

## Clinical Criteria

<b>Subject:</b>	Iron Agents		
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### Overview

This document addresses the use of injectable agents for the treatment of iron deficiency anemia (IDA). Agents addressed in this document include:

- Feraheme (ferumoxytol)
- Ferrlecit (sodium ferric gluconate/sucrose complex)
- Infed (iron dextran)
- Injectafer (ferric carboxymaltose)
- Monoferic (ferric derisomaltose)
- Triferic, Triferic AVNU (ferric pyrophosphate citrate)
- Venofer (iron sucrose)

Iron is a mineral in the body that is an essential component for blood production, enabling them to carry oxygen throughout the body. The majority of body iron are found in circulating red blood cells called hemoglobin, while the remaining is stored as ferritin or bound to myoglobin in muscle cells. Individuals with iron deficiency anemia may have mild to severe symptoms, ranging from fatigue, shortness of breath, and chest pain to heart failure and developmental delays in children (NHLBI 2019).

The causes of iron deficiency anemia are numerous, including gastrointestinal bleeding or other blood loss, chronic kidney disease, celiac disease, multiple blood donations, and cancer or chemotherapy-related etiologies. Diagnosis of IDA is typically confirmed by evaluating levels of serum ferritin, transferrin saturation (TSAT), absence of stainable iron in the bone marrow, or resolution of anemia upon iron administration (Auerbach 2020).

While the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines for anemia in chronic kidney disease do not provide any guidance on preference of available IV iron agents over another, they do suggest that a trial oral iron for 1 to 3 months can be appropriate for individuals with IDA prior to initiating IV iron. The National Comprehensive Cancer Network (NCCN) guidelines for Hematopoietic Growth Factors provides a category 2A recommendation for use of Feraheme, Ferrlecit, Infed (IV only; IM not recommended), Injectafer, Venofer, and Monoferic for the management of cancer- and chemotherapy-induced anemia. NCCN also suggests that a trial of oral iron for at least 4 weeks can be appropriate prior to initiating IV iron.

Both Feraheme and Infed have black box warnings for fatal and serious hypersensitivity reactions including anaphylaxis, and as such, the administration of which should only occur when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions.

### Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

**Feraheme (ferumoxytol), Ferlecit (sodium ferric gluconate/sucrose complex), Infed (iron dextran), Injectafer (ferric carboxymaltose), Venofer (iron sucrose)**

Requests for Feraheme (ferumoxytol), Ferlecit (sodium ferric gluconate/sucrose complex), Infed (iron dextran), Injectafer (ferric carboxymaltose), Venofer (iron sucrose) may be approved if the following criteria are met:

- I. Individual has a diagnosis of chronic kidney disease (CKD); **AND**
  - A. Individual is dialysis dependent; **AND**
  - B. Individual has iron deficiency anemia (IDA);
- OR**
- II. Individual has a diagnosis of iron deficiency anemia (IDA); **AND**
- III. Individual is non-dialysis dependent; **AND**
- IV. Diagnosis is confirmed by one of the following:
  - A. For IDA associated with CKD or inflammatory conditions (for example, inflammatory bowel disease [IBD], heart failure), individual meets *one* of the following within the last four (4) weeks (De Franceschi 2017):
    - 1. Serum ferritin levels less than 100 ng/mL; **OR**
    - 2. TSAT levels less than 20%; **OR**
    - 3. Serum ferritin is less than or equal to 500 ng/mL **and** TSAT is less than or equal to 30% (KDIGO 2012); **OR**
    - 4. Bone marrow demonstrates inadequate iron stores; **OR**
  - B. For IDA associated with cancer/chemotherapy or non-inflammatory conditions (for example, blood loss, malabsorption, malnutrition), individual meets *one* of the following within the last four (4) weeks (NCCN 2021, De Franceschi 2017):
    - 1. Serum ferritin levels less than 30 ng/mL; **OR**
    - 2. TSAT levels less than 20%; **OR**
    - 3. Bone marrow demonstrates inadequate iron stores; **AND**
- V. Individual has had a four (4) week trial of and inadequate response, or intolerance to oral iron supplementation (NCCN 2020, KDIGO 2012).

- OR**
- VI. Individual has iron deficiency anemia in pregnancy; **AND**
- VII. Diagnosis is confirmed by one of the following:
  - A. Serum ferritin levels less than 30 ng/mL; **OR**
  - B. TSAT levels less than 20%; **OR**
  - C. Bone marrow demonstrates inadequate iron stores; **AND**
- VIII. Individual is past 14 weeks of pregnancy and has had a four (4) week trial of and inadequate response, or intolerance to oral iron supplementation (Muñoz 2017); **OR**
- IX. Individual is past 14 weeks of pregnancy and diagnosed with severe iron deficiency anemia, defined as Hemoglobin (HGB) less than 8 g/dL; **OR**
- X. Individual is past 34 weeks of pregnancy

Feraheme (ferumoxytol), Ferlecit (sodium ferric gluconate/sucrose complex), Infed (iron dextran), Injectafer (ferric carboxymaltose), or Venofer (iron sucrose) may not be approved when the above criteria are not met and for all other indications.

**Approval Duration** (dialysis-dependent use excluded)  
3 months

**Monoferric (ferric derisomaltose)**

Requests for Monoferric (ferric derisomaltose) may be approved if the following criteria are met:

- I. Individual has a diagnosis of iron deficiency anemia (IDA); **AND**
- II. Individual is non-dialysis dependent; **AND**
- III. Diagnosis is confirmed by one of the following:
  - A. For IDA associated with CKD or inflammatory conditions (for example, inflammatory bowel disease [IBD], heart failure), individual meets *one* of the following within the last four (4) weeks (De Franceschi 2017):
    - 1. Serum ferritin levels less than 100 ng/mL; **OR**
    - 2. TSAT levels less than 20%; **OR**
    - 3. Serum ferritin is less than or equal to 500 ng/mL **and** TSAT is less than or equal to 30% (KDIGO 2012); **OR**
    - 4. Bone marrow demonstrates inadequate iron stores; **OR**
  - B. For IDA associated with cancer/chemotherapy or non-inflammatory conditions (for example, blood loss, malabsorption, malnutrition), individual meets *one* of the following within the last four (4) (NCCN 2024<sup>2</sup>, De Franceschi 2017):
    - 1. Serum ferritin levels less than 30 ng/mL; **OR**
    - 2. TSAT levels less than 20%; **OR**
    - 3. Bone marrow demonstrates inadequate iron stores; **AND**
- IV. Individual has had a four (4) week trial of and inadequate response, or intolerance to oral iron supplementation (NCCN 2024<sup>2</sup>, KDIGO 2012).

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Monoferic (ferric derisomaltose) may not be approved for the following:

- I. Individual has hemodialysis dependent chronic kidney disease (CKD); **OR**
- II. When the above criteria are not met and for all other indications.

**Approval Duration** 3 months

#### Triferic/Triferic AVNU (ferric pyrophosphate citrate)

Requests for Triferic/Triferic AVNU (ferric pyrophosphate citrate) may be approved if the following criteria are met:

- I. Individual has a diagnosis of chronic kidney disease (CKD); **AND**
  - A. Individual is hemodialysis dependent; **AND**
  - B. Individual has iron deficiency anemia (IDA).

Triferic/Triferic AVNU (ferric pyrophosphate citrate) may not be approved for the following:

- I. Peritoneal dialysis; **OR**
- II. When the above criteria are not met and for all other indications.

## Step Therapy

#### Summary of FDA-approved and NCCN 2A recommended indications for agents for Iron Deficiency Anemia (IDA):

Agent	Route	Oral iron intolerant or unresponsive IDA	CKD	Dialysis-dependent CKD only	NCCN
Feraheme (ferumoxytol)	IV	x	x		x
Ferlecit (sodium ferric gluconate/sucrose complex)	IV			x*	x
Infed (iron dextran)	IV, IM	x*			x (IV only)
Injectafer (ferric carboxymaltose)	IV	x	x		x
Monoferic (ferric derisomaltose)	IV	x	x		x
Triferic, Triferic AVNU (ferric pyrophosphate citrate)	IV			x	
Venofer (iron sucrose)	IV		x*		x

\*Includes FDA-approved pediatric indication

**Note:** When an IDA agent is deemed approvable based on the clinical criteria above, the benefit plan may have additional criteria requiring the use of a preferred<sup>1</sup> agent or agents.

#### Non-Preferred Iron Deficiency Anemia (IDA) Step Therapy

A list of the preferred iron deficiency anemia agents is available [here](#).

Requests for a non-preferred agent for IDA may be approved when the following criteria are met:

- I. Individual has had a trial and inadequate response or intolerance to two (2) preferred agents;
- OR**
- II. The preferred agent(s) are not acceptable due to concomitant clinical conditions, including but not limited to known hypersensitivity to any active or inactive component which is not also associated with the requested non-preferred agent;
- OR**
- III. Individual is dialysis-dependent and using iron in conjunction with dialysis.

<sup>1</sup>Preferred, as used herein, refers to agents that were deemed to be clinically comparable to other agents in the same class or disease category but are preferred based upon clinical evidence and cost effectiveness.

## Quantity Limits

#### Iron Deficiency Anemia Agents Quantity Limits

Drug	Limit
Feraheme (ferumoxytol) 510 mg/17 mL vial*	2 vials per 6 days <sup>‡</sup>
Ferrlecit (sodium ferric gluconate/sucrose complex) 62.5 mg/5 mL vial*	16 vials per 8 weeks <sup>Δ</sup>
Injectafer (ferric carboxymaltose) 750 mg/15 mL vial*	2 vials per 14 days <sup>‡</sup>
Injectafer (ferric carboxymaltose) 1000 mg/20 mL vial*	1 vial per 7 days
Monoferic (ferric derisomaltose) 100 mg/mL vial	4 vials per day
Monoferic (ferric derisomaltose) 500 mg/5 mL vial	1 vial per day
Monoferic (ferric derisomaltose) 1000 mg/10 mL vial	1 vial per day <sup>‡</sup>
Venofer (iron sucrose) 50 mg/2.5 mL vial*	6 vials per 12 weeks
Venofer (iron sucrose) 100 mg/5 mL vial*	3 vials per 12 weeks
Venofer (iron sucrose) 200 mg/10 mL vial*	5 vials per 14 days <sup>‡</sup>
Override Criteria	
*Use in dialysis-dependent individuals excluded from quantity limits.	

<sup>‡</sup>Limit represents FDA-approved maximum dose recommendations per course of therapy (excluding dialysis-dependent diagnosis).

<sup>Δ</sup>Limit according to NCCN guidelines for hematopoietic growth factors (v4.2021).

## Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. 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.

### HCPCS

<b>J1443</b>	Injection, ferric pyrophosphate citrate solution, 0.1 mg of iron [Triferic]
<b>J1445</b>	Injection, ferric pyrophosphate citrate solution (Triferic AVNU), 0.1 mg of iron
<b>J1437</b>	Injection, ferric derisomaltose, 10 mg [Monoferic]
<b>Q0138</b>	Injection, ferumoxytol, for treatment of iron deficiency anemia, 1 mg (for non-ESRD on dialysis) [Feraheme]
<b>J2916</b>	Injection, sodium ferric gluconate complex in sucrose injection, 12.5 mg [Ferrlecit]
<b>J1750</b>	Injection, iron dextran, 50 mg [Infed]
<b>J1756</b>	Injection, iron sucrose, 1 mg [Venofer]
<b>J1439</b>	Injection, ferric carboxymaltose, 1 mg [Injectafer]

### ICD-10 Diagnosis

<b>D50.0-D50.9</b>	Iron deficiency anemia
<b>D63.0-D63.8</b>	Anemia in chronic diseases classified elsewhere
<b>D64.81</b>	Anemia due to antineoplastic chemotherapy
<b>K50.00-K50.919</b>	Crohn's disease [regional enteritis]
<b>K90.0-K90.9</b>	Celiac disease
<b>N18.1-N18.5</b>	Chronic kidney disease, stages I-V
<b>O99.011</b>	Anemia complicating pregnancy, first trimester
<b>O99.012</b>	Anemia complicating pregnancy, second trimester
<b>O99.013</b>	Anemia complicating pregnancy, third trimester
<b>O99.019</b>	Anemia complicating pregnancy, unspecified trimester

## Document History

Revised: 08/19/2022

Document History:

- 08/19/2022 – Annual Review: Add criteria for iron deficiency anemia in pregnancy, wording and formatting changes. Coding reviewed: Added ICD-10-CM O99.011, O99.012, O99.013. O99.019.
- 04/25/2022 – Step therapy table update.
- 03/28/2022 – Step therapy table update.

- 08/20/2021 – Annual Review: Update criteria to update approval durations to three months for all requests, and remove continuation approval duration. Add timeframe parameters for lab values for Feraheme, Infed, Venofer, Ferrlecit, Injectafer, and Monoferic. Update Monoferic non-approvable criteria to restrict use in hemodialysis patients per label. Remove QL override criteria for Monoferic. Add generically available version of Feraheme to step therapy criteria. Update Injectafer QL to include new strength. Clarify use in hemodialysis dependent CKD patients. Update references, and wording and formatting changes. Coding reviewed: Added HCPCS J1445.
- 08/23/2021 – Step Therapy table update.
- 07/26/2021 – Step Therapy table update.
- 04/26/2021 – Step Therapy table update.
- 08/21/2020 – Annual Review: Add new clinical criteria document, including PA, step therapy, and quantity limits, for Injectafer, Infed, Venofer, Triferic/Triferic AVNU, Feraheme, Monoferic, and Ferrlecit. Coding Reviewed: Added HCPCS codes- J1443, J1437, Q0138, J2916, J1750, J1439, J1756. Added ICD-10-CM codes-D50.0-D50.9, D63.0-D63.8, D64.81, K50.00-K50.919, K90.0, K90.4, K90.9, N18.1-N18.5. Effective 2/1/2021 extended ICD-10-CM K50.00-K50.919, Extended K90.0-K90.9, Removed K90.4, and K90.9.

## References

1. Achebe MM, Gaftner-Gvili A. How I treat anemia in pregnancy: iron, cobalamin, and folate. *Blood*. 2017;129(8):940-949. doi:10.1182/blood-2016-08-672246
2. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. "Anemia in Pregnancy: ACOG Practice Bulletin, Number 233." *Obstetrics and gynecology* vol. 138,2 (2021): e55-e64. doi:10.1097/AOG.0000000000004477
3. Auerbach M. Causes and diagnosis of iron deficiency and iron deficiency anemia in adults. Last updated June 2021. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed: June 27, 2022.
4. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2022. URL: <http://www.clinicalpharmacology.com>. Updated periodically.
5. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. <http://dailymed.nlm.nih.gov/dailymed/about.cfm>. Accessed: June 27, 2022.
6. De Franceschi L, Iolascon A, Taher A, Cappellini MD. Clinical management of iron deficiency anemia in adults: Systemic review on advances in diagnosis and treatment. *Eur J Intern Med*. 2017;42:16–23.
7. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
8. Ferritin in Pediatrics. American Association for Clinical Chemistry (AACC Academy). 2022. Available at: <https://www.aacc.org/advocacy-and-outreach/optimal-testing-guide-to-lab-test-utilization/a-f/ferritin-in-pediatrics>. Accessed on June 27, 2022.
9. Haymond, Shannon. American Association for Clinical Chemistry (AACC Academy). 2022. Available at: <https://www.aacc.org/science-and-research/clinical-chemistry-trainee-council/trainee-council-in-english/pearls-of-laboratory-medicine/2015/iron-deficiency-anemia>. Accessed on: June 27, 2022.
10. Iron-Deficiency Anemia. National Heart, Lung, and Blood Institute (NHLBI). 2022. Available at <https://www.nhlbi.nih.gov/health-topics/iron-deficiency-anemia>. Accessed on: June 27, 2022.
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. Available from: [https://www.kidney.org/professionals/guidelines/guidelines\\_commentaries/anemia](https://www.kidney.org/professionals/guidelines/guidelines_commentaries/anemia). Accessed on: June 27, 2022.
12. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2022; Updated periodically.
13. Muñoz, M et al. "Patient blood management in obstetrics: management of anaemia and haematologic deficiencies in pregnancy and in the post-partum period: NATA consensus statement." *Transfusion medicine* (Oxford, England) vol. 28,1 (2018): 22-39. doi:10.1111/tme.12443
14. NCCN Clinical Practice Guidelines in Oncology™. © 2021 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: <http://www.nccn.org/index.asp>. Accessed on June 27, 2022.
  - a. Hematopoietic Growth Factors. V1.2022. Revised December 22, 2021.
15. Pavord, Sue et al. "UK guidelines on the management of iron deficiency in pregnancy." *British journal of haematology* vol. 188,6 (2020): 819-830. doi:10.1111/bjh.16221
16. Peyrin-Biroulet L, Williet N, Cacoub P. Guidelines on the diagnosis and treatment of iron deficiency across indications: a systematic review. *Am J Clin Nutr*. 2015;102(6):1585–1594.
17. Short MW, Domagalski JE. Iron deficiency anemia: evaluation and management. *Am Fam Physician*. 2013;87(2):98-104.

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**ING-CC-0182**  
**Agents for Iron Deficiency Anemia**

**Commercial Medical Benefit**

<b>Effective Date</b>	<b>Preferred Agents</b>	<b>Non-Preferred Agents</b>
05/01/2021	Ferrlecit Infed Venofer	Feraheme Injectafer Monoferric

**Medicaid Medical Benefit**

<b>Effective Date</b>	<b>Preferred Agents</b>	<b>Non-Preferred Agents</b>
08/01/2021 - GA, MD, NJ, SC, WI, WNY  09/01/2021 - VA, NV, NY  10/01/2021 - AR  04/01/2022 – FL Healthy Kids, IA, KY, LA, TN  06/01/2022 - CA	Ferrlecit Infed Venofer	Feraheme Injectafer Monoferric

**Medicare Medical Benefit**

<b>Effective Date</b>	<b>Preferred Agents</b>	<b>Non-Preferred Agents</b>
05/01/2021	Ferrlecit Infed Venofer	Feraheme Injectafer Monoferric