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Coverage Policy Number **IP0222**

Intravenous Iron Replacement Therapy

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Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for the following Intravenous Iron Replacement Therapies:

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

Coverage varies across plans and requires the use of preferred products in addition to the criteria listed below. Refer to the customer's benefit plan document for coverage details.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Initial Therapy Criteria

Intravenous iron replacement therapies (Feraheme, ferumoxytol, Injectafer, Monoferric) are considered medically necessary for iron deficiency when the individual meets ALL of the following criteria:

1. Documentation of **ONE** of the following (A or B):
   A. Iron deficiency
   B. Prior history of iron deficiency with current downward trend in iron stores and known source of blood loss
2. Documentation of **ONE** of the following (A or B):
   A. Failure or intolerance to oral iron therapy
   B. **ONE** of the following: (i, ii, iii, iv, v, vi, vii, viii or ix)
      i. Chronic kidney disease
      ii. Cancer-associated or chemotherapy-associated iron deficiency
      iii. Currently receiving an erythroid stimulating agent
      iv. Gastric bypass surgery and/or subtotal gastric resection where absorption of oral iron may be impaired
      v. Inflammatory bowel disease or other gastrointestinal disorder that would be aggravated by oral iron
      vi. New York Heart Association (NYHA) functional class II or III heart failure
      vii. Rapid loss of iron (blood) where oral iron cannot compensate for the loss
      viii. Scheduled for major abdominal surgery
      ix. Third trimester of pregnancy
3. Where preferred products required, refer to the table below:

Non-Preferred Product	Criteria
Feraheme (ferumoxytol) **Ferumoxytol**	Documentation of **ONE** of the following (1, 2 or 3): 1. Failure, contraindication or intolerance to Venofer (iron sucrose) 2. Chronic Kidney Disease and is on Dialysis 3. Initiated a course of Feraheme/ferumoxytol and requires further medication to complete the current course of therapy
Injectafer (ferric carboxymaltose)	Documentation of **ONE** of the following (1, 2, 3 or 4): 1. Failure, contraindication or intolerance to Venofer (iron sucrose) 2. Less than 2 years of age 3. Chronic Kidney Disease and is on Dialysis 4. Initiated a course of Injectafer and requires further medication to complete the current course of therapy
Monoferric (ferric derisomaltose)	Documentation of **ONE** of the following (1, 2 or 3): 1. Failure, contraindication or intolerance to Venofer (iron sucrose) 2. Chronic Kidney Disease and is on Dialysis 3. Initiated a course of Monoferric and requires further medication to complete the current course of therapy

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Continuation of Therapy Criteria

Intravenous Iron Replacement Therapy is considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration is up 12 months.

Reauthorization approval duration is up to 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven.

Coding

This list of codes may not be all-inclusive.

Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

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

Background

OVERVIEW
All iron replacement products are used for the treatment of **iron deficiency anemia**.[1-4] Feraheme, Injectafer, Monoferric, and Venofer are indicated in patients with **chronic kidney disease** (CKD). Some are noted to be used in certain types of CKD as follows: Injectafer and Monoferric in patients who have non-dialysis dependent CKD; Venofer in patients with hemodialysis-dependent CKD, non-dialysis dependent CKD, and peritoneal dialysis-dependent CKD. All of these agents are administered intravenously. Injectafer and Feraheme are recommended to be given only as two doses; the other products generally have lower doses of iron given multiple times over longer periods of time. Feraheme is only recommended to be given as an intravenous infusion over at least 15 minutes. Venofer has recommended dosing for selected indications in patients aged ≥ 2 years.

FDA-Approved Indications of the Injectable Iron Replacement Products.[1-4]

	Indications	Description/ Mechanism of Action
Feraheme® (ferumoxytol injection)	Treatment of **IDA in adults** who have: • **Intolerance to oral iron or have had unsatisfactory response to oral iron** • **CKD**	Feraheme is a **superparamagnetic iron oxide that is coated with a carbohydrate shell**, which helps to isolate the bioactive iron from plasma components until the iron-carbohydrate complex enters the reticuloendothelial system.

	Indications	Description/ Mechanism of Action
Injectafer® (ferric carboxymaltose injection)	Treatment of **IDA in adults patients** who have: • **Intolerance to oral iron or have had unsatisfactory response to oral iron** • **NDD-CKD**	**Ferric carboxymaltose is a colloidal iron (III) hydroxide in complex with carboxymaltose**, a carbohydrate polymer that releases iron.
Monoferric® (ferric derisomaltose injection)	Treatment of **IDA in patients ≥ 18 years of age** who have: • **Intolerance to oral iron or have had unsatisfactory response to oral iron** • **NDD-CKD**	A complex of **iron (III) hydroxide and derisomaltose**, an iron carbohydrate oligosaccharide that releases iron. Iron binds to transferrin for transport to erythroid precursor cells to be incorporated into hemoglobin.
Venofer® (iron sucrose injection)	Treatment of **IDA in patients with CKD**. Dosing information is provided regarding the following patient populations: • **Adults with HDD-CKD** • **Adults with NDD- CKD** • **Adults with PDD-CKD** • **Pediatric patients (≥ 2 years of age) with HDD-CKD** for iron maintenance treatment • **Pediatric patients (≥ 2 years of age) with NDD-CKD or PDD-CKD** who are on erythropoietin therapy for iron maintenance treatment.	The agent is an aqueous complex of **poly-nuclear iron (III)-hydroxide in sucrose**. When given intravenously, the agent is dissociated into iron and sucrose and the iron is transported as a complex with transferrin to target cells.

IDA – Iron deficiency anemia; CKD – Chronic kidney disease; NDD-CKD – Non-dialysis dependent chronic kidney disease; HDD-CKD – Hemodialysis dependent chronic kidney disease; PDD-CKD – Peritoneal dialysis dependent chronic kidney disease.

Administration of the Injectable Iron Replacement Products. [1-4]

	Dosing/Administration	How Supplied
Feraheme® (ferumoxytol injection)	The recommended dose is an **initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later. Administer as an IV infusion over at least 15 minutes**. For patients receiving hemodialysis, administered once stable after completion of at least 1 hour of hemodialysis. Allow at least 30 minutes between administration of Feraheme and administration of other medications (e.g., chemotherapy) that could potentially cause serious hypersensitivity reactions and/or hypotension.	Single-dose vials: • 510 mg/17 mL
Injectafer® (ferric carboxymaltose injection)	Administered by slow IV push (100 mg [2 mL] per minute) or via IV infusion over at least 15 minutes. Two doses are given separated by 7 days. **A total cumulative dose not to exceed 1,500 mg of iron per course**. • Patients weighing ≥ 50 kg, dose is 750 mg • Patients weighing < 50 kg, dose is 15 mg/kg	Single-dose vials: • 750 mg/15 mL
Monoferric® (ferric derisomaltose injection)	Administered by **IV infusion over at least 20 minutes as a single dose**. Repeat dose if IDA reoccurs. • Patients weighing ≥ 50 kg, dose is 1,000 mg • Patients weighing < 50 kg, dose is 20 mg/kg of actual body weight	Single-dose vials: • 100 mg/mL • 500 mg/5 mL • 1,000 mg/10 mL
Venofer® (iron sucrose injection)	• **Adults with HDD-CKD:** Give 100 mg undiluted as a slow IV injection over 2 to 5 minutes or as an infusion of 100 mg over at least 15 minutes per consecutive hemodialysis session. Give	Single-dose vials: • 50 mg/2.5 mL • 100 mg/5 mL

	Dosing/Administration	How Supplied
	early during the dialysis session (generally within the first hour). The usual total treatment course is 1,000 mg. • **Adults with NDD-CKD:** Administer 200 mg undiluted as a slow IV injection over 2 to 5 minutes or as a 200 mg infusion over 15 minutes. Administer on five different occasions over a 14-day period. There is some experience with giving 500 mg over 3.5 to 4 hours on Day 1 and Day 14. • **Adults with PDD-CKD:** Give in three divided doses by slow IV infusion within a 28-day period: two 300 mg infusions over 1.5 hours 14 days apart, then one 400 mg infusion over 2.5 hours 14 days later. • **Pediatric patients (≥ 2 years of age) with HDD-CKD for iron maintenance:** 0.5 mg/kg, not to exceed 100 mg per dose, once every two weeks for 12 weeks undiluted by slow IV injection over 5 minutes or as an infusion over 5 to 60 minutes. • **Pediatric patients (≥ 2 years of age) with NDD-CKD or PDD-CKD who are on erythropoietin for iron maintenance:** 0.5 mg/kg (not to exceed 100 mg per dose) once every 4 weeks for 12 weeks by slow IV injection over 5 minutes or as an infusion over 5 to 60 minutes.	• 200 mg/10 mL

IV – Intravenous; HDD-CKD – Hemodialysis dependent chronic kidney disease; IM – Intramuscular; * Total doses have been given as a single dose; IDA – Iron deficiency anemia; NDD-CKD – Non-dialysis dependent chronic kidney disease; PDD-CKD – Peritoneal dialysis dependent chronic kidney disease.

Guidelines

Iron Deficiency Anemia (IDA)

IDA is a very broad diagnosis and can have many different etiologies; underlying causes should be corrected when appropriate.[5] No definitive guidelines exist, but initial treatment consists of dietary supplementation with iron-rich foods. Oral iron preparations (e.g., ferrous sulfate, ferrous gluconate, ferrous fumarate) are usually the next step and lead to adequate treatment for many patients. Response to oral iron therapy is generally first noted after 2 weeks of therapy. However, oral iron therapies can be poorly tolerated, mainly due to GI AEs (e.g., constipation, nausea, vomiting). Also, absorption may be impaired when given with food (depending upon the formulation) and drug-drug interactions must also be considered. It should be noted that as the dose increases, the absorption of the iron decreases. Patients can have impaired absorption due to medical conditions. Blood transfusions are an option but are usually reserved in hemodynamic compromise.

Anemia in Chronic Kidney Disease (CKD)

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[6] Iron supplementation is widely utilized in patients with CKD to treat iron deficiency, to prevent the development of iron deficiency in patients receiving ESAs, to elevate Hb levels in patients receiving ESA therapy, and to reduce ESA doses. For adults with CKD and anemia not on iron or ESA therapy, a trial of IV iron (or in NDD-CKD, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration without starting ESA treatment is desired and TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. For adults with CKD on ESA therapy who are not receiving iron supplementation, a trial of IV iron (or in NDD-CKD patients, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. For NDD-CKD, the route of iron administration should be based on various factors such as the severity of iron deficiency, availability of venous access, response to prior oral therapy, and tolerance of previous oral or parenteral iron therapy. For all pediatric patients with CKD with anemia not on iron or ESA therapy, oral iron (or IV iron in patients receiving hemodialysis) is recommended when TSAT is ≤ 20% and ferritin is ≤ 100 ng/mL. For all

pediatric patients with CKD who are receiving ESA therapy but not receiving iron supplementation, it is recommended to administer oral iron (or IV iron for patients receiving hemodialysis) to maintain TSAT > 20% and ferritin > 100 ng/mL.

The KDIGO guidelines recognize that the evidence to support specific recommendations is limited, with few available randomized, controlled trials.[6] Iron intervention trials have not been sufficiently powered or of adequate duration to assess long-term safety or clinical benefit. There is some evidence supporting the preference of the IV route of iron administration for patients with CKD who are on dialysis. IV iron therapy may be given as a single large dose or as repeated smaller doses depending on the specific IV iron preparation. Iron given via intramuscular injection is not routinely used. It is common practice to provide an initial course of IV iron amounting to approximately 1,000 mg, which may be repeated if the initial dose does not provide adequate results. Repeated small doses are also utilized. Regarding IV iron preparations, certain iron dextrans have been associated with reactions characteristic of anaphylaxis. The rate of these reactions is estimated to occur in approximately 0.6% to 0.7% of patients treated. This rate may be lower in low molecular weight iron dextran compared with high molecular weight iron dextran. Non-dextran IV iron products are less often associated with anaphylactic and other severe AEs.

Heart Failure (HF)

A 2017 focused update of the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure discusses that in patients with New York Heart Association class II and III HF and IDA (ferritin < 100 ng/mL, or 100 to 300 ng/mL if TSAT is < 20%), IV iron replacement may be reasonable to improve functional status and quality of life.[7] Supportive trials and meta-analyses were cited (CONFIRM-HF, FAIR-HF [both involving Injectafer]).[8-10] Benefits noted with IV iron therapies included improvement in functional capacity, improvements in the six-minute walk test, and improved functional capacity.

References

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