam Physician. 2013 Jan 15;87(2):98-104.