Clinical Criteria

Subject:	Agents for Iron Deficiency Anemia		
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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)
- Monoferric (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. 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 (version 2.2020) provides a category 2A recommendation for use of Feraheme, Ferrlecit, Infed (IV only; IM not recommended), Injectafer, and Venofer for the management of cancer- and chemotherapy-induced anemia. NCCN had yet to incorporate the use of Monoferric in its guidelines at the time of this review. NCCN also suggests that a trial 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.

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
Ferrlecit (sodium ferric gluconate/sucrose complex)	IV			x*	x
Infed (iron dextran)	IV, IM	x*			x (IV only)
Injectafer (ferric carboxymaltose)	IV	x	x		x
Monoferric (ferric derisomaltose)	IV	x	x		

Triferic, Triferic AVNU (ferric pyrophosphate citrate)	IV			x	
Venofer (iron sucrose)	IV		x*		x

*Includes FDA-approved pediatric indication

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), Ferrlecit (sodium ferric gluconate/sucrose complex), Infed (iron dextran), Injectafer (ferric carboxymaltose), Venofer (iron sucrose)

Requests for Feraheme (ferumoxytol), Ferrlecit (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;

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 (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 (NCCN 2020, 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).

Requests for Feraheme (ferumoxytol), Ferrlecit (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)
Initial requests: 3 months
Continuation requests: 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 (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 (NCCN 2020, 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 2020, KDIGO 2012).

Requests for Monoferric (ferric derisomaltose) may not be approved when the above criteria are not met and for all other indications

Approval Duration (dialysis-dependent use excluded)
Initial requests: 3 months
Continuation requests: 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.

Requests for 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

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[1] 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.

[1]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‡
Ferrlecit (sodium ferric gluconate/sucrose complex) 62.5 mg/5 mL vial*	16 vials per 8 weeksΔ
Injectafer (ferric carboxymaltose) 750 mg/15 mL vial*	2 vials per 14 days‡
Monoferric (ferric derisomaltose) 100 mg/mL vial*	4 vials per day
Monoferric (ferric derisomaltose) 500 mg/5 mL vial*	1 vial per day
Monoferric (ferric derisomaltose) 1000 mg/10 mL vial*	1 vial per day ‡
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‡
Override Criteria	

*Use in dialysis-dependent individuals excluded from quantity limits.

‡Limit represents FDA-approved maximum dose recommendations per course of therapy (excluding dialysis-dependent diagnosis).
ΔLimit according to NCCN guidelines for hematopoietic growth factors (v2.2020).

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

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

ICD-10 Diagnosis

D50.0-D50.9	Iron deficiency anemia
D63.0-D63.8	Anemia in chronic diseases classified elsewhere
D64.81	Anemia due to antineoplastic chemotherapy
K50.00-K50.919	Crohn's disease [regional enteritis]
K90.0-K90.9	Celiac disease
N18.1-N18.5	Chronic kidney disease, stages I-V

Document History

New: 08/21/2020
Document History:

- 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, Monoferric, 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. Auerbach M. Causes and diagnosis of iron deficiency and iron deficiency anemia in adults. Last updated June 2020. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed: July 13, 2020.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2020. URL: http://www.clinicalpharmacology.com. Updated periodically.
3. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: July 13, 2020.
4. 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.
5. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
6. Iron-Deficiency Anemia. National Heart, Lung, and Blood Institute (NHLBI). Available at https://www.nhlbi.nih.gov/health-topics/iron-deficiency-anemia. Accessed on July 13, 2020.

7. 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. Accessed on: July 13, 2020.
8. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2020; Updated periodically.
9. NCCN Clinical Practice Guidelines in Oncology™. © 2020 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on July 13, 2020.
    a. Hematopoietic Growth Factors. V2.2020. Revised January 27, 2020.
10. 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.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

ING-CC-0182 Agents for Iron Deficiency Anemia

Commercial Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
5/1/2021	Ferrlecit Infed Venofer	Feraheme Injectafer Monoferric

Medicaid Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
8/1/2021: GA, MD, NJ, SC, WI, WNY 9/1/2021: VA, NV, NY 10/1/2021: AR	Ferrlecit Infed Venofer	Feraheme Injectafer Monoferric

Medicare Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
5/1/2021	Ferrlecit Infed Venofer	Feraheme Injectafer Monoferric