

# Ferric Citrate (AURYXIA™)

## National Drug Monograph

### April 2015

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 when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.*

#### FDA Approval Information<sup>1</sup>

<b>Description/Mechanism of Action</b>	Ferric citrate binds dietary phosphate in the gastrointestinal (GI) tract, thereby decreasing absorption and lowering concentrations of serum phosphorus.
<b>Indication(s) Under Review in this document</b>	Ferric citrate is a phosphate binder indicated for the control of serum phosphorus levels in patients with chronic kidney disease (CKD) on dialysis.
<b>Dosage Form(s) Under Review</b>	Ferric citrate is available as 210 mg (ferric iron) tablets, equivalent to 1 gram ferric citrate.
<b>REMS</b>	<input type="checkbox"/> REMS <input checked="" type="checkbox"/> No REMS <input checked="" type="checkbox"/> Post-marketing requirements (pediatric study) <i>See Other Considerations for additional REMS information</i>
<b>Pregnancy Rating</b>	Category B

#### Executive Summary

Efficacy <sup>1-6</sup>	<ul style="list-style-type: none"> <li>• Treatment with ferric citrate for 4 weeks in patients with CKD on dialysis and elevated serum phosphorus resulted in a greater reduction in the primary efficacy endpoint of a difference in serum phosphorus compared to placebo (adjusted mean treatment difference -2.18mg/dl, 95% CI -2.59 to -1.77; P&lt;0.001).</li> <li>• This study also reported no significant difference in serum phosphorus between ferric citrate and the active control group (sevelamer carbonate, calcium acetate, or both) during the 52-week treatment period (adjusted mean difference 0.01 mg/dl, 95% CI -0.30 to 0.32; P=0.95).</li> <li>• Results for the additional secondary endpoints showed treatment with ferric citrate significantly increased serum ferritin and transferrin saturation (TSAT) compared to the active control group, and significantly decreased the use of intravenous (IV) iron and erythropoiesis-stimulating agents (ESAs).</li> </ul>
Safety <sup>1-3</sup>	<ul style="list-style-type: none"> <li>• Iron absorption from ferric citrate may lead to excessive elevations in iron stores. It is recommended to monitor ferritin and TSAT prior to initiating ferric citrate and during therapy. Ferric citrate is contraindicated in patients with iron overload syndromes (e.g., hemochromatosis).</li> <li>• The most common adverse reactions with ferric citrate include diarrhea, nausea, constipation, vomiting and cough. Due to the iron content, ferric citrate is associated with dark stools, which do not affect laboratory tests for fecal occult blood.</li> <li>• Safety has not been established in patients with active, symptomatic GI bleeding or inflammatory bowel disease as these patients were excluded from the clinical trials with ferric citrate.</li> </ul>
Other Considerations <sup>1-10</sup>	<ul style="list-style-type: none"> <li>• Safety and efficacy for use in patients with CKD not on dialysis (off-label) or in patients with CKD to treat iron deficiency anemia (off-label) has yet to be established.</li> <li>• The potential cost-effectiveness for use in patients with CKD on dialysis and elevated phosphorus being treated for concomitant iron deficiency anemia with iron replacement therapy and/or ESAs requires further evaluation.</li> </ul>

<p>Potential Impact<sup>1,2,6-8,11-13,16-25</sup></p>	<ul style="list-style-type: none"> <li>Projected place in therapy: Ferric citrate may be considered in patients with CKD on dialysis who meet criteria for a VA National Formulary non-calcium, non-aluminum phosphate binder (i.e., lanthanum carbonate, sevelamer carbonate; refer to VA <a href="#">Criteria for Use</a>) and 1) documented intolerance or inadequate efficacy after a trial of lanthanum carbonate and a trial of sevelamer carbonate; or 2) patient is pregnant and risk vs. benefit has been considered and it has been determined that the patient will continue on a phosphate binder, or the patient is of child-bearing potential and it has been determined that the patient will continue on a phosphate binder if the patient becomes pregnant. The role of ferric citrate for its effects on iron parameters and potential impact on utilization of iron replacement therapy and/or ESAs in patients with CKD on dialysis being treated for elevated phosphorus has yet to be established. Adequate data on the long-term safety and efficacy of ferric citrate in patients with CKD not on dialysis are not available at this time to determine its place in therapy in these patients.</li> </ul>
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## Background

### Purpose for review

Recent FDA approval.

Issues to be determined:

- ✓ Does the evidence show that ferric citrate is effective for the treatment of elevated phosphorus in patients with CKD on dialysis?
- ✓ Are there other beneficial effects of ferric citrate?
- ✓ Does ferric citrate offer advantages to currently available alternatives?
- ✓ Does ferric citrate offer advantages over current VANF agents?
- ✓ What safety issues need to be considered with the use of ferric citrate?
- ✓ Does ferric citrate have specific characteristics best managed by the non-formulary process or criteria for use?

### Other therapeutic options<sup>11-13</sup>

The most frequently used calcium-based phosphate binders that are listed on the VANF include calcium acetate and calcium carbonate. Non-aluminum, non-calcium phosphate binders that are available on the VANF or non-formulary are listed below:

Select Formulary Alternatives	FDA Indication	Dose	Other Considerations
Lanthanum carbonate 250,500,750mg,1gm chewable tablets	Reduce phosphorus in ESRD	1 to 3 gm/day divided 3 times daily	Restricted to CFU
Sevelamer carbonate 800mg tablets	Control phosphorus in CKD on dialysis	2.4 to 7.2gm/day divided 3 times daily	Restricted to CFU
Select Non-Formulary Alternatives <sup>a</sup>			
Sucroferric oxyhydroxide 500mg chewable tablets	Control phosphorus in CKD on dialysis	1.5 to 3gm/day divided 3 times daily	Recommendations for Place in Therapy

<sup>a</sup>Sevelamer hydrochloride and sevelamer carbonate powder also available non-formulary  
CFU=criteria for use; CKD=chronic kidney disease; ESRD=end-stage renal disease

## Efficacy (FDA Approved Indications)<sup>1-6</sup>

### Literature Search Summary

A literature search was performed on PubMed/Medline (1976 to February 2015) using the search term ferric citrate. The search was limited to clinical trials performed in humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials. Randomized controlled Phase 3 trials published in peer-reviewed journals evaluating the FDA approved indications were included.

## Review of Efficacy

- FDA labeling for ferric citrate in patients with CKD on dialysis for the control of serum phosphorus was based on two published trials: one long-term active-controlled safety and efficacy trial that included a short-term primary efficacy endpoint compared to placebo (Lewis et al.)<sup>2</sup> and one short-term dose-finding study (Dwyer et al.)<sup>3</sup>; details of which are provided below. These trials were funded by Keryx Biopharmaceuticals, Inc.
- Additional support for the FDA approved indication includes a published study conducted in Japan;<sup>4</sup> a brief summary of the trial is provided. Another trial conducted in Japan is briefly reviewed for report of its long-term data.<sup>5</sup>
- Results from the primary efficacy study reported a statistically significant reduction in serum phosphorus with ferric citrate compared to placebo after 4 weeks in patients with CKD on dialysis and elevated serum phosphorus.<sup>2</sup> This study also reported a similar reduction in serum phosphorus with ferric citrate compared to the active control group after 52 weeks of treatment.<sup>2</sup>
- Results for the additional secondary endpoints showed treatment with ferric citrate to significantly increase serum ferritin and TSAT compared to the active control group, and to significantly decrease the amount of IV iron and ESA.<sup>2,6</sup>
- Overall, there is moderate quality of evidence for the use of ferric citrate to reduce serum phosphorus in patients with elevated phosphorus and CKD on dialysis (Refer to Appendix A).

### Lewis et al.<sup>2</sup>

- The study published by Lewis et al., was a Phase 3 multicenter, multinational (U.S. and Israel), open-label, sequential trial that, after a 2-week wash out period of their previously prescribed phosphate binder, randomized 441 patients with end-stage renal disease (ESRD) on dialysis (hemodialysis or peritoneal dialysis) and serum phosphorus  $\geq 6.0$  mg/dl to ferric citrate (N=292) or active-control (calcium acetate or sevelamer carbonate, alone or in combination; N=149) for 52 weeks. Approximately 34% of patients in the ferric citrate treatment group discontinued therapy (36% of these due to an adverse event) compared to approximately 23% in the active control group. Patients who completed the ferric citrate treatment period (N=195) were re-randomized (N=192) to continue ferric citrate (N=96) or to receive placebo (N=96) for 4 weeks.
- The primary outcome of the trial was the change in serum phosphorus with ferric citrate compared to placebo at the end of the 4-week treatment period. The main secondary outcomes of the trial were the change in ferritin and TSAT, and the cumulative doses of IV iron and ESAs, with ferric citrate over the 52-week active-control treatment period.
- During the 52-week and 4-week treatment periods, respectively, study participants included: 53% and 59% Black or African American, 42% and 37% Caucasian. Overall, median age of participants was 55 years, and 61% were male. During the 52-week treatment period, 82% of patients were receiving an ESA at baseline, and 61% were being treated with IV iron. These treatments could be adjusted per protocol, at the discretion of the provider.
- The primary efficacy endpoint of a difference in serum phosphorus after 4 weeks was statistically significant in favor of treatment with ferric citrate compared to placebo (adjusted mean treatment difference -2.18mg/dl, 95% CI -2.59 to -1.77; P<0.001). The study also reported no significant difference in serum phosphorus between ferric citrate and the active control group (of 149 patients, 73 received sevelamer carbonate, 36 were on calcium acetate, and 40 patients were taking both) during the 52-week treatment period (adjusted mean difference 0.01 mg/dl, 95% CI -0.30 to 0.32; P=0.95). The median daily dose according to the number of tablets was reported as follows: 8.0 tablets/day ferric citrate; 7.7 tablets/day calcium acetate; and 9.0 tablets/day sevelamer carbonate. Results for the secondary pre-specified endpoints showed treatment with ferric citrate to significantly increase serum ferritin and TSAT compared to the active control group, and to significantly decrease the amount of IV iron and ESA. It was also reported that during the last 6 and 9 months of the 52-week treatment period, 43.8% and 47.7% of patients treated with ferric citrate, compared with 63.0% and 80.1% of patients in the active control group, respectively, received any IV iron (P<0.001). The change in mean hemoglobin (Hgb) levels was also slightly but statistically significantly greater with ferric citrate compared to the active control group. Details of these results are provided in the table below.

**Lewis et al. Study Results<sup>2</sup>**

Endpoint (4-week period)	Ferric Citrate (N=91)	Placebo (N=91)	Adjusted Mean Difference (95% CI)	P
	Mean Baseline <sup>a</sup> vs. End			
Phosphorus (mg/dl) <sup>b,c</sup>	5.12 vs. 4.86	5.44 vs. 7.21	-2.18 (-2.59 to -1.77)	<0.001

  

Endpoint (52-week period)	Ferric citrate (N=292)	Active Control (N=149)	Adjusted Mean Difference (95% CI)	P
	Mean Baseline vs. End			
Phosphorus (mg/dl)	7.41 vs. 5.36	7.56 vs. 5.38	0.01 (-0.30 to 0.32)	0.95
Ferritin (ng/ml)	593 vs. 899	609 vs. 628	282 (197 to 366)	<0.001
TSAT (%)	31.2 vs. 39.3	30.9 vs. 29.7	9.5 (6.4 to 12.6)	<0.001
IV iron (mg/week) <sup>d</sup>	12.9	26.8	-12.5 (-17.2 to -7.9)	<0.001
ESA dose (units/week) <sup>d</sup>	5303	6954	-1191 (-2632 to 0)	0.04
Hgb (g/dl)	11.61 vs. 11.42	11.71 vs. 11.14	0.33 (0.06 to 0.60)	0.02

<sup>a</sup> Baseline levels after 52-week treatment period with ferric citrate

<sup>b</sup> Primary endpoint

<sup>c</sup> 91 patients analyzed in ferric citrate and placebo groups

<sup>d</sup> Summarized for entire follow-up period; mean baseline dose or mean end dose not provided

Additional details of the difference in iron parameters and IV iron/ESA use with ferric citrate compared to active control were reported at different time points throughout the 52-week period. The authors reported that an increase in ferritin and TSAT with ferric citrate compared with active control were seen by week 12 (change in ferritin 114.1 ng/ml, P<0.001; change in TSAT 8.62%, P<0.001), with a plateau in the change in TSAT at 12 weeks, and a continued increase in change in ferritin through week 24. In addition to the difference in IV iron and ESA use as reported in the table above, 85.4% of patients treated with ferric citrate compared to 69.0% of patients in the active control group did not receive treatment with IV iron at 52-weeks (P<0.001).<sup>5</sup>

**Dwyer et al.<sup>3</sup>**

- Fixed-doses of 1 gm, 6 gm, or 8 gm daily ferric citrate were studied in a Phase 3 multicenter (U.S.), open-label randomized trial of 151 patients with elevated phosphorus and CKD on hemodialysis who received up to 28 days of therapy.
- The primary endpoint of the trial was the change in serum phosphorus from baseline to end of treatment with ferric citrate.
- At Week 28, there was a dose-dependent reduction in serum phosphorus, with a mean change of -0.10±1.3 mg/dl in the 1 gm/day ferric citrate (equivalent to one tablet, or 210mg as ferric iron) treatment group, compared to -1.9±1.7 and -2.1±2.0 mg/dl in the 6 gm/day and 8 gm/day treatment groups, respectively. The difference between the higher doses and the lower treatment dose was statistically significant (P<0.001 for both the 6 gm/day and 8 gm/day doses). The difference between the 6 gm/day and 8 gm/day doses were not statistically significant.
- Yokoyama et al.<sup>4</sup> conducted a Phase 3, multicenter (Japan), randomized, open-label, parallel-group study in 229 patients with elevated serum phosphorus and CKD on hemodialysis to compare treatment with ferric citrate (JTT-751 250 mg; approximately 62 mg iron) with dose adjusted between 1.5 and 6.0 gm/day, and sevelamer hydrochloride with dose adjusted between 3.0 and 9.0 gm/day, for 12 weeks. The achieved maintenance dose was 3.25 gm/day ferric citrate and 4.94 gm/day sevelamer hydrochloride. The primary endpoint of a change in serum phosphorus from baseline to end of treatment was statistically significant in both treatment groups (P<0.001), with a mean change of -0.82 mmol/L (-2.53 mg/dl) in the ferric citrate treatment group and -0.78 mmol/L (-2.40 mg/dl) in the sevelamer hydrochloride treatment group. The between-group comparison determined the two treatments to be non-inferior (-0.10 mg/dl, 95% CI -0.39 to 0.20 mg/dl).<sup>4</sup>
- Another study published by Yokoyama et al.<sup>5</sup> reported results from a Phase 3, multicenter (Japan), open-label, dose titration safety and efficacy study of ferric citrate in 180 patients with CKD on hemodialysis, with an elevated serum phosphorus or who previously received medications for hyperphosphatemia. Seventy-one percent of patients completed the 52-week trial. The mean dose of ferric citrate (as JTT-751 250 mg) at the end of treatment was 2.73 gm/day (10.9 tablets per day). The efficacy endpoint was a mean serum phosphorus of 5.42 mg/dl at the end of treatment, with a change from baseline of -0.11 mg/dl (note that there was no wash-out period in this trial). The safety endpoint reported 38 serious adverse events, where one (abdominal pain) was considered to be related to the study drug. In addition, there were 9 adverse events resulting in drug

discontinuation (3 elevated Hgb levels above baseline; 2 diarrhea; 1 each of elevated ferritin, extrasystole, liver dysfunction, elevated serum aluminum). Adverse drug reactions were reported in 27.2% of patients and were most commonly GI related (19%). This study also reported the following change in iron parameters from baseline to end of treatment, respectively: ferritin 57.35 ng/ml vs. 209.50 ng/ml; TSAT 23.0% vs. 35.6%. It was also reported that the mean weekly dose of ESA was reduced by 25% (baseline 4,541 units/week vs. 3,412 units/week at end of treatment). The mean 4-weekly doses of IV iron were reported as follows: baseline to week 12: 57.3 mg; weeks 12 to 28: 12.8 mg; weeks 28 to 52: 3.6 mg.<sup>5</sup>

**Potential Off-Label Use<sup>2,5-8</sup>**

- Ferric citrate is FDA approved for the management of elevated phosphorus in patients with CKD on dialysis. One placebo-controlled trial, conducted in 149 patients with CKD stage 3 to 5 (not on dialysis), evaluated treatment with ferric citrate for 12 weeks. The co-primary endpoints included the change in serum phosphorus and TSAT, with a treatment effect difference of: TSAT 11.3% (95% CI 8.0% to 14.7%; P<0.001), with 22%±7% at baseline vs. 32%±14% at the end of treatment (whereas the levels remained stable in the placebo group); serum phosphorus -0.47 mg/dl (95% CI -0.67 to -0.26; P<0.001). Secondary endpoints included the treatment effect difference in ferritin of 77.5 ng/ml (P<0.001) and Hgb 0.6 g/dl (P<0.001). Treatment with an ESA or IV iron was not allowed during the study.<sup>7</sup> Another clinical trial (conducted in Japan) has also been published evaluating treatment with ferric citrate in 86 patients with CKD (93% of patients enrolled were CKD stage 5) not on dialysis. The primary endpoint of reduction in serum phosphorus from baseline to end of treatment at 12 weeks was -1.29 mg/dl (95% CI -1.63 to -0.96; P<0.001) with ferric citrate (mean dose 3.5 gm/day), the difference which was statistically significant compared to placebo (-1.31 mg/dl, 95% CI -1.80 to -0.82; P<0.001).<sup>8</sup> The long-term safety and efficacy of ferric citrate in patients with CKD not on dialysis has not been established.
- Although not a primary endpoint of the trial, data have been reported on the effect of ferric citrate on iron parameters, that showed an increase in ferritin and TSAT, as well as a reduction in use of IV iron and ESAs, in patients with CKD on dialysis being treated for an elevated serum phosphorus.<sup>2,5,6</sup> Additional clinical trials are needed to determine the clinical benefit of ferric citrate compared to other treatment options in patients with CKD and elevated phosphorus with, or being treated for, iron deficiency anemia.

**Safety<sup>1</sup>**

(for more detailed information refer to the product package insert)

	<b>Comments</b>
<b>Boxed Warning</b>	<ul style="list-style-type: none"> <li>• None</li> </ul>
<b>Contraindications<sup>1</sup></b>	<ul style="list-style-type: none"> <li>• Iron overload syndromes (e.g., hemochromatosis)</li> </ul>
<b>Warnings/Precautions<sup>1,2</sup></b>	<ul style="list-style-type: none"> <li>• <b>Iron overload</b> Iron absorption from ferric citrate may lead to excessive elevations in iron stores. Monitor ferritin and TSAT prior to initiating ferric citrate and during therapy. In a clinical trial where concomitant IV iron was allowed, more patients receiving ferric citrate had ferritin levels &gt; 1500 ng/ml compared to patients in the active control group; patients may require a reduction in dose or discontinuation of IV iron.</li> <li>• <b>Accidental overdose of iron containing compounds</b> Iron containing compounds are the leading cause of fatal poisoning in children less than 6 years of age. Keep ferric citrate out of reach of children. In case of an accidental overdose, contact a doctor or poison control center immediately.</li> <li>• <b>Gastrointestinal bleeding or inflammation</b> Safety has not been established in patients with active, symptomatic gastrointestinal bleeding or inflammatory bowel disease as these patients were excluded from the clinical trials with ferric citrate.</li> </ul>

**Safety Considerations<sup>1,2,14</sup>**

- In an active-controlled trial, reports of adverse events with ferric citrate appeared to be similar to those reported in the group being treated with sevelamer carbonate and/or calcium acetate, with GI complaints being the most common reported adverse event.<sup>1,2</sup> Patients with active, symptomatic GI bleeding or inflammatory bowel

disease were excluded from the clinical trials, so the safety of ferric citrate in these patients is unknown.<sup>1,2</sup>

- As citrate is associated with an increase in aluminum absorption, it has been suggested that there may be an increased risk for aluminum toxicity with the administration of ferric citrate.<sup>14</sup> In the 52-week pivotal trial, it was reported that there was no significant difference in serum bicarbonate or serum aluminum between ferric citrate and the active control group.<sup>2</sup>
- As iron absorption from ferric citrate may occur, leading to excessive elevations in iron stores, ferritin and TSAT should be monitored prior to initiating ferric citrate and during therapy.<sup>1</sup> Ferric citrate is contraindicated in patients with iron overload syndromes (e.g., hemochromatosis).<sup>1</sup> Treatment with ferric citrate for elevated phosphorus in patients with CKD on dialysis has demonstrated an increase in ferritin and TSAT, as well as a reduction in use of IV iron and ESAs;<sup>2</sup> the safety of ferric citrate for use in patients receiving treatment for iron deficiency anemia or in patients not on dialysis, has yet to be established.

**Adverse Reactions<sup>1,2</sup>**

Common adverse reactions <sup>1</sup>	Diarrhea (21%), nausea (11%), constipation (8%), vomiting (7%), cough (6%) were reported in > 5% patients treated with ferric citrate. Due to the iron content ferric citrate is associated with dark stools, which do not affect laboratory tests for fecal occult blood.
Death/Serious adverse reactions <sup>1,2</sup>	During the long-term safety and efficacy trial, 4.5% (13 of 292) of patients receiving ferric citrate died and 5.4% (8 of 149) patients in the active control group died. It was reported that no deaths were considered to be due to study drug treatment. Treatment-emergent serious adverse events occurred in 39.1% of patients treated with ferric citrate (113 of 289) compared to 49.0% of patients receiving active control (73 of 149). Serious adverse events with ferric citrate vs. active control were classified as follows: GI 6.9% vs. 12.8%; infection 12.5% vs. 18.1%; cardiac 7.3% vs. 12.1%, respectively.
Discontinuations due to adverse reactions <sup>1,2</sup>	Ferric citrate was discontinued due to an adverse event in 21% of patients compared to 15% receiving active control; noting that tolerability to active control was an inclusion criterion of the study. The most common reason for discontinuation with ferric citrate was due to a GI adverse reaction (14%).

**Drug Interactions<sup>1</sup>**

**Drug-Drug Interactions<sup>1</sup>**

- Consider separating the administration of ferric citrate with medications where an effect on bioavailability may alter the safety or efficacy of the drug. Monitor clinical response or drug levels of medications with a narrow therapeutic range, as indicated. Refer to the product package insert for a list of medications that can be administered concomitantly with ferric citrate. It is recommended that doxycycline be taken at least 1 hour before ferric citrate.

**Risk Evaluation**

As of January 27, 2015

	Comments															
Sentinel event advisories	<ul style="list-style-type: none"> <li>• None</li> </ul>															
Look-alike/sound-alike error potentials	<table border="1"> <thead> <tr> <th>NME Drug Name</th> <th>Lexi-Comp</th> <th>First DataBank</th> <th>ISMP</th> <th>Clinical Judgment</th> </tr> </thead> <tbody> <tr> <td>Ferric citrate 210 mg tablet</td> <td>None</td> <td>None</td> <td>None</td> <td>Ferric gluconate</td> </tr> <tr> <td>AURYXIA</td> <td>None</td> <td>None</td> <td>None</td> <td>Arixtra Arava Avandia</td> </tr> </tbody> </table> <ul style="list-style-type: none"> <li>• Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)</li> </ul>	NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment	Ferric citrate 210 mg tablet	None	None	None	Ferric gluconate	AURYXIA	None	None	None	Arixtra Arava Avandia
NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment												
Ferric citrate 210 mg tablet	None	None	None	Ferric gluconate												
AURYXIA	None	None	None	Arixtra Arava Avandia												

## Other Considerations<sup>2,5-7,9,10,15</sup>

- The role of ferric citrate for its effects on iron parameters and potential impact on utilization of iron replacement therapy and/or ESAs in patients with CKD, on dialysis or not on dialysis, with iron deficiency anemia being treated for elevated phosphorus, has yet to be established.<sup>2,5-7</sup>
- Pill burden with ferric citrate (8.0 tablets/day) appeared to be similar to treatment with calcium acetate (7.7 tablets/day) and sevelamer carbonate (9.0 tablets/day).<sup>2</sup> A mean of approximately 3 tablets/day of sucroferric oxyhydroxide (also an iron-based phosphate binder) was reported to be used in a comparison trial with sevelamer carbonate (approximately 8 tablets/day).<sup>15</sup> Direct comparison data with ferric citrate and sucroferric oxyhydroxide are not available.
- According to one cost model, the total annual cost for an ESA and IV iron would be reduced by approximately \$1 billion (based on Centers for Medicare and Medicaid Services base rate) or \$870 million (based on 2011 actual utilization) for outpatients undergoing hemodialysis in the U.S.,<sup>9</sup> based on a 20% reduction in use of an ESA and 40% reduction in IV iron as a result of treatment with ferric citrate.<sup>4,9</sup> It should be noted that this cost model did not take into account the price for treatment with the phosphate binder(s).<sup>9</sup> A cost-offset model reported that the total monthly cost for dialysis care (including dialysis, ESAs and IV iron) was reduced by \$80,214 per 500 patients with end-stage renal disease (ESRD) when treated with ferric citrate compared to other phosphate binders. The model included an expected mean dose reduction of ESA (epoetin alfa) of 500.2 units per session, and mean reduction in IV iron of 5.79 mg per session. The monthly cost per 500 patients with ESRD for an ESA was reported to be reduced by 8.15% (or \$50,808), and for IV iron by 33.2% (or \$29,406), with ferric citrate compared to other phosphate binders. This model assumed the price for phosphate binders would be cost neutral.<sup>10</sup> The proposed potential reduction in treatment cost with IV iron and/or an ESA with the use of ferric citrate needs to also take into account the price difference between ferric citrate and the other available phosphate binders.

## Dosing and Administration<sup>1</sup>

- The recommended starting dose of ferric citrate is 210 mg (ferric iron; equivalent to 1 gm ferric citrate), 2 tablets taken orally three times daily with meals.
- Doses should be adjusted by 1 to 2 tablets as needed (at an interval of one week or more) to maintain a serum phosphorus at target levels, up to a maximum of 12 tablets daily.

## Special Populations (Adults)<sup>1</sup>

	Comments
<b>Elderly<sup>1</sup></b>	<ul style="list-style-type: none"> <li>• No obvious differences in efficacy or tolerability were noted in patients 65 years of age or older treated with ferric citrate.</li> </ul>
<b>Pregnancy<sup>1</sup></b>	<ul style="list-style-type: none"> <li>• Ferric citrate is Pregnancy Category B</li> <li>• There are no adequate and well-controlled trials in pregnant women.</li> <li>• In addition, ferric citrate's effect on the absorption of vitamins or other nutrients has not been studied in pregnant women.</li> <li>• The package insert notes that an iron overdose in pregnant women may increase the risk for spontaneous abortion, gestational diabetes and fetal malformation.</li> </ul>
<b>Lactation<sup>1</sup></b>	<ul style="list-style-type: none"> <li>• Iron has been shown to be transferred to breast milk in rats; therefore, the infant may be exposed to iron if nursed by a woman receiving ferric citrate.</li> </ul>
<b>Renal Impairment</b>	<ul style="list-style-type: none"> <li>• No data identified.</li> </ul>
<b>Hepatic Impairment</b>	<ul style="list-style-type: none"> <li>• No data identified.</li> </ul>
<b>Pharmacogenetics/genomics</b>	<ul style="list-style-type: none"> <li>• No data identified.</li> </ul>

## Projected Place in Therapy

- It is estimated that approximately 25% of the U.S. population 60 years of age and older has CKD.<sup>16</sup> In 2012, it was reported that the prevalence of ESRD in the U.S. was nearly 637,000, with close to 409,000 patients on hemodialysis.<sup>17</sup> According to recent 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.<sup>16</sup> With declining kidney function, there is an alteration in mineral homeostasis including an effect on serum and tissue concentrations of phosphorus and calcium, as well as changes in vitamin D and parathyroid hormone levels, with therapy frequently initiated in an effort to correct these laboratory abnormalities. As kidney function continues to decline, changes in these parameters may have adverse effects on bone and extraskelatal calcification, with observational studies proposing an association between these disorders of mineral metabolism and cardiovascular disease and mortality.<sup>19</sup>
- In patients with CKD on dialysis, treatment guidelines suggest lowering serum phosphorus levels toward the normal range,<sup>19</sup> with use of a phosphate restricted diet as well as initiation of a phosphate binder, as indicated.<sup>19</sup> Calcium-based phosphate binders are often considered as initial therapy; non-aluminum, non-calcium phosphate binders have also been developed as an alternative due to the potential for hypercalcemia, and possible increased risk for vascular calcifications, with the use of calcium-based binders.<sup>19</sup> With conflicting data, however, further research is needed to determine whether there is a difference in long-term clinical outcomes with calcium-based vs. non-calcium based phosphate binders in patients with CKD.<sup>19</sup> More recently, iron-based phosphate binders have also been developed, including sucroferric oxyhydroxide and ferric citrate.<sup>20</sup>
- Anemia is also 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.<sup>21-23</sup> In addition, iron deficiency can decrease the response to ESAs;<sup>22</sup> therefore, iron replacement therapy is often used in conjunction with an ESA when it is prescribed for the management of anemia in CKD, and will help to lower the amount of ESA required to obtain target hemoglobin.<sup>21,25</sup> 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.<sup>18,21,24,25</sup> As seen in the clinical trial evaluating ferric citrate for elevated serum phosphorus in patients with CKD on dialysis, at baseline, approximately 82% of patients were being treated with an ESA and approximately 60% were receiving IV iron.<sup>2</sup> Although this trial reported a decrease in the amount of IV iron and ESA used, and a reduction in the percent of patients being treated with IV iron, in the group receiving ferric citrate compared to active controls, the clinical significance of this will need to be determined in a clinical trial designed to specifically evaluate this potential treatment effect.<sup>2</sup>
- If non-pharmacologic measures are inadequate to maintain serum phosphorus within the desired range, initiation of pharmacologic management may include:
  - A calcium-based phosphate binder (calcium acetate, calcium carbonate available on the VA National Formulary)
  - If a calcium-based phosphate binder is not tolerated or inadequate in achieving goal serum phosphorus, a non-aluminum, non-calcium phosphate binder may be considered (lanthanum carbonate, sevelamer carbonate available on VA National Formulary); refer to Phosphate Binder (Lanthanum, Sevelamer), [Criteria for Use](#).
  - Efficacy of the iron-based phosphate binders (ferric citrate, sucroferric oxyhydroxide) appear to be similar to other phosphate binders (ferric citrate compared to sevelamer carbonate, calcium acetate, or both; sucroferric oxyhydroxide compared to sevelamer carbonate) and may be considered if a trial of lanthanum carbonate and a trial of sevelamer carbonate are not tolerated or not effective in reducing serum phosphorus to the desired range in patients with CKD on dialysis. Refer to [Drug Monographs](#) for recommendations for place in therapy of sucroferric oxyhydroxide. Both ferric citrate and sucroferric oxyhydroxide are Pregnancy Category B<sup>1,13</sup> (as opposed to lanthanum carbonate<sup>10</sup> and sevelamer carbonate<sup>12</sup> that are Pregnancy Category C) and may be preferred if a patient is pregnant and the risk vs. benefit has been considered and it has been determined that the patient will continue on a non-calcium non-aluminum phosphate binder, or the patient is of child-bearing potential and it has been determined that the patient will continue on a non-calcium non-aluminum phosphate binder if the patient becomes pregnant.

- Of the available iron-based phosphate binders, treatment with ferric citrate has also demonstrated an increase in ferritin and TSAT (adjusted mean difference vs. active treatment of 282 ng/ml ferritin and 9.5% TSAT), as well as a reduction in the use of IV iron and ESAs (adjusted mean difference vs. active treatment -12.5 mg/week IV iron and -1191 units/week ESA), when being used for elevated phosphorus in patients with CKD on dialysis.<sup>2,6</sup> The clinical significance as to whether treatment with ferric citrate in patients with CKD on dialysis with elevated phosphorus and iron-deficiency anemia would result in a meaningful reduction in the dose or need for IV iron or ESA therapy is unknown at this time. Additional data from clinical trials specifically designed to evaluate the effect of ferric citrate on iron parameters and potential effect on utilization of iron replacement therapy and/or ESAs are needed to determine the role and long-term safety and efficacy of ferric citrate in patients with CKD on dialysis being treated for elevated phosphorus as well as for use in these patients receiving treatment for iron deficiency anemia.<sup>1,2,20</sup> Until additional data are available, use of ferric citrate in this patient population should only be done under careful consideration of the risk vs. benefit on a case by case basis. Sucroferric oxyhydroxide has not been shown to appreciably affect iron parameters.<sup>13,20</sup>
- Treatment with ferric citrate was reported to reduce serum phosphorus compared to placebo (difference of -0.47 mg/dl<sup>7</sup>; -1.31 mg/dl<sup>8</sup>) in patients with CKD not on dialysis; and according to one 12-week U.S. trial, provided a beneficial effect on iron parameters (mean treatment difference of increase in TSAT 11.3% vs. placebo).<sup>7</sup> Whether treatment with ferric citrate in patients with CKD not on dialysis with elevated phosphorus and iron-deficiency anemia would decrease the need for initiation of IV iron or ESA therapy is unknown at this time. Ferric citrate is not FDA approved for the reduction of elevated phosphorus in patients with CKD not on dialysis.<sup>1</sup> Use of ferric citrate in this patient population should only be done under careful consideration of the risk vs. benefit on a case by case basis until additional data as to the long-term safety and efficacy are available.<sup>1,19</sup>
- Gastrointestinal complaints were the most common reported adverse event with ferric citrate. Patients with active, symptomatic GI bleeding or inflammatory bowel disease were excluded from the clinical trials, so the safety of ferric citrate in these patients is unknown.<sup>1,2</sup> As iron absorption from ferric citrate may occur, leading to excessive elevations in iron stores, ferritin and TSAT should be monitored prior to initiating ferric citrate and during therapy.<sup>1</sup> Ferric citrate is contraindicated in patients with iron overload syndromes (e.g., hemochromatosis).<sup>1</sup>
- Overall, there is moderate quality of evidence for the use of ferric citrate for the treatment of elevated phosphorus in patients with CKD on dialysis. (Refer to Appendix A as well as sections on Efficacy and Other Considerations).

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**Appendix A: GRADEing the Evidence**

Designations of Quality

Quality of evidence designation Description

High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. *Ann Intern Med* 2010;153:194-199.