Ferric Derisomaltose (MONOFERRIC) National Drug Monograph March 2022

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information[1]

Description/Mechanism of Action

- Ferric derisomaltose is an iron replacement product consisting of a matrix structure of interchanging layers of ferric 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.

Indication(s) Under Review in This Document

- Ferric derisomaltose is indicated for the treatment of iron deficiency anemia (IDA) in adult patients:
  - who have intolerance to oral iron or have had unsatisfactory response to oral iron
  - who have non-hemodialysis dependent chronic kidney disease (NDD-CKD)

Dosage Form(s) Under Review

- Ferric derisomaltose is available as 1000 mg/10ml (100 mg/ml) single dose vial
  - For patients weighing 50 kg or more: Administer ferric derisomaltose 1,000 mg as an intravenous (IV) infusion as a single dose over at least 20 minutes.
  - For patients weighing less than 50 kg: Administer ferric derisomaltose as 20 mg/kg actual body weight as an IV infusion as a single dose over at least 20 minutes.
  - Instruction per the product information are to withdraw the appropriate volume of ferric derisomaltose and dilute in 100 ml to 500 ml of 0.9% Sodium Chloride Injection, USP.
  - Repeat dose if iron deficiency anemia reoccurs.

Clinical Evidence Summary[1-3]

Efficacy Considerations[1-3]

- Data for approval of ferric derisomaltose are based primarily on two phase 3 randomized, open-label, multicenter studies that evaluated treatment with ferric derisomaltose compared to iron sucrose (FERWON program): one trial was conducted in patients with IDA who experienced intolerance or had an unsatisfactory response to oral iron (FERWON-IDA); the other trial was in patients with IDA and NDD-CKD (FERWON-NEPHRO). Treatment duration in both trials were 8 weeks in duration.
- FERWON-IDA included patients with IDA of various etiologies, who had intolerance or lack of response to oral iron, or screening hemoglobin (Hgb) requiring rapid repletion of iron stores. Patients with Hgb <=11 g/dl, transferrin saturation (TSAT) < 20%, and ferritin < 100 ng/ml for run-in (<= 800 ng/ml after run-in) were enrolled. Treatment with an erythropoiesis-stimulating agent (ESA) was not allowed during the trial. In FERON-NEPHRO, patients with Hgb <=11 g/dl, ferritin <= 100 ng/ml (or <= 300 ng/dl if TSAT <= 30%), and chronic kidney disease not on dialysis were enrolled. Treatment with a stable dose of an ESA was allowed during the trial.

- The primary efficacy outcome of both trials was the change in Hgb from baseline to week 8 and are included in Table 1 below. In both trials, the change in Hgb from baseline to week 8 was non-inferior for ferric derisomaltose compared to iron sucrose.

Table 1: Primary Efficacy Outcome Results in FERWON-IDA[2] and FERWON-NEPHRO[3]

Primary Outcome	Ferric Derisomaltose	Iron Sucrose
FERWON-IDA	N=1009	N=503
Mean baseline Hgb (SD)	9.25 (1.28)	9.17 (1.27)
Change in Hgb (g/dl)	2.49 (95% CI 2.41 to 2.56)	2.49 (95% CI 2.38 to 2.59)
FERWON-NEPHRO	N=967	N=475
Mean baseline Hgb (SD)	9.66 (1.14)[a]	9.71 (1.12)[a]
Change in Hgb (g/dl)	1.22 (95% CI 1.14 to 1.31	1.14 (95% CI 1.03 to 1.26)

[a] ferric derisomaltose (N=1026); iron sucrose (N=511)
SD=standard deviation

- In both trials, treatment with ferric derisomaltose was 1000 mg IV infusion administered over 20 minutes, or iron sucrose 200 mg IV injection up to 5 times. In FERWON-IDA, the mean dose of ferric derisomaltose was 975 mg, and 905 mg of iron sucrose; in FERWON-NEPHRO the mean doses were 993 mg and 899 mg, respectively.

Safety Results from Clinical Trials[1-4]

- A co-primary endpoint in the FERWON-IDA and FERWON-NEPHRO trials were the incidence of adjudicated serious or severe hypersensitivity reactions which was reported in 0.3% of patients treated with ferric derisomaltose in both trials vs. 0.4% of patients who received iron sucrose in the FERWON-IDA trial, and 0% in the FERWON-NEPHRO trial. Adverse events as reported per a pre-specified combined safety analysis of the two clinical trials in the FERWON program (FERWON-IDA, FERWON-NEHRO) are included in Table 2 below. Hypophosphatemia (serum phosphate < 2.0 mg/dl) was reported in 3.9% (FERWON-IDA) and 3.2% (FERWON-NEPHRO) of patients treated with ferric derisomaltose compared to 2.3% and 0.8% of patients receiving iron sucrose, in the two trials, respectively.

Table 2: Adverse Events with Ferric Derisomaltose Compared to Iron Sucrose[1,4]

Adverse Events	Ferric Derisomaltose N=2008 (%)	Iron Sucrose N=1000 (%)
Total adverse drug reactions	172 (8.6)	90 (9.0)
Adjudicated serious or severe hypersensitivity reactions	6 (0.3)	2 (0.2)
Composite cardiovascular adverse events[a]	50 (2.5)	41 (4.1)
Nausea[b]	24 (1.2)	11 (1.1)
Rash[b]	21 (1.0)	1 (0.1)

[a] most frequent cardiovascular adverse events were hypertension, congestive heart failure, atrial fibrillation
[b] most common adverse drug reactions

Safety Considerations[1]

- **Boxed warning:** None.
- **Contraindications:** History of serious hypersensitivity to ferric derisomaltose or any of its components (see warnings / precautions below).
- **Warnings / precautions**:
  - Hypersensitivity reactions: Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving ferric derisomaltose. Per the product information, reactions have included shock, clinically significant hypotension, loss of consciousness, and/or collapse. It is recommended to monitor patients for signs and

symptoms of hypersensitivity during and after administration of ferric derisomaltose for at least 30 minutes and until clinically stable following completion of the infusion. Ferric derisomaltose should only be administered when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions.

- Iron overload: excess iron storage and possibly iatrogenic hemosiderosis or hemochromatosis can occur with excessive IV iron therapy. It is recommended to monitor hemoglobin, hematocrit, serum ferritin and transferrin saturation during IV iron therapy. Ferric derisomaltose should not be administered to patients with iron overload.

Other Considerations[1-14]

- Recommendations for ferric derisomaltose is to administer the total dose during one IV infusion over 20 minutes. Other IV iron products with data or labeling for total dose infusion include iron dextran,[5] ferric carboxymaltose,[5,6] and ferumoxytol.[5,7,8]
- Additional data to support the FDA approval for ferric derisomaltose include: one 5-week clinical trial comparing ferric derisomaltose with iron sucrose in 511 patients with IDA intolerant or unresponsive to oral iron that reported ferric derisomaltose (mean cumulative dose 1640 mg) was noninferior as well as superior to iron sucrose (mean cumulative dose 1128 mg) in the percent of patients achieving an increase in Hgb >=2 g/dL compared to baseline (68.5% vs. 51.6%, respectively);[9] two trials including 245 patients with IDA intolerant or unresponsive to oral iron that reported a lower rate of hypophosphatemia with ferric derisomaltose (trial A: 7.9%; trial B: 8.1%) compared to ferric carboxymaltose (trial A: 75.0%; trial B: 73.7%);[10] and one trial in 351 patients with IDA and NDD-CKD that reported ferric derisomaltose to be noninferior to oral iron in the primary endpoint of change in Hgb from baseline to week 4 (treatment difference ferric derisomaltose vs. iron sulfate 0.22 g/dL).[11] Data have also been published in patients with IDA on hemodialysis that found similar efficacy and safety with ferric derisomaltose compared to iron sucrose;[12] a trial evaluating IDA in patients with inflammatory bowel disease that was unable to demonstrate non-inferiority with ferric derisomaltose compared to oral iron sulfate (i.e., trend was that iron sulfate was more effective);[13] and in patients with anemia receiving chemotherapy that reported ferric derisomaltose to be non-inferior to treatment with oral iron sulfate at 4 weeks.[14]

Other Therapeutic Options[1,6,15-18]

Intravenous iron products available on the VA National Formulary are listed in Table 3 below.

Table 3 IV Iron Products[1,5-8,15-18]

IV Iron	Formulary status	FDA Indications	Comments
Ferric derisomaltose	NF	IDA in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron, or who have NDD-CKD	Total dose infusion
Iron sucrose	VANF	IDA in patients with chronic kidney disease	Administer in divided doses per product labeling (e.g., 10 doses) Off-label: IDA unable to use oral iron in patients without chronic kidney disease
Ferric sodium gluconate	VANF	IDA in adult patients and in pediatric patients age 6 years and older with chronic kidney disease receiving hemodialysis who are receiving supplemental epoetin therapy	Administer in divided doses per product labeling (e.g., 8 doses) Off-label use: IDA unable to use oral iron in patients not on dialysis
Iron dextran (LMW)	VANF	documented iron deficiency in whom oral administration is unsatisfactory or impossible	Boxed Warning: Risk for anaphylactic-type reactions Test dose prior to first therapeutic dose Administer in divided doses per product labeling; data with total dose infusion Off-label: restless leg syndrome
Ferumoxytol	NF	IDA in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron, or who have chronic kidney disease	Boxed Warning: Risk for serious hypersensitivity/anaphylaxis Administer in divided doses per product labeling (e.g., 2 doses); data with total dose infusion
Ferric carboxymaltose	NF	IDA in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron, or who have NDD-CKD	Warning/precaution: hypophosphatemia (monitor serum phosphate in patients at risk for hypophosphatemia who require repeat treatment course) Administer in divided doses (e.g., 2 doses), alternative total dose infusion per product labeling Off-label: abdominal surgery, major (perioperative anemia management); chemotherapy-associated anemia; IDA in inflammatory bowel disease; iron deficiency in heart failure with reduced ejection fraction; restless legs syndrome

LMW=lower molecular weight; NF=non-formulary; PA-F=prior authorization, facility level; VANF=VA National Formulary

Projected Place in Therapy[1-8,15-26]

- Anemia is common and reported to affect approximately one quarter of the population, with iron deficiency being the cause in approximately half of patients with anemia. Potential reasons for IDA include malabsorption, gastrointestinal disorders, blood loss, nutritional deficiency or increased nutritional demand, infectious disease, malignancy, as well as impaired production of red cells as in chronic kidney disease.[19] Other causes of anemia in patients with chronic kidney disease include blood loss, decreased red blood cell survival, iron deficiency, chronic inflammation, and hemodialysis.[20,21]
- The decision to manage iron deficiency anemia with oral or IV iron therapy may depend on several factors including etiology of anemia, response to iron supplementation or patient tolerability, convenience of

administration, and cost.[19-23] In general, IV iron therapy is considered in the management of IDA when oral iron is not tolerated or there is a lack of response, or in conditions where IV iron may be preferred as initial therapy, as in patients with IDA and chronic kidney disease on hemodialysis.[20,24-26]

- Among the IV iron therapies, treatment selection may depend on availability, convenience (e.g., administration time, number of doses required for repletion), and cost. Intravenous iron therapies available on the VA National Formulary include ferric sodium gluconate, iron sucrose, and LMW iron dextran. Product labeling for these agents include recommendations for iron replacement therapy to be administered in divided doses;[15-17] although, LMW iron dextran has also been administered as a total dose infusion over 1 hour.[5] A test dose is required prior to the first dose of iron dextran.[17] Ferumoxytol and ferric carboxymaltose are available nonformulary, and both are labeled for administration as two doses per treatment course, with a single dose as an alternative administration option for ferric carboxymaltose;[6,18] ferumoxytol has also been administered as a total dose infusion.[7,8] Patient populations or circumstances at a site may warrant consideration of the use of ferumoxytol or ferric carboxymaltose as preferred therapy (due to economic considerations or convenience) which should be determined on a case by case basis at the local level.
- Ferric derisomaltose is the most recently approved IV iron, with labeled recommendations for administration as a single dose infusion over at least 20 minutes.[1] As shown in the FERWON-IDA and FERWON-NEPHRO trials, the change in Hgb from baseline to week 8 was non-inferior with ferric derisomaltose compared to iron sucrose, with no difference in serious or severe hypersensitivity reactions.[2-4] As with ferumoxytol and ferric carboxymaltose, patient populations or circumstances at a site may warrant consideration of the use of ferric derisomaltose as preferred therapy (due to economic considerations or convenience) which should be determined on a case by case basis at the local level.

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