09-J2000-10

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Subject: Injectable Iron Therapy [Ferric carboxymaltose (Injectafer®), Ferric Derisomaltose (Monoferric®), Ferric Pyrophosphate Citrate (Triferic AVNU®)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Iron deficiency anemia (IDA) is the most common cause of anemia worldwide and is most often due to blood loss or chronic dietary insufficiency; it may be diagnosed when iron deficiency is accompanied by anemia. Anemia may be a relatively nonspecific finding and further testing is necessary to establish the specific etiology of iron deficiency. Tests to further identify the cause as iron deficiency include serum iron, total iron binding capacity (TIBC), ferritin, serum transferrin receptor, and transferrin saturation. Low serum iron in the presence of elevated total iron-binding capacity and low serum ferritin is considered diagnostic for iron deficiency. A ferritin level of 15 mcg/L or less is a marker of depleted or absent iron stores, and confirms iron deficiency anemia in the presence of low hemoglobin.

Current treatment options for IDA include oral iron (as ferrous sulfate) and a number of injectable iron products, including sodium ferric gluconate (Ferrlecit), iron sucrose (Venofer), iron dextran (INFeD, Dexferrum), ferumoxytol (Feraheme), ferric derisomaltose (Monoferric) and ferric carboxymaltose (Injectafer). Ferric pyrophosphate citrate (Triferic AVNU) is an iron replacement product indicated for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease.

Ferric carboxymaltose (Injectafer) was approved by the U.S. Food and Drug Administration (FDA) in 2013 as a parenteral iron replacement product for the treatment of IDA. The safety and effectiveness of ferric carboxymaltose were evaluated in a randomized, open-label clinical trial of patients with iron deficiency anemia (hemoglobin < 12 g/dL, ferritin < 100 ng/mL) with an unsatisfactory response (n=495) or

intolerance (n=482) to oral iron. All participants received 14 days of oral iron. Participants who had an unsatisfactory response to oral iron were randomized to receive ferric carboxymaltose IV (n=244) 15 mg/kg every 7 days for two doses or oral iron (n=251) for 14 days. Participants who were intolerant to oral iron were randomized to either ferric carboxymaltose IV (n=245) 15 mg/kg every 7 days for two doses or to another IV iron product (n=237; 90% received iron sucrose). Changes in hemoglobin levels from baseline to the highest value between baseline and day 35 were significantly greater with ferric carboxymaltose than with comparator in both cohorts (Table 1).

Table 1

Mean Change (SD) in Hemoglobin Levels From Baseline (Modified Intent-to-Treat Population)				
	Unresponsive to Oral Iron		**Intolerant of Oral Iron**	
	Injectafer (n=244)	**Oral Iron (n=251)**	**Injectafer (n=245)**	**IV Iron (n=237)**
Baseline hemoglobin (SD)	10.6 (1)	10.6 (1)	9.1 (1.6)	9 (1.5)
Highest hemoglobin (SD)	12.2 (1.1)	11.4 (1.2)	12 (1.2)	11.2 (1.3)
Change from baseline to highest value (SD)*	1.6 (1.2)	0.8 (0.8)	2.9 (1.6)	2.2 (1.3)
* p=0.001 for comparisons of change from baseline to highest value in both groups				

Ferric carboxymaltose may cause hypertension (3.8% of patients treated with the agent in clinical trials) and serious hypersensitivity reactions, including anaphylaxis. Overestimation of serum or transferrin-bound iron may occur on laboratory assays for 24 hours post-administration.

POSITION STATEMENT:

NOTE: Iron dextran (INFeD, Dexferrum), iron sucrose (Venofer), and sodium ferric gluconate complex (Ferrlecit) do not require prior authorization.

Initiation and continuation of injectable iron therapy meets the definition of **medical necessity** when **ALL** of the following criteria are met:

1. Indication for use is one of the following:
    a. Iron deficiency anemia – ferric carboxymaltose (Injectafer), ferric derisomaltose (Monoferric) **ONLY**
    b. Replacement of iron to maintain hemoglobin – ferric pyrophosphate citrate (Triferic AVNU) **ONLY**
2. Diagnosis is confirmed by either of the following:
    a. For IDA associated with CKD or inflammatory conditions (for example, inflammatory bowel disease [IBD], heart failure), member meets one of the following – documentation of laboratory results within the last four weeks must be submitted:
        i. Serum ferritin levels less than 100 ng/mL
        ii. TSAT levels less than 20%

iii. Serum ferritin is less than or equal to 500 ng/mL and TSAT is less than or equal to 30%

b. For IDA associated with cancer/chemotherapy or non-inflammatory conditions (for example, blood loss, malabsorption, malnutrition), member meets one of the following – documentation of laboratory results within the last four weeks must be submitted:

i. Serum ferritin levels less than 30 ng/mL

ii. TSAT levels less than 20%

3. Member meets one of the following:

a. Member has tried and failed (as evidenced by laboratory values) a three week trial of one of the following – laboratory documentation must be submitted:

i. Iron dextran (INFeD, Dexferrum)

ii. Iron sucrose (Venofer)

iii. Sodium ferric gluconate complex (Ferrlecit)

b. Member has a contraindication or intolerance to ALL of the following products and the specific contraindication or intolerance is documented in the medical record:

i. Iron dextran (INFeD, Dexferrum)

ii. Iron sucrose (Venofer)

iii. Sodium ferric gluconate complex (Ferrlecit)

4. Member meets product specific criteria outlined in Table 1

Table 1

Product	Brand	Criteria
Ferric carboxymaltose	*Injectafer*	Initiation **meets the definition of medical necessity** when **ALL** criteria are met: 1. Indication for use is iron deficiency anemia 2. Member meets **ONE** of the following: a. Member is diagnosed with chronic kidney disease and is not dependent on dialysis b. Member has tried and failed four week trial of oral iron therapy c. Member has a contraindication or intolerance to treatment with oral iron 3. Dose does not exceed 750 mg every 7 days (maximum 2 doses per treatment course) **Approval duration**: 6 months

		Continuation **meets the definition of medical necessity** when **ALL** of the following criteria are met: 1. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for treatment of iron deficiency anemia or other FDA-approved diagnosis, **OR** the member has previously met all indication-specific initiation criteria 2. Dose does not exceed 750 mg every 7 days (maximum 2 doses per treatment course) **Approval duration**: 6 months
Ferric Derisomaltose	*Monoferric*	Initiation **meets the definition of medical necessity** when **ALL** criteria are met: 1. Indication for use is iron deficiency anemia 2. Member meets **ONE** of the following: a. Member is diagnosed with chronic kidney disease and is not dependent on dialysis b. Member has tried and failed four week trial of oral iron therapy c. Member has a contraindication or intolerance to treatment with oral iron 3. Dose does not exceed 1000 mg (maximum 2 doses per treatment course) **Approval duration**: 6 months Continuation **meets the definition of medical necessity** when **ALL** of the following criteria are met: 1. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for treatment of iron deficiency anemia or other FDA-approved diagnosis, **OR** the member has previously met all indication-specific initiation criteria 2. Dose does not exceed 1000 mg (maximum 2 doses per treatment course) **Approval duration**: 6 months

Ferric pyrophosphate citrate	*Triferic AVNU*	Initiation and continuation **meets the definition of medical necessity** when **ALL** criteria are met: 1. Indication for use is replacement of iron to maintain hemoglobin 2. Member has hemodialysis-dependent chronic kidney disease 3. Dose will be administered at member's hemodialysis procedure **Approval duration**: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING IT'S USAGE.

FDA-approved

Injectafer

- Weight 50 kg (110 lb) or more: 750 mg IV every 7 days x 2 doses (total dose 1500 mg per course)
- Weight less than 50 kg (110 lb): 15 mg/kg IV every 7 days x 2 doses
- Treatment may be repeated if iron deficiency anemia reoccurs.

Monoferric

- Weight 50 kg (110 lb) or more: 1000 mg IV
- Weight less than 50 kg (110 lb): 20 mg/kg IV
- Treatment may be repeated if iron deficiency anemia reoccurs.

Triferic AVNU

- 6.75 mg iron (III) undiluted as a slow continuous intravenous infusion over 3 to 4 hours via the pre-dialyzer infusion line, post-dialyzer infusion line, or via a separate connection to the venous blood line during hemodialysis
- Administer at each dialysis procedure for as long as patients are receiving maintenance hemodialysis therapy for CKD

Dose Adjustments

- None

Drug Availability

Injectafer

- 750 mg iron/15 mL single-use vial

Monoferric

- 1,000 mg iron /10 mL (100 mg/mL) single-dose vial
- 500 mg iron/5 mL (100 mg/mL) single-dose vial
- 100 mg iron/mL single-dose vial

Triferic AVNU

- 6.75 mg iron (III) per 4.5 mL solution (1.5 mg iron (III) per mL) in single-dose luer lock ampule

PRECAUTIONS:

Boxed Warning

Injectafer

- None

Monoferric

- None

Triferic AVNU

- None

Contraindications

- Hypersensitivity

Precautions/Warnings

- Hypersensitivity: Monitor during and after administration for at least 30 minutes
- Hypertension

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding:

J1437	Injection, ferric derisomaltose, 10 mg
J1439	Injection, ferric carboxymaltose, 1 mg
J1445	Injection, ferric pyrophosphate citrate solution (triferic avnu), 0.1 mg of iron

ICD-10 Diagnosis Codes That Support Medical Necessity:

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
D63.0	Anemia in neoplastic disease
D63.1	Anemia in chronic kidney disease
D63.8	Anemia in other chronic diseases classified elsewhere
D64.81	Antineoplastic chemotherapy-induced anemia

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

DEFINITIONS:

Chronic Renal Failure (CRF): the Glomerular Filtration Rate (GFR) is less than 20 to 25% of normal. The kidneys cannot regulate volume and solute composition and patients develop edema, metabolic acidosis and hypocalcemia.

Erythroid: pertaining to any of the cells in the developmental series ending in erythrocytes.

Erythropoietin: a protein naturally made in the kidneys, which acts on the bone marrow to stimulate the body's production of red blood cells.

ESRD: end-stage renal disease (kidney failure).

Hematocrit: a method for determining the volume of packed red blood cells in a blood specimen.

Hemoglobin: a method for measuring the oxygen carrying capacity of the red blood cells.

Renal failure: kidney failure, often requiring dialysis.

RELATED GUIDELINES:

Erythropoiesis Stimulating Agents (09-J0000-31)

OTHER:

None

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 05/08/24.

GUIDELINE UPDATE INFORMATION:

03/15/14	New Medical Coverage Guideline.
07/01/14	Quarterly coding update.
01/01/15	Revision to guideline; consisting of annual HCPCS coding update.
05/15/15	Revision to guideline; updated references.
11/01/15	Revision: ICD-9 Codes deleted.
03/15/19	Revised position statement
12/15/19	Revision to guidelines; addition of continuation criteria to position statement
01/15/20	Revised postion statement
03/15/20	Revised postion statement and coding
06/15/20	Revised postion statement and coding to include Monoferric and Triferic AVNU
10/01/20	Revision: Added HCPCS code J1437 (for Monoferric)
10/01/21	Revision: Added HCPCS code J1445 (for Triferic AVNU) and removed code J3490.
01/01/22	Revised position statement and coding to include Feraheme
03/15/23	Revised position statement to remove Feraheme.
06/15/24	Revised position statement to update lab requirements for IDA.