Ferric Maltol (ACCRUFER) National Drug Monograph February 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 maltol is an iron replacement that contains iron in a stable ferric state as a complex with a trimaltol ligand, that delivers iron for uptake across the intestinal wall and transfer to transferrin and ferritin.

Indication(s) Under Review in This Document

- Ferric maltol is indicated for the treatment of iron deficiency in adults.

Dosage Form(s) Under Review

- Ferric maltol is available as 30 mg capsules. The recommended dose is 30 mg twice daily, taken one hour before or two hours after a meal. The capsules should not be opened for chewed.

Clinical Evidence Summary[1-4]

Efficacy Considerations[1-4]

- Data for approval of ferric maltol are based primarily on three phase 3 randomized, double-blind, placebo-controlled studies. Two trials (AEGIS 1 and 2) evaluated 12 weeks of treatment with ferric maltol in patients with inflammatory bowel disease (IBD) and iron deficiency anemia (IDA), analyzed as a single data set with the results reported in a single publication. The third trial (AEGIS 3, or AEGIS-CKD) was conducted in patients with IDA and chronic kidney disease (CKD) not on dialysis and evaluated 16 weeks of treatment with ferric maltol.
- In AEGIS 1 and 2, inclusion criteria for IDA was defined as a screening hemoglobin (Hgb) >= 9.5 g/dL and < 12.0 g/dL for females and >= 9.5 g/dL and < 13.0 g/dL for males, and serum ferritin levels < 30 mcg/L. Patients were also required to have a history of intolerance or lack of efficacy to oral iron. In AEGIS-CKD, enrollment included patients with IDA defined as a Hgb of 8.0 to < 11.0 g/dl, and either ferritin < 250 ng/mL with transferrin saturation (TSAT) < 25% or ferritin < 500 ng/mL with TSAT < 15%. The primary efficacy outcome was the change in Hgb from baseline to end of treatment (week 12 in AEGIS 1 and 2; week 16 in AEGIS-CKD) and are included in Table 1 below.

Table 1: Primary Efficacy Outcome Results in AEGIS 1 and 2[2] and AEGIS-CKD[3]

Primary Outcome	Ferric Maltol	Placebo
AEGIS 1 and 2	N=64	N=64
Mean baseline Hgb (SD)	11.0 (1.03)	11.1 (0.85)
Mean Hgb (SD) at week 12	13.2 (1.04)	11.2 (0.98)
Difference in Hgb (SE) at week 12	Ferric maltol vs. Placebo 2.25 (0.19) g/dL (P < 0.0001)	
AEGIS-CKD	N=111	N=56
Mean baseline Hgb (SD)	10.1 (0.8)	10.0 (0.8)
Change in Hgb (SD)	0.6 (1.3)	-0.1 (1.0)
Difference in Hgb[a] (SE) at week 16	0.5 (0.2) g/dL (P = 0.01)	

SD=standard deviation; SE=standard error

- Results of the trials in patients with IDA and IBD or CKD reported a statistically significant increase in Hgb with ferric maltol compared to placebo at the respective study timepoints.
- In AEGIS 1 and 2, Hgb normalized in 66% of patients treated with ferric maltol at week 12 compared to 13% of patients in the placebo group. The secondary endpoints of ferritin and TSAT improved with ferric maltol (increase 17.3 mcg/L and 18.0%, respectively) compared to minimal change in the placebo group. In AEGIS-CKD, 27% of patients treated with ferric maltol achieved a Hgb > 11 g/dL by week 16 compared to 13% of patients in the placebo group. The secondary endpoint iron indices were noted to be increased with ferric maltol and decreased in the placebo group (difference between groups: ferritin 32.7 ng/mL, TSAT 4.6%, serum iron 1.9 mmol/L) at week 16.
- Eighty-nine percent of patients with IDA and IBD who continued ferric maltol and 83% of those switched to ferric maltol from placebo were noted to have normalization of Hgb at 52 weeks in the AEGIS 1 and 2 open-label extension phase. In the 36-week open-label extension phase of AEGIS-CKD, Hgb was reported to be sustained in patients with IDA and CKD continuing ferric maltol and increased in patients who were switched from placebo to ferric maltol.
- In AEGIS 1 and 2 and AEGIS-CKD, treatment with ferric maltol was 30 mg twice daily to be administered on an empty stomach. Treatment adherence was reported as 98% in the AEGIS 1 and 2 trials (not reported in AEGIS-CKD).

Safety Results from Clinical Trials[1-4]

- In AEGIS 1 and 2, treatment-emergent adverse events (TEAE) were reported in 58% of patients treated with ferric maltol compared to 72% of patients in the placebo group; and in 80% of patients overall who received treatment with ferric maltol that included those in the open-label extension phase. Discontinuation due to adverse events (all gastrointestinal) occurred in 8 patients (13%) treated with ferric maltol and 5 patients (8%) on placebo. Serious adverse events were reported in two patients receiving ferric maltol and two patients on placebo, none of which were considered to be related to treatment. In AEGIS-CKD, any TEAE was reported in 68% of patients on ferric maltol vs. 75% on placebo; and 88% randomized to ferric maltol compared to 90% randomized to placebo in the open-label extension phase. Ferric maltol was withdrawn due to an adverse event in 7 patients (6%) compared to 5 patients (9%) in the placebo group. Serious adverse events were reported in 21% of patients receiving ferric maltol and 21% in the placebo group, none of which were considered to be attributable to study treatment. Pooled results of adverse events reported in the clinical trials and as noted in the product information are included in Table 2 below.

Table 2: Adverse Reactions in >=1% Patients Treated with Ferric Maltol or Placebo (pooled results)[1-3]

Adverse Reactions[a]	Ferric Maltol N=175	Placebo N=120
Flatulence	4.6%	0
Diarrhea	4%	1.7%
Constipation	4%	0.8%
Feces discolored	4%	0.8%
Abdominal pain	2.9%	2.5%
Nausea	1.7%	0.8%
Vomiting	1.7%	0
Abdominal discomfort	1.1%	0
Abdominal distention	1.1%	0

[a] most common adverse drug reactions

Safety Considerations[1]

- **Boxed warning:** None.

- **Contraindications:**
  - Hypersensitivity to ferric maltol: reactions could include shock, clinically significant hypotension, loss of consciousness, and/or collapse.
  - Hemochromatosis and other iron overload syndromes: use may result in iron overdose.
  - Receiving repeated blood transfusions: use may result in iron overload.
- **Warnings / precautions**:
  - Increased risk of IBD flare: avoid use in patients with active IBD flare due to potential risk for increased inflammation in the gastrointestinal tract.
  - Iron overload: excess iron storage and possibly iatrogenic hemosiderosis can occur with excessive therapy with iron products. It is recommended that iron parameters be assessed prior to treatment with ferric maltol as well as monitored while on therapy. Ferric maltol should not be administered to patients with iron overload or those receiving IV iron.
  - Risk of overdose in children due to accidental ingestion: it is noted that in children under 6, accidental overdose of iron containing products is a leading cause of fatal poisoning. Keep product out of reach of children. It is recommended to call a doctor or poison control center immediately in case of accidental overdose.

Other Considerations[1-12]

- The oral iron products listed on VA National Formulary (ferrous gluconate, ferrous sulfate) are available over-the-counter; ferric maltol requires a prescription.
- There are insufficient data on drug interactions between ferric maltol and other oral medications. The product information notes that concomitant use of some drugs may reduce the bioavailability of iron after administration of ferric maltol; it is recommended to separate administration of ferric maltol from these medications. In addition, concomitant use of ferric maltol may decrease the bioavailability of some other oral medications. The product information recommends to separate administration of ferric maltol (by at least 4 hours) from these other oral medications where a decrease in bioavailability may result in a clinically significant effect on safety or efficacy.
- Ferric maltol is a non-salt oral iron, which has been suggested to increase bioavailability as well as reduce gastrointestinal toxicity compared to other oral iron salts. Ferric maltol was studied in patients intolerant or refractory to treatment with oral iron therapy; however, there are no head-to-head trials with other oral iron products, including use of oral iron salts at lower doses or every other day dosing, to compare efficacy and tolerability in IDA in order to determine place in therapy of ferric maltol.
- An initial trial of oral iron therapy is generally recommended in patients with IDA. Intravenous (IV) iron may be considered in patients where oral iron therapy is ineffective or not tolerated, in selected patients with impaired absorption or ongoing blood loss, or in patients with IDA and CKD on dialysis.
- In an open-label trial of 150 patients with IDA and IBD, 67% of patients receiving oral iron therapy with ferric maltol responded with an increase in Hgb >= 2 g/dL compared to 84% of patients treated with IV ferric carboxymaltose; oral ferric maltol did not demonstrate non-inferiority to IV ferric carboxymaltose, which was the primary endpoint of the trial. Treatment-emergent adverse events were noted in 59% of patients receiving oral ferric maltol compared with 36% in the IV ferric carboxymaltose treatment group.

Other Therapeutic Options[1-12]

A general comparison of ferric maltol with other oral iron products available on the VA National Formulary are listed in Table 3 below. Intravenous iron therapy is not included but may also be considered where oral iron therapy is ineffective or not tolerated, or in select patient circumstances as noted in Other Considerations.

Table 3 Oral Iron Products[a]

Oral Iron	Formulary status[b]	Indication(s)	Comments
Ferric maltol	NF	Treatment of iron deficiency in adults	Available by prescription only Dose reflects amount of elemental iron (i.e., 30 mg capsule contains 30 mg elemental iron) Dose (per product information): 30 mg twice daily; (per Lexicomp) 30 to 60 mg once every other day (or every Monday, Wednesday, Friday)
Ferrous gluconate	VANF	Prevention and treatment of IDA	Available without a prescription ~12% elemental iron per mg (e.g., 324 mg tablet contains ~38 mg elemental iron) Dose (per Lexicomp): 27 to 38 mg elemental iron once every other day (or every Monday, Wednesday, Friday)
Ferric sulfate	VANF	Prevention and treatment of IDA	Available without a prescription ~20% elemental iron per mg (e.g., 325 mg tablet contains 65 mg elemental iron) Dose (per Lexicomp): 65 mg elemental iron once every other day (or every Monday, Wednesday, Friday)

[a] Ferrous fumarate also available non-formulary
[b] NF=non-formulary; VANF=VA National Formulary

Projected Place in Therapy[1-13]

- Iron deficiency 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.[10,11,13]
- An initial trial of oral iron therapy is generally recommended in patients with IDA. 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. Intravenous iron may be considered in patients where oral iron therapy is ineffective or not tolerated, in selected patients with impaired absorption or ongoing blood loss, or in patients with IDA and CKD on dialysis.[7-11,13]
- Oral ferric maltol was studied in patients with IDA and IBD or CKD, conditions commonly associated with anemia. Results of the pivotal clinical trials demonstrated that treatment with ferric maltol resulted in a significant increase in Hgb compared to placebo over the 12 to 16 week blinded comparison phase of the studies. Adverse events were primarily gastrointestinal and reported in approximately 1% to 5% of patients on ferric maltol, compared to 0 to 2.5% on placebo.[1-5]
- Among the oral iron therapies, ferrous gluconate and ferrous sulfate are available on the VA National Formulary. These products are also available without a prescription. Oral ferric maltol is approved for iron deficiency and requires a prescription. As shown in the pivotal clinical trials for approval, ferric maltol was effective in increasing Hgb compared to placebo at 12 or 16 weeks of treatment in patients with IDA and IBD or CKD, respectively. Ferric maltol was studied in patients intolerant or refractory to treatment with oral iron therapy; however, as there are no direct comparison trials with other oral iron products, including use of oral iron salts at lower doses or every other day dosing,[6] data are not available to determine whether ferric maltol provides an advantage in efficacy or tolerability in the management of IDA compared to oral iron therapies available on VA National Formulary. It is also unknown if ferric maltol would provide an advantage over IV iron therapy, if indicated, as ferric maltol did not demonstrate noninferiority when compared to IV ferric carboxymaltose in one open-label comparison trial in patients with IDA and IBD.[12] At this time, oral iron therapies available on VA National Formulary should be used for management of IDA in patients where oral iron is indicated. If IV iron is determined to be appropriate for management of the patient with IDA, several products are available, with selection based on patient specific factors. As data with ferric maltol are insufficient to determine benefit over current available options for IDA, oral or IV, use in VA may be determined on a case by case basis, depending on patient specific considerations including efficacy or tolerability to current available options, convenience, and cost.

References

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