STATE OF IOWA DEPARTMENT OF
Health AND Human
SERVICES

Injectafer (ferric carboxymaltose)
PAM-049

Iowa Medicaid Program:	Prior Authorization	**Effective Date:**	10/01/2022
Revision Number:	2	**Last Rev Date:**	01/19/2024
Reviewed By:	Medicaid Medical Director	**Next Rev Date:**	01/17/2025
Approved By:	Medicaid Clinical Advisory Committee	**Approved Date:**	01/20/2023

Overview

Medication:[1]	ferric carboxymaltose
Brand Name:	Injectafer®
Pharmacologic Category:	Iron preparations
FDA-Approved Indication(s):	Iron replacement product indicated for the treatment of: 1. Iron deficiency anemia (IDA) in: • Adults and pediatric patients 1 year of age and older who have either intolerance to oral iron or an unsatisfactory response to oral iron. • Adult patients who have non-dialysis dependent chronic kidney disease. 2. Iron deficiency in adult patients with heart failure and New York Heart Association class II/III to improve exercise capacity. ➢ New indication (FDA-approved 5/31/2023)
How Supplied:	Injection: 50 mg/mL in a single-dose vial. Three available vial sizes: • 100 mg iron/2 mL • 750 mg iron/15 mL • 1,000 mg iron/20 mL
Dosage and Administration:	1. Iron Deficiency Anemia • Administer via intravenous infusion. • Patient weight ≥ 50 kg: 750 mg in 2 doses separated by at least 7 days for a total cumulative dose of 1,500 mg of iron per course. For adult patients weighing 50 kg or more, an alternative dose of 15 mg/kg up to a maximum of 1,000 mg may be administered intravenously as a single-dose treatment course. • Patient weight < 50 kg: 15 mg/kg in 2 doses separated by at least 7 days per course. 2. Iron Deficiency with Heart Failure

	Weight less than 70 kg			Weight 70 kg or more		
	Hemoglobin (Hb), g/dL			Hemoglobin (Hb), g/dL		
	< 10	10 to 14	> 14 to > 15	< 10	10 to 14	> 14 to > 15
Day 1	1,000 mg	1,000 mg	500 mg	1,000 mg	1,000 mg	500 mg
Week 6	500 mg	No dose	No dose	1,000 mg	500 mg	No dose

- Administer a maintenance dose of 500 mg at 12, 24 and 36 weeks if serum ferritin < 100 ng/mL or serum ferritin 100 – 300 ng/mL with transferrin saturation < 20 %. There are no data available to guide dosing beyond 36 weeks or with Hb > 15 g/dL.
- Administer Injectafer intravenously, either as an undiluted slow intravenous push or by infusion.

Benefit Category:	Medical

Abbreviations

- CKD – chronic kidney disease
- CV – cardiovascular
- EPO – erythropoietin
- ESA – erythropoiesis-stimulating agents
- HgB – hemoglobin
- IDA – iron deficiency anemia
- MCHC – mean corpuscular HgB concentration
- MCV – mean corpuscular volume
- RBC – red blood cell
- TIBC – total iron binding capacity
- TSAT – transferrin saturation
- WHO – World Health Organization

Descriptive Narrative

Iron deficiency affects greater than 12 percent of the world's population, especially women, children, and individuals living in under-resourced and middle-income countries. In men and postmenopausal women, the most frequent cause is chronic occult bleeding, usually from the gastrointestinal tract. In premenopausal women, cumulative menstrual blood loss is a common cause. While blood loss is the most common cause, iron deficiency may also be due to hemolysis, malabsorption, or increased demand for iron (e.g., in pregnancy, lactation, or periods of rapid growth in children).

The usual presenting symptoms in adults with iron deficiency are primarily due to anemia. Individuals may have mild to severe symptoms, ranging from fatigue, shortness of breath, and chest pain to heart failure and developmental delays in children.[2]

The development of iron deficiency occurs in progressive stages. In the first stage, iron requirement exceeds intake, causing progressive depletion of bone marrow iron stores. As stores decrease, absorption of dietary iron increases in compensation. During later stages, deficiency impairs red blood cell (RBC) synthesis, ultimately causing anemia. Severe and prolonged iron deficiency may also cause dysfunction of iron-containing cellular enzymes.[3]

Anemia is a complication that affects a majority of individuals with advanced chronic kidney disease (CKD). The prevalence of anemia increases across the advancing stages of CKD, with estimates anywhere from 7 percent to over 50 percent in the more advanced stages of the disease. Multiple mechanisms contribute to the development of anemia in CKD, the most important being relative deficiency of erythropoietin (EPO). As such, erythropoiesis-stimulating agents (ESAs) have been considered a staple for the management of anemia in patients with CKD. Several well conducted studies in patients with CKD indicate that use of ESAs to normalize Hgb in patients with CKD may worsen cardiovascular (CV) outcomes. Thus, the current guidelines advise a target Hgb below the definition of normal in patients with CKD.

Many patients with anemia and CKD suffer from iron-deficiency anemia (IDA). This is due to both scarcity of iron stores (absolute iron deficiency) and inefficient utilization of iron stores (functional iron deficiency). Underlying chronic inflammation contributes to the functional iron deficiency. Repletion of iron stores is often necessary in patients with CKD for the treatment of IDA and to maximize the efficacy of ESAs.[4]

Limitation of exercise capacity is one of the cardinal manifestations of heart failure, varying directly with the severity of the disease. Symptoms of anemia such as dyspnea and fatigue may be difficult to distinguish from symptoms of heart failure. In patients with heart failure, oxygen

delivery may be impaired due to reduced cardiac output, and thus symptoms may arise at higher hemoglobin levels in patients with anemia and heart failure.[5] The CONFIRM-HF trial evaluated the efficacy and safety of Injectafer® in adults with chronic heart failure and iron deficiency. In the study, results showed that treatment with Injectafer® significantly improved exercise capacity compared with placebo in iron-deficient patients with heart failure.[6]

Laboratory findings in iron deficiency [7,8]

- Serum iron may be low in anemia of chronic disease or increased by a recent meal or normal diurnal variation and by itself cannot be used to diagnose iron deficiency.
- Serum ferritin may be increased by other conditions such as acute inflammation, liver disease, and idiopathic pulmonary hemosiderosis.
- Transferrin saturation (TSAT) is the ratio of serum iron to total iron binding capacity (TIBC). If there is concern that oral iron intake has affected the serum iron level, using a fasting sample may be helpful.
- Bone marrow iron stain (the gold standard) and erythrocyte zinc protoporphyrin (a nonspecific finding) are not routinely used in the evaluation or diagnosis of iron deficiency.

The development of iron deficiency occurs in progressive stages. RED font illustrates the progression of changes and the tests most likely to define the various stages of iron deficiency. Decreased serum ferritin and absent bone marrow iron are the earliest changes, followed by decreases in transferrin saturation (TSAT).

	Normal	Iron deficiency without anemia	Iron deficiency with mild anemia	Iron deficiency with severe anemia
Hemoglobin	Normal range*	Normal range*	9-12 g/dL (90-120 g/L)	6-7 g/dL (60-70 g/L)
Red blood cell size and appearance	Normal	Normal	Normal or slight hypochromia (slight decrease in MCHC)	Microcytosis (decrease in MCV) and hypochromia (decrease in MCHC)
Serum ferritin	40-200 ng/mL (40-200 mcg/L)	<40 ng/mL (<40 mcg/L)	<20 ng/mL (<20 mcg/L)	<10 ng/mL (<20 mcg/L)
Serum iron	60-150 mcg/dL (10.7-26.7 microM/L)	60-150 mcg/dL (10.7-26.7 microM/L)	<60 mcg/dL (<10.7 microM/L)	<40 mcg/dL (<7.1 microM/L)
Total iron-binding capacity (TIBC; transferrin)	300-360 mcg/dL (53.7-64.4 microM/L)	300-390 mcg/dL (53.7-69.8 microM/L)	350-400 mcg/dL (62.6-71.6 microM/L)	>410 mcg/dL (>73.4 microM/L)
Transferrin saturation (serum iron/TIBC)	20 to 50%	20%	<15%	<10%
Reticulocyte hemoglobin	30.6-35.4 pg	22.3-34.7 pg	14.8-34.0 pg	Data not available
Bone marrow iron stain	Adequate iron present	Iron absent	Iron absent	Iron absent
Erythrocyte zinc protoporphyrin	30-70 ng/mL RBC	30-70 ng/mL RBC	100-200 ng/mL RBC	100-200 ng/mL RBC

* Normal ranges for hemoglobin (g/dL)	lower limit	upper limit
Adult male	14.0	17.5
Adult female	12.3	15.3
Pediatric (6 months to < 2 years)	11.0 ‡	13.5
Pediatric (2 to 6 years)	11.0 ‡	13.7
Pediatric (6 to 12 years)	11.2	14.5
Adolescent male (12 to < 18 years)	12.4	16.4
Adolescent female (12 to < 18 years)	11.4	14.7

‡ The lower limit of normal for HgB (i.e., 2.5th percentile) at these ages is slightly less than 11 g/dL. However, for the purposes of screening for iron deficiency anemia in infants and young children, many experts use a cutoff of HgB <11 g/dL to define an abnormal screen.

Guidelines

Guidelines regarding iron deficiency anemia have been developed by multiple organizations.

- World Health Organization (WHO) guideline on use of ferritin concentrations to assess iron status in individuals and populations (2020)[9]
- Patient Blood Management: Recommendations From the 2018 Frankfurt Consensus Conference[10]
- Kidney Disease – Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Anemia in Chronic Kidney Disease (2012)[11]
    - KDIGO is in the process of creating an update to this guideline.

Criteria

Prior authorization is required.

Iron deficiency anemia in adults and pediatric patients 1 year of age

Injectafer® is considered medically necessary when **ALL** of the following are met:

1. Diagnosis of iron deficiency anemia (IDA); **AND**
2. Diagnosis is confirmed by any of the following within the past month:
    a. Serum ferritin < 15 ng/mL (or 30 ng/mL if pregnant); or
    b. Serum ferritin ≤ 41 ng/mL **AND** hemoglobin (HgB) is either < 12 g/dL (women) or < 13 g/dL (men); or
    c. Transferrin saturation (TSAT) < 20 percent; or
    d. Absence of stainable iron in bone marrow; **AND**
3. Documentation that member has had an inadequate response, or tolerance to, oral iron supplementation [Δ] after a minimum four (4) week trial; **AND**
4. Member is 1 year of age or older; **AND**
5. Dose meets **ONE** of the following (a, b, or c, depending on member age and weight):
    a. Member weight < 50 kg and dose does not exceed 15 mg/kg in 2 doses separated by at least 7 days (2 dose treatment course); **OR**
    b. Member weight ≥ 50 kg and dose is 750 mg in 2 doses separated by at least 7 days (2 dose treatment course); **OR**
    c. Member is an adult weighing 50 kg or more and dose is 15 mg/kg (up to a maximum of 1,000 mg) given as a single-dose treatment course.

[Δ] *Oral iron therapy may not be considered optimal if any of the following exist:*

- Transferrin saturation (TSAT) < 12 %
- Hemoglobin (HgB) < 7 g/dL
- Symptomatic anemia
- Oral iron intolerance
- Severe or ongoing blood loss
- Unable to achieve therapeutic targets with oral iron
- Co-existing condition that may be refractory to oral iron therapy

Iron deficiency anemia in adults with non-dialysis dependent chronic kidney disease (CKD)

Injectafer® is considered medically necessary when **ALL** of the following are met:

1. Diagnosis of iron deficiency anemia (IDA); **AND**
2. IDA diagnosis is confirmed by any of the following within the past month:
    a. Serum ferritin < 100 ng/mL; **OR**
    b. Transferrin saturation (TSAT) < 20 percent; **OR**
    c. Serum ferritin ≤ 500 ng/mL when TSAT ≤ 30 percent; **AND**
3. Member has chronically impaired renal function, but is not dependent on dialysis; **AND**
4. Documentation that member has had an inadequate response, or tolerance to, oral iron supplementation [Δ] after a minimum four (4) week trial; **AND**
5. Member is 18 years of age or older; **AND**
6. Dose meets **ONE** of the following (a or b, depending on member weight):
    a. Member weight < 50 kg and dose does not exceed 15 mg/kg in 2 doses separated by at least 7 days; **OR**
    b. Member weight ≥ 50 kg and dose is either 750 mg in 2 doses (separated by at least 7 days), **OR** 15 mg/kg (maximum 1,000 mg) given as a single-dose treatment course.

[Δ] *Oral iron therapy may not be considered optimal if any of the following exist:*

- Transferrin saturation (TSAT) < 12 %
- Hemoglobin (HgB) < 7 g/dL
- Symptomatic anemia
- Oral iron intolerance
- Severe or ongoing blood loss
- Unable to achieve therapeutic targets with oral iron
- Co-existing condition that may be refractory to oral iron therapy

Iron deficiency in adults with heart failure and NYHA II/III to improve exercise capacity

Injectafer® is considered medically necessary when **ALL** of the following are met:

1. Diagnosis of iron deficiency confirmed by one of the following (a or b):
    a. Serum ferritin levels less than 100 µg/L; or
    b. Transferrin saturation (TSAT) levels < 20 percent and ferritin level 100–300 µg/L; **AND**
2. Diagnosis of chronic heart failure (HF) and member meets ALL of the following:
    a. HF is classified as New York Heart Association (NYHA) class II or class III; **AND**
    b. Left ventricular ejection fraction (LVEF) is less than 45 percent; **AND**
    c. Hemoglobin (Hb) is less than 15 g/dL; **AND**
3. Member is 18 years of age or older; **AND**
4. Member is using to improve exercise capacity; **AND**
5. Dose does not exceed 1,000 mg per infusion/injection.

Continuation Criteria

Injectafer® is considered medically necessary for continuation of therapy if:

1. Diagnosis of **Iron Deficiency Anemia** and both of the following are met:
    a. Documentation of lab results and chart notes supporting additional need due to continued low hemoglobin levels; **AND**
    b. Member has not experienced intolerable adverse effects or drug toxicity; **AND**
    c. Request meets one of the following (i or ii):
        i. Regimen prescribed does not exceed FDA-approved dosing; or
        ii. Regimen is supported by clinical practice guidelines. Supporting clinical documentation must be provided with any request for which regimen prescribed does not align with FDA-approved labeling;

OR

2. Diagnosis of **Iron Deficiency with Heart Failure** and all of the following are met:
    a. Documentation of lab results and chart notes supporting additional need due to:
        i. Continued hemoglobin less than 15 g/dL AND ferritin less than 100 ng/mL; OR
        ii. Ferritin less than or equal to 300 ng/mL when transferrin saturation (TSAT) is less than 20 percent; **AND**
    b. Member has not experienced intolerable adverse effects or drug toxicity; **AND**
    c. Dose does not exceed 1,000 mg per infusion/injection; **AND**
    d. Continuation will be for no longer than 6 months (no data available to guide dosing beyond 36 weeks for iron deficiency with heart failure).

Approval Duration and Quantity Limits

<table>
<tr><th colspan="5">IRON DEFICIENCY ANEMIA</th></tr>
<tr><td>Age</td><td>Member Weight</td><td>Approval Duration</td><td># of Doses per Course</td><td>Dosage Limits</td></tr>
<tr><td rowspan="2">Pediatrics (ages 1-17)</td><td>< 50 kg</td><td>3 months (up to one treatment course)</td><td>2</td><td>• 15 mg/kg per dose
• 2 doses separated by at least 7 days</td></tr>
<tr><td>≥ 50 kg</td><td>3 months (up to one treatment course)</td><td>2</td><td>• 750 mg per dose
• 2 doses separated by at least 7 days</td></tr>
<tr><td rowspan="4">Adults (ages 18+)</td><td>< 50 kg</td><td>3 months (up to one treatment course)</td><td>2</td><td>• 15 mg/kg per dose
• 2 doses separated by at least 7 days</td></tr>
<tr><td rowspan="3">≥ 50 kg</td><td rowspan="3">3 months (up to one treatment course)</td><td>2</td><td>• 750 mg per dose
• 2 doses separated by at least 7 days</td></tr>
<tr><td colspan="2">OR</td></tr>
<tr><td>1</td><td>• 15 mg/kg (max 1,000 mg) as one-time dose</td></tr>
<tr><td colspan="5">Continuation Duration (all ages): 3 months</td></tr>
</table>

IRON DEFICIENCY IN ADULTS WITH HEART FAILURE AND NYHA II/III		
	Initial Authorization	Continuation Authorization
Quantity Limits	Maximum 1,000 mg per dose	3 months
Approval Duration	Maximum 1,000 mg per dose	Not to exceed a total of 6 months of treatment

Coding and Product Information

The following list(s) of codes and product information are provided for reference purposes only and may not be all inclusive. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment, nor does the exclusion of a code imply that its association to the HCPCS code is inappropriate.

HCPCS	Description
J1439	Injection, ferric carboxymaltose, 1 mg

ICD-10	Description
D50.0 – D50.9	Iron deficiency anemia
D63.0 – D63.8	Anemia in chronic diseases classified elsewhere
I50 – I50.9	Heart failure
N18.1 – N18.5	Chronic kidney disease, stages 1 - V

NDC	Strength	Labeler	Dosage	Pkg Size	Pkg Qty	Units/Pkg
00517-0602-01	100 mg/2 mL	American Regent, Inc.	1 mg	1	EA	100
00517-0650-01	750 mg/15 mL	American Regent, Inc.	1 mg	1	EA	750
00517-0620-01	1,000 mg/20 mL	American Regent, Inc.	1 mg	1	EA	1,000

Compliance

1. Should conflict exist between this policy and applicable statute, the applicable statute shall supersede.
2. Federal and State law, as well as contract language, including definitions and specific contract provisions or exclusions, take precedence over medical policy and must be considered first in determining eligibility for coverage.
3. Medical technology is constantly evolving, and Iowa Medicaid reserves the right to review and update medical policy on an annual or as-needed basis.

Medical necessity guidelines have been developed for determining coverage for member benefits and are published to provide a better understanding of the basis upon which coverage decisions are made. Medical necessity guidelines are developed for selected physician-administered medications found to be safe and proven to be effective in a limited, defined population or clinical circumstances. They include concise clinical coverage criteria based on current literature review, consultation with practicing physicians in the service area who are medical experts in the particular field, FDA and other government agency policies, and standards adopted by national accreditation organizations. Criteria are revised and updated annually, or more frequently if new evidence becomes available that suggests needed revisions.

References

[1] Injectafer prescribing information (05/2023). American Regent, Inc.: Shirley, NY. Available online at injectaferhcp.com. Accessed December 17, 2023.

[2] Iron-Deficiency Anemia. National Heart, Lung, and Blood Institute (NHLBI). 2022. Available online at www.nhlbi.nih.gov/health/anemia/iron-deficiency-anemia. Accessed January 7, 2023.

[3] Braunstein EM. Iron Deficiency Anemia (Anemia of Chronic Blood Loss; Chlorosis). Merck Manual, Professional Version. Available online at www.merckmanuals.com/professional/hematology-and-oncology/anemias-caused-by-deficient-erythropoiesis/iron-deficiency-anemia. Accessed January 6, 2023.

[4] Batchelor EK, Kapitsinou P, et al. Iron Deficiency in Chronic Kidney Disease: Updates on Pathophysiology, Diagnosis, and Treatment. J Am Soc Nephrol. 2020 Mar;31(3):456-468. Epub 2020 Feb 10. PMID: 32041774.

[5] Colucci WS. Evaluation and management of anemia and iron deficiency in adults with heart failure. Dardas TF and Tirnauer JS, ed. UpToDate. Waltham, MA: UpToDate Inc. www.uptodate.com. Accessed December 17, 2023.

[6] A Study to Compare the Use of Ferric Carboxymaltose with Placebo in Patients with Chronic Heart Failure and Iron Deficiency (CONFIRM-HF). ClinicalTrials.gov identifier: NCT01453608. Updated March 8, 2015. www.clinicaltrials.gov/study/NCT01453608. Accessed December 17, 2023.

[7] Aeurbach M. Causes and diagnosis of iron deficiency and iron deficiency anemia in adults. Tirnauer JS, Givens J, ed. UpToDate. Waltham, MA: UpToDate Inc. www.uptodate.com. Accessed January 6, 2023.

[8] Powers JM, Sandoval C. Approach to the child with anemia. Armsby C, ed. UpToDate. Waltham, MA: UpToDate Inc. www.uptodate.com. Accessed January 7, 2023.

[9] WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations. Geneva: World Health Organization; 2020. PMID: 33909381.

[10] Mueller MM, Van Remoortel H, et al; ICC PBM Frankfurt 2018 Group. Patient Blood Management: Recommendations From the 2018 Frankfurt Consensus Conference. JAMA. 2019 Mar 12;321(10):983-997. PMID: 30860564.

[11] Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney Inter. 2012; Suppl 2: 279–335.

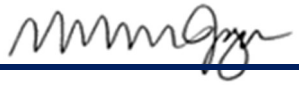
Development of utilization management criteria may also involve research into other state Medicaid programs, other payer policies, consultation with experts and review by the Medicaid Clinical Advisory Committee (CAC). These sources may not be referenced individually unless they are specifically published and are otherwise applicable to the criteria at issue.

Criteria Change History

Change Date	Changed By	Description of Change	Version
[mm/dd/yyyy]			
Signature			

Change Date	Changed By	Description of Change	Version
[mm/dd/yyyy]			
Signature			

Change Date	Changed By	Description of Change	Version
01/19/2024	CAC	Annual review. New indication for iron deficiency in adult patients with heart failure and NYHA II/III to improve exercise capacity (FDA-approved 5/31/23) – updated overview table and added criteria for new indication. Added continuation criteria for all indications. Updated Quantity Limits and Authorization Duration tables for all indications.	2
Signature William (Bill) Jagiello, DO			

Change Date	Changed By	Description of Change	Version
01/20/2023	CAC	Criteria implementation.	1
Signature William (Bill) Jagiello, DO			

CAC = Medicaid Clinical Advisory Committee