

Ferric Pyrophosphate Citrate (TRIFERIC) National Drug Monograph February 2020

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 Information¹

Description/Mechanism of Action

- Ferric pyrophosphate citrate is a mixed-ligand iron complex in which iron is bound to pyrophosphate and citrate. Iron, in the form of ferric pyrophosphate citrate, is added to hemodialysate solution for administration to patients by transfer across the dialyzer membrane, entering the circulation for binding to transferrin for transport to erythroid precursor cells to be incorporated into hemoglobin (Hgb).

Indication(s) Under Review in This Document

- Ferric pyrophosphate citrate is an iron replacement product indicated for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD).

Dosage Form(s) Under Review

- Ferric pyrophosphate citrate solution:
 - 27.2 mg of elemental iron per 5 mL in a 5 mL ampule. One 5 mL ampule is added to 2.5 gallons of bicarbonate concentrate.
 - 272 mg per 50 mL in a 50 mL ampule. One 50 mL ampule is added to 25 gallons of master bicarbonate mix.
- Ferric pyrophosphate citrate powder:
 - 272 mg of elemental iron in a single use packet. One powder packet is added to 25 gallons of master bicarbonate mix.

Clinical Evidence Summary¹⁻³

Efficacy Considerations^{2,3}

- The Continuous Replacement Using Iron Soluble Equivalents (CRUISE) 1 and 2 trials were Phase 3 multicenter, multinational (U.S. and Canada), single-blind, placebo-controlled trials to determine the effect of 48 weeks of treatment with ferric pyrophosphate citrate on maintaining Hgb in patients with HDD-CKD.
- Efficacy data for the primary endpoint are summarized in Table 1.

Table 1: Efficacy Results from Clinical Trials (Primary Endpoint)

CRUISE 1 and 2 (combined results)	Ferric Pyrophosphate Citrate (N 290)	Placebo (N=295)
Baseline Hgb (g/dL), mean ± SD	11.0 ± 0.6	10.9 ± 0.6
End-of-treatment Hgb (g/dL), mean ± SD	10.9 ± 1.3	10.5 ± 1.3
Change Hgb (g/dL), mean ± SD	-0.1 ± 1.2	-0.4 ± 1.2
Mean difference (95% CI)	0.4 ± 0.1 (0.2 to 0.6)	

- Results demonstrated that treatment with ferric pyrophosphate citrate maintained Hgb from baseline to end of treatment compared to a decrease of 0.4 g/dL in patients in the placebo group. There was a significantly smaller mean decrease from baseline to end of treatment in the secondary endpoints of serum ferritin (-69.7 mcg/L vs. -133.1 mcg/L), reticulocyte hemoglobin content (CHr) (-0.4 pg vs. -0.9 pg), serum iron (-1.3 mcg/dL vs. -6.7 mcg/dL), and transferrin saturation (TSAT) (-1.0% vs. -3.2%) with ferric pyrophosphate citrate compared to placebo, respectively.
- Oral and intravenous (IV) iron were not allowed, and the dose of erythropoiesis-stimulating agent (ESA) was maintained during the study. Per protocol, completion of randomized treatment was considered at 48 weeks; Hgb < 9.0 or > 12.0 g/dL; ferritin < 100 mcg/L; or Hgb > 11.5 g/dL with Hgb ≥ 1.0 g/dL over 4 weeks. It was noted that 51.6% of patients completed the treatment phase as a result of protocol-mandated changes in management of anemia. Withdrawals from the study due to blood transfusions occurred in 9 patients in the ferric pyrophosphate citrate group compared to 23 patients in the placebo group.

Safety Results from Clinical Trials²

- A summary of treatment emergent adverse events (TEAE) are reported in Table 2 below. It was noted that none of the serious TEAEs or deaths were considered related to study drug.

Table 2: Safety Results from Clinical Trials

CRUISE 1 and 2 (combined results)	Ferric Pyrophosphate Citrate	Placebo
≥ 1 TEAE	78.4%	75.3%
Serious TEAE	27.7%	27.4%
Drug-related TEAE	7.5%	4.1%
Discontinuation due to TEAE	4.5%	2.4%
Death	10	6

Safety Considerations^{1,2}

- **Boxed warnings:** None
- **Contraindications:** None
- **Other warnings / precautions:** Serious hypersensitivity reactions, including some that have been life-threatening and fatal, have been reported in patients receiving parenteral iron products. It is recommended to observe the patient for signs and symptoms of hypersensitivity during and after hemodialysis and until the patient is clinically stable. Personnel and therapies should be immediately available for treatment of serious hypersensitivity reactions if they were to occur. Hypersensitivity was reported in one patient (0.3%) receiving ferric pyrophosphate citrate in clinical trials.
- **Adverse reactions**
 - **Common:** the most common adverse reaction with ferric pyrophosphate citrate was procedural hypotension (21.6%; vs. 19.3% placebo).

Other Considerations¹⁻⁵

- The role of ferric pyrophosphate citrate for its potential impact on utilization of iron replacement therapy and/or ESAs in patients with HDD-CKD has yet to be established. Results of a Phase 2 trial to evaluate the difference in ESA dose to maintain Hgb in patients with HDD-CKD receiving ferric pyrophosphate citrate compared to placebo, the Physiological Replenishment Iron Maintenance Equivalency (PRIME) study, were also submitted to the FDA to support the request for approval of the indication for ferric pyrophosphate citrate to reduce the dose of ESA to maintain goal Hgb. From baseline to end of treatment, ESA dose was increased 4.9% in patients receiving ferric pyrophosphate citrate compared to an increase of 39.8% in patients on placebo; with a significant difference between treatment groups. Use of IV iron was reported in 21.2% of patients treated with ferric pyrophosphate citrate compared to 39.2% of patients in the placebo group; and overall, patients in the treatment group required

51% less IV iron compared to placebo.⁴ Based on the exploratory analysis and results, it was concluded that the data were insufficient to support the additional indication, and that further study was warranted.³ In addition, it was noted that in the CRUISE 1 and CRUISE 2 trials, the prescribed ESA dose was higher in the ferric pyrophosphate citrate group compared to placebo during weeks 10 to 24, then higher in the placebo group compared to treatment with ferric pyrophosphate citrate after week 24 to the end of treatment.^{2,3}

- According to the manufacturer, treatment with ferric pyrophosphate citrate results in an iron concentration of dialysate of 2 mmol/L (110 mcg/L), which would be equivalent to 5 to 7 mg iron administered to a patient during each dialysis session; the amount that is estimated to be lost during hemodialysis treatment.^{1,5} Data from a Phase 1 study of 12 patients on hemodialysis to determine the amount of iron transferred during treatment with ferric pyrophosphate citrate and under various conditions were reviewed by the FDA. Based on the reference amount of iron delivery by treatment (mean 692 mcg; median 348 mcg), and reviewer calculations of amount provided over one year of hemodialysis sessions, it was felt the amount of iron delivered by treatment with ferric pyrophosphate citrate alone may be insufficient to adequately replace iron loss.³
- Ferric pyrophosphate citrate is added to bicarbonate concentrate to be used in the dialysate. As multiple doses can be added to the master bicarbonate mix (at a ratio of one 5 ml ampule to each 2.5 gallons bicarbonate concentrate, or one 50 ml ampule or one powder packet to each 25 gallons bicarbonate concentrate) at a dialysis center, patients receiving treatment at a dialysis facility with a central bicarbonate delivery system will need to have treatment individualized based on whether or not ferric pyrophosphate citrate is indicated.^{1,5}

Other Therapeutic Options^{1,6}

Ferric pyrophosphate citrate is used as an iron replacement product in the dialysate in patients with HDD-CKD. Select IV iron products listed on the VA National Formulary that have been used for maintenance after initial repletion in iron deficiency anemia in patients with HDD-CKD are provided in Table 3 below. Ferric carboxymaltose (approved for iron deficiency anemia in patients with inadequate response or unable to tolerate oral iron, or in patients with non-dialysis dependent CKD) and ferumoxytol (approved for iron deficiency anemia in patients with inadequate response or unable to tolerate oral iron, or in patients with CKD) are not listed in the table below – these products are available non-formulary in VA. Oral iron therapy products are also available as an option in patients with iron deficiency anemia and HDD-CKD.

Table 3 Select Iron Products Used in HDD-CKD

Drug	Formulary status	FDA Indications	Other Considerations
Ferric pyrophosphate citrate	TBD	Iron replacement to maintain Hgb in HDD-CKD	Only available product for iron replacement that is added to the dialysate to be administered during the hemodialysis session. Product added to bicarbonate concentrate for hemodialysis; use within 24 hours of preparation. Warnings and precautions for serious hypersensitivity reactions; monitor patient.
Iron dextran (LMW)	F	IDA in CKD (oral inadequate or unable to take)	Boxed warning for anaphylactic-type reactions; administer initial test dose; monitor patient. Individualize maintenance if needed after initial repletion.
Iron sucrose	F	IDA in CKD	Warnings and precautions for serious hypersensitivity reactions; monitor patient. Individualize maintenance if needed after initial repletion.
Sodium ferric gluconate	F	IDA in HDD-CKD on ESA	Warnings and precautions for serious hypersensitivity reactions; monitor patient. Individualize maintenance if needed after initial repletion.

CKD=chronic kidney disease; ESA=erythropoiesis-stimulating agent; F=VA National Formulary; HDD=hemodialysis dependent; IDA=iron deficiency anemia; LMW=lower molecular weight; TBD=to be determined

Projected Place in Therapy

- It is reported that the overall prevalence of CKD in the general population is approximately 14%.⁷ Over 661,000 Americans have kidney failure, with nearly 64% of these patients on hemodialysis.⁸ According to VA/DoD guidelines on the management of CKD, compared to the general population, CKD is increased by approximately one third in the Veteran population given the patient demographics and prevalence of comorbidities associated with CKD including hypertension and diabetes mellitus.⁹
- Anemia is common in patients with CKD and is primarily caused by decreased kidney production of erythropoietin. Other causes of anemia in patients with CKD include blood loss, decreased red blood cell survival, iron deficiency, and chronic inflammation. Iron deficiency is especially likely to occur in patients on hemodialysis due to frequent blood drawing or from the process of dialysis itself.^{6,10,11} In addition, iron deficiency can decrease the response to ESAs; therefore, iron replacement therapy is often used in conjunction with an ESA when it is prescribed for the management of anemia in CKD, and may help to lower the amount of ESA required to obtain target Hgb.^{6,10,12}
- Clinical practice guidelines recommend that, for patients with anemia and CKD on hemodialysis, the preferred administration of iron is by the IV route, taking into consideration the risk vs. benefit.^{6,12} In clinical trials evaluating ferric pyrophosphate citrate in patients with HDD-CKD, at baseline, approximately 98% of patients were being treated with an ESA and nearly 80% were previously receiving IV iron.²
- Overall, there is moderate quality evidence for the use of ferric pyrophosphate citrate to maintain Hgb in patients with HDD-CKD.² Ferric pyrophosphate citrate is mixed with the dialysate and administered during the hemodialysis session. Whether the amount of iron replacement provided by ferric pyrophosphate citrate during each hemodialysis session is sufficient to adequately replace iron loss requires confirmation. Additional study is also needed to determine the clinical significance of potential reduction in IV iron or ESA dose with use of ferric pyrophosphate citrate.

References

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