Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

New Drug Evaluation: Ferric Citrate tablets, oral

Date of Review: December 2015
Generic Name: ferric citrate
PDL Class: Phosphate Binders

End Date of Literature Search: October 2015
Brand Name (Manufacturer): Auryxia™ (Keryx Biopharmaceuticals)
Dossier Received: not available via AMCP

Research Questions:

- Is ferric citrate superior in efficacy to other phosphate binders (calcium acetate, lanthanum carbonate, sevelamer hydrochloride, sevelamer carbonate, and ferric oxyhydroxide) in lowering serum phosphorus in patients who have chronic kidney disease (CKD), are on dialysis, and have hyperphosphatemia?
- Is ferric citrate effective in improving mortality or morbidity associated with hyperphosphatemia, and is ferric citrate effective in lowering serum phosphorus levels in patients with CKD on dialysis?
- Is ferric citrate superior in safety, tolerance, and compliance to other phosphate binders in CKD dialysis patients with hyperphosphatemia?

Conclusions:

- There is no evidence ferric citrate is superior to other phosphate binders or improves mortality or morbidity associated with hyperphosphatemia in CKD patients on dialysis. However, there is low quality evidence ferric citrate is effective in lowering serum phosphorus. The efficacy of ferric citrate is supported by two phase 3 open-label, randomized trials: Trial 304 and Trial 305. Trial 304 was a sequential, three-phase study with a 2-week washout period, followed by a 52-week active-controlled safety period, followed by a 4-week placebo-controlled efficacy period. Patients who completed the 52-week safety period were re-randomized to ferric citrate (n=91) or placebo (n=91) for the efficacy period. The efficacy period showed that the adjusted mean difference in serum phosphorus levels for subjects on ferric citrate vs subjects on placebo was -2.2 mg/dL. Trial 305 was a 4-week non-controlled dose-ranging and efficacy study comparing the mean change in serum phosphorus for subjects on fixed-dose 1-g, 6-g, and 8-g ferric citrate daily. The mean reduction in serum phosphorus from baseline to week 4 was 0.1 mg/dL, 1.9 mg/dL, and 2.1 mg/dL for the 1-g, 6-g, and 8-g arms, respectively, with a statistically significant difference in the 8-g vs 1-g and 6-g vs 1-g arms in pairwise comparison.

  Among several validity concerns were the following: (1) Both trials used an open-label design, which was mitigated by the objective nature of the outcome; however, it was unclear whether laboratory personnel were blinded; (2) Both trials excluded patients intolerant to phosphate binders, which limits determining the drug's effectiveness in a general population of CKD patients on dialysis who have hyperphosphatemia; (3) The efficacy assessment periods of both trials were short in comparison to the chronic nature of the condition; (4) Only patients completing the 52-week safety period of Trial 305 were randomized to the efficacy period, which resulted in exclusion of 39% of subjects between the start of the safety phase and the start of the efficacy phase.

- Two primary safety concerns exist with all phosphate binders: (1) drug-drug interactions resulting in the reduced bioavailability of concomitant medications and (2) gastrointestinal (GI) adverse events. Two major safety concerns specific to iron-based phosphate binders are the masking of GI bleeding and iron

overload, particularly in patients with genetic predisposition (i.e., hemochromatosis). No empirical data are available on drug interactions between ferric citrate and most oral drugs often taken concomitantly by patients with CKD. During the 52-week safety period of Trial 304, 21% of patients on ferric citrate discontinued treatment because of an adverse event versus 14% patients on active control (calcium acetate or sevelamer carbonate or both). However, the study excluded patients intolerant to any of the active control treatments. At 14% (vs 4% for active control), GI adverse reactions were the most common reason for discontinuation. Researchers observed elevated serum ferritin and transferrin saturation (TSAT) levels in clinical trials. Although, in Trial 304, 19% of patients treated with ferric citrate vs 9% of patients treated with active control had a ferritin level >1500 ng/mL, no elevated risk of iron overload was detected when reviewing adverse events indicative of iron overload. However, the ability to detect complications due to iron overload may have been limited by study size and duration. Ferric citrate is associated with dark stools, which can visually mask GI bleeding. However, laboratory tests for occult bleeding are unaffected by this dark staining of feces, because the tests detect heme rather than non-heme iron.

- There is no evidence ferric citrate is superior to other phosphate binders, and evidence supporting its effectiveness is of low quality. Additionally, GI adverse events indicate patients may be less tolerant to ferric citrate in comparison with calcium acetate and sevelamer carbonate, and safety questions with regard to iron overload have not yet been resolved.

Recommendations:

- Designiate ferric citrate as non-prefered at this time and incorporate into current prior authorization (see Appendix 2).

Background:

Auryxia (ferric citrate) is a phosphate binder indicated for the control of serum phosphorus levels in patients with CKD on dialysis. Ferric citrate is approved as Riona in Japan and as Fexeric in the European Union (EU). However, clinical trials in Japanese subjects used a ferric citrate formulation different from the main clinical trials used to form the basis of approval for Auryxia and Fexeric (JTT-751 for Japanese vs KRX-0502).[1, 2]

Derangement of phosphate homeostasis in CKD results in hyperphosphatemia, which is associated with increased mortality. The two main consequences of hyperphosphatemia of CKD are bone disease and ectopic calcification in the soft tissue and blood vessels, which is thought to contribute to the high cardiovascular risk and increased cardiovascular mortality seen in patients with end-stage kidney disease.[3] Observational studies have shown hemodialysis patients have a 10- to 100-fold higher cardiovascular mortality and total mortality than age-matched controls.[4]

Placebo-controlled randomized trials showing decreased morbidity or mortality from the use of phosphate binders in hyperphosphatemia of CKD are lacking.[5] However, prospective cohort studies have shown an association between the use of phosphate binders in dialysis patients and significantly lower mortality.[6, 7]

The FDA has approved six types of phosphate binders: calcium acetate, lanthanum carbonate, sevelamer hydrochloride, sevelamer carbonate, and ferric oxyhydroxide. Generally, intolerability (e.g., GI intolerability or hypercalcemia) and noncompliance (e.g., pill burden) limit phosphate binder use. Aluminum hydroxide, magnesium hydroxide or carbonate, and calcium carbonate also have been used off-label to treat hyperphosphatemia; however, their use is limited by toxicities.[1]

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) 2010 guidelines recommend treating hyperphosphatemic CKD dialysis patients with phosphate binders, in addition to management of diet and dialysis frequency, and suggest reducing serum phosphorus levels to the reference range. The guidelines state one phosphate binder has not been proven to be superior over another. Therefore, binders may be chosen based on effectiveness and adverse effect profiles, and binders may be combined to minimize adverse effects that may result from using high doses of one agent.[5]

National Institute for Health and Clinical Excellence (NICE) guidelines on the management of hyperphosphatemia in CKD (2013) recommend, for children and adults, a calcium-based phosphate binder as the first-line therapy, in addition to dietary management; however, the guidelines also recommend taking into account patient preference, ease of administration, and clinical circumstances. For children and young people, the guidelines further recommend considering combining a calcium-based binder with sevelamer hydrochloride if serum calcium measurements show a trend toward the age-adjusted upper limit of normal (ULN) or if hyperphosphatemia remains and serum calcium rises above the age-adjusted ULN. In the latter case, switching to sevelamer hydrochloride may also be considered. For adults with stage 5 CKD on dialysis who remain hyperphosphatemic despite adhering to the maximum recommended or tolerated dose of calcium-based binder, combining the calcium-based binder with or switching to a non-calcium-based binder may be considered. For adults who have serum phosphate levels controlled by diet and a calcium-based binder but also have serum calcium levels elevated above the ULN or low serum parathyroid hormone levels, either combining the calcium-based binder with, or switching to, sevelamer hydrochloride or lanthanum carbonate may be considered.[3]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
The FDA primarily based its approval of ferric citrate for the treatment of hyperphosphatemic CKD dialysis patients on two phase 3 trials: KRX-0502-304 (Trial 304) and KRX-0502-305 (Trial 305).[1]

Trial 304
Lewis, et al. (2014) performed a sequential three-period, 58-week, open-label, randomized-controlled trial to determine the efficacy and safety of ferric citrate as a phosphate binder, as well as to evaluate ferric citrate's ability to supplement iron stores and reduce the use of intravenous (IV) iron and erythropoiesis-stimulating agents (ESA). The study included adult patients with end stage renal disease (ESRD) who were on hemodialysis or peritoneal dialysis 3-times weekly for at least 3 months before screening, were prescribed 3 to 18 doses of phosphate binder daily, and had serum ferritin <1000 ng/mL, TSAT <50%, and phosphorus ≥2.5 and ≤8 mg/dL at screening. The study excluded patients who absolutely required oral iron or vitamin C or were intolerant to calcium acetate and sevelamer. The study allowed vitamin D therapy, cinacalcet, calcium supplementation, erythropoietin-stimulating agents (EMA), and IV iron as concomitant therapies.[8]

The trial included an up to 2-week washout period, a 52-week active-controlled safety period, and a 4-week placebo-controlled efficacy assessment period. Subjects who had a serum phosphorus level between 6 and 10 mg/dL during the 2-week phosphate-binder wash-out period were randomized 2:1 into the ferric citrate group (n=292) or the active-control (calcium citrate or sevelamer carbonate or both) group (n=149) for the safety period. Following the safety period, subjects in the ferric citrate group and subjects in the active control group who had been switched to ferric citrate were eligible to be re-randomized 1:1 into the efficacy period if they had completed the final visit of the safety period on the study drug. The eligible subjects (n=193 from ferric citrate group; n=2 from active control group) either continued on the ferric citrate doses they were on at the end of the efficacy assessment visit or switched to placebo. During the safety and efficacy periods, the ferric citrate dose was titrated based on serum phosphate level, with the goal of maintaining the level between 3.5 and 5.5 mg/dL. The mean baseline serum phosphorus levels of subjects entering the efficacy period were 5.12 for the ferric citrate arm and 5.44 for the placebo arm.[1, 8]

The primary endpoint as specified in the final statistical analysis plan in the placebo-controlled efficacy period was change in serum phosphorus from baseline (Visit 21, Week 52) to end of the 4-week efficacy period. Efficacy analysis was performed using the population of subjects who took at least one dose of study medication, had baseline assessments, and had at least one post-baseline efficacy assessment.[1] The efficacy period's final sample size provided at least a 95% power at a two-sided significance level of 5% to detect a mean difference in phosphorus level between ferric citrate and placebo groups of 1.2 mg/dL, assuming the two groups had a common SD of 2 mg/dL. The primary analysis was performed using last observation carried forward (LOCF) analysis of covariance (ANCOVA), controlling for baseline phosphorus, and was repeated in a sensitivity analysis adjusted for sex, ferritin, and hemoglobin, which were imbalanced between the treatment groups at baseline.[8]

For the efficacy period, both analyses found a mean difference in phosphorus levels between the ferric citrate group (n=91) and placebo group (n=91) of -2.2±0.2 mg/dL (mean±SEM) ($p<0.001$). Treatment failures with a serum phosphorus level ≥9 mg/dL included 21 subjects on placebo and 1 subject on ferric citrate. During the safety period, the mean serum phosphorus level was not significantly different between the ferric citrate and active control groups at the end of 52 weeks: 5.4±1.6 mg/dL (mean±SD) for the ferric citrate group vs 5.4±1.7 and 5.3±1.4 mg/dL for the sevelamer carbonate group ($p=0.94$) and the calcium acetate group ($p=0.84$), respectively.[8]

Trial 305

Dwyer et al. (2013) performed phase 3, randomized, uncontrolled, open-label, dose-ranging and efficacy study in adult patients with ESRD on thrice-weekly hemodialysis. Additional eligibility criteria included taking 3 to 15 doses daily of calcium acetate 667 mg or sevelamer as hydrochloride or carbonate 800 mg daily and having a serum ferritin level <1,000 mcg/L, TSAT ≤50%, and phosphorus level ≥3.5 to ≤8 mg/dL at the screening visit. Major exclusion criteria included active GI bleeding or inflammatory bowel disease (IBD), severe hyperphosphatemia (≥10 mg/dL) within 3 months of screening, malignancy within 5 years of screening, or an absolute requirement for oral iron therapy, vitamin C, or calcium-, magnesium-, or aluminum-containing drugs. Permitted concomitant therapies included cinacalcet, calcium, vitamin D therapy, IV iron therapy, and ESA.[9]

Following a 1- to 2-week washout period, 151 patients with serum phosphorus levels ≥6 mg/dL were randomly assigned 1:1:1 to a fixed dose of ferric citrate 1, 6, or 8 g daily. The researchers determined patient sample sizes to provide at least 90% power to detect a treatment difference in serum phosphorus level of at least 1.4 mg/dL, assuming a common SD of 2 mg/dL. Patients who had both baseline and post-baseline assessments comprised the ITT population. Patients considered treatment failures were those who discontinued study drug due to a serum phosphorus level ≤2.5 mg/dL at day 7 or ≤2.5 or ≥9 mg/dL at day 14 or day 21. The primary analysis of change in serum phosphorus level from baseline to the end of the 28-day treatment period was performed using a regression model with dose effect, while the secondary efficacy assessment employed a LOCF ANCOVA for a pairwise comparison of dose, using treatment as the fixed class effect and baseline phosphorus level as the covariate.[9]

About 79% of patients completed the study, and 10% discontinued treatment but completed all study assessments. Following the initiation of treatment, serum phosphorus levels decreased in a dose-dependent manner, with mean changes of −0.1 ± 1.3, −1.9 ± 1.7, and −2.1 ± 2 mg/dL in the 1-g daily, 6-g daily, and in 8-g daily groups, respectively. The pairwise comparison revealed significant mean differences in change from baseline values between the 1-g daily and the 6- and 8-g daily groups ($p<0.001$), but not between the 6- and 8-g daily groups. About 15% (n=22) of patients were considered treatment failures by the end of treatment, with 73% of the 15 treatment failures with phosphorus levels ≥9 mg/dL coming from the 1-g daily group and all seven of the treatment failures with phosphorus levels ≤2.5 mg/dL split between the 6-g and 8-g daily groups.[9]

Trials 304 and 305 had several limitations. The internal validity concerns included the following: (1) Both trials used an open-label design, which was mitigated by the objective nature of the outcome; however, it was unclear whether laboratory personnel were blinded; (2) The number of subjects in both trials was small; (3) Both studies used last observation carried forward and had high rates of attrition despite limiting the study to patients tolerant to phosphate binders; (4) Trial 304 had an imbalance in sex, ferritin, and hemoglobin between the study arms, but a sensitivity analysis was performed, which showed the mean treatment difference persisted; (5) The statistical plan for Trial 304 was finalized after the trial finished; however the FDA determined this did not affect the study's findings;[1] and (6) The method of randomization for Trial 305 was unclear ("randomization list provided by the statistician").

The external validity concerns included the following: (1) Both studies used serum phosphorus level as a surrogate outcome; however, it is an accepted one; (2) Both trials excluded patients intolerant to phosphate binders, which limits determining the drug's effectiveness in a general population of CKD patients on dialysis who have hyperphosphatemia; (3) The efficacy assessment periods of both trials was short in comparison to the chronic nature of the condition; (4) Only patients completing the 52-week safety period of Trial 305 were randomized to the efficacy period, which resulted in exclusion of 39% of subjects between the start of the safety phase and the start of the efficacy phase; and (5) Trial 305 did not have a comparator.

Clinical Safety:

Two primary safety concerns exist with all phosphate binders: (1) drug-drug interactions resulting in the reduced bioavailability of concomitant mediations, including drug binding by phosphate binders and (2) GI adverse events, including diarrhea, constipation, and obstruction. Two major safety concerns specific to iron-based phosphate binders are the masking of GI bleeding and iron overload, particularly in patients with genetic predisposition (i.e., hemochromatosis).[1]

Researchers observed elevated serum ferritin and TSAT levels in clinical trials. In Trial 304, 55 (19%) of patients treated with ferric citrate vs 13 (9%) of patients treated with active control had a ferritin level >1500 ng/mL. Therefore, prescribing information contraindicates ferric citrate in patients with iron overload syndromes (e.g., hemochromatosis) and recommends assessing iron parameters before initiating ferric citrate and during therapy and reducing the dose or discontinuing of IV iron therapy when required.[10]

The pooled safety data set for ferric citrate comes from active control Trial 304 and 3 short-term trials (uncontrolled Trial 305, pharmaceutical grade ferric citrate trial PBB00101, and uncontrolled phase 2 Trial 201). Across the 4 trials, 557 unique patients received ferric citrate, ranging from up to 28 days for short-term trials and up to 52 weeks for Trial 304 with dosage regimens ranging from 210 mg to 2,520 mg of ferric iron daily (equivalent to 1 to 12 ferric citrate tablets). Similar adverse events were reported for ferric citrate versus active control groups.[1, 10]

Adverse events reported in greater than 5% of patients treated with ferric citrate included diarrhea (21%), nausea (11%), constipation (8%), vomiting (7%), and cough (6%). During the 52-week, active-control period of Trial 304, 21% of patients on ferric citrate (n=60) discontinued treatment because of an adverse event versus 14% patients (n=21) on active control. However, the study excluded patients intolerant to any of the active control treatments. At 14% (vs 4% for active control), GI adverse reactions were the most common reason for discontinuation.[10]

No empirical data are available on drug interactions between ferric citrate and most oral drugs often taken concomitantly by patients with CKD. Therefore, the prescribing information recommends (1) considering separating the timing of the administration of oral medications where reduced bioavailability of that medication would significant affect its safety or efficacy and (2) monitoring clinical responses or blood levels of concomitant medications that have a narrow therapeutic range.[10]

Ferric citrate is associated with dark stools, which can visually mask GI bleeding. However, laboratory tests for occult bleeding are unaffected by this dark staining of feces because the tests detect heme rather than non-heme iron.[10]

Unanswered safety questions:

- How safe is ferric citrate in pediatric patients? The safety and efficacy of ferric acid have not been established in pediatric patients.
- How safe is ferric citrate in patients with GI disorders? Clinical trials excluded patients with IBD or active, symptomatic GI bleeding. Therefore safety has not been established in these populations.
- Which adverse events are associated with ferric citrate versus CKD and its morbidities? Data comparing ferric acid with placebo are limited. Some adverse events described in clinical trials may be disease-related, rather than treatment-related.
- What is the safety profile of ferric citrate compared with other phosphate binders? The study excluded patients intolerant to any of the active control treatments, making it difficult to compare adverse event rates between ferric citrate and the active controls.
- What is the true risk for iron overload? The ability to detect complications due to iron overload may have been limited by study size and duration.[1]

Look-alike / Sound-alike Error Risk Potential: Oracea, Oracit, Oraqix, various ferric and ferrous iron dietary supplements and prescription drugs

Pharmacology and Pharmacokinetic Properties: [10]

Parameter	
Mechanism of Action	Ferric citrate reacts with dietary phosphate in the GI tract to form ferric phosphate, an insoluble precipitate that is excreted in the feces. Decreasing phosphate absorption lowers serum phosphate concentration.
Oral Bioavailability	No data*
Distribution and Protein Binding	No data*
Elimination	No data*
Half-Life	No data*
Metabolism	No data*

*No formal pharmacokinetic studies have been performed. However, serum iron parameters show systemic absorption of iron from ferric citrate.

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Improved mortality
2) Improved morbidity, e.g., cardiovascular outcomes
3) Improved serum phosphorus levels
4) Safety: Iron overload
5) Tolerability: GI adverse events

Primary Study Endpoint:
1) For Trial 304, change in serum phosphorus from baseline (visit 21, week 52) to end of the 4-week efficacy period (compared with placebo)

2) For Trial 305, change in serum phosphorus from baseline to the end of the 28-day treatment period.

Comparative Evidence Table [1, 8, 9, 11]

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Lewis 2014; Umanath 2013; and FDA Medical Review 2014 December 2010 to November 2012 60 sites in US and Israel Phase 3, sequential three-period, randomized, open-label, efficacy and safety trial	Efficacy 1. FC (6 to 12 caplets daily; median 8-g daily) 2. PLA Duration: 4 weeks Safety 1. FC 2. AC Duration: 52 weeks	Demographics: (FC, PLA) · Age (yr), median 54, 56 · Men (%) 73, 49 · Race (%) Black 65, 53 White 31, 43 · Heart disease (%): CHF 34, 33 MI/CAD 38, 30 · ESA (%) 60, 66 · IV iron (%) 16, 22 · vit D/analogs (%) 85, 81 · Phos (mg/dl) median 5.1, 5.3 · Calcium (mg/dl) median 9.23, 9.20 · Ferritin (mg/dl) median 858, 932 · TSAT (%) median 36, 34 · Hemoglobin (g/dl) median 11.4, 10.9 Key Inclusion Criteria: · adults w/ ESRD · 3x-week HD or PD for ≥3 months · 3–18 doses phosphate binder daily · ferritin <1000 ng/mL · TSAT <50% · phosphorus ≥2.5 and ≤8 mg/dl Key Exclusion Criteria: · active GI bleed/IBD · parathyroidectomy <6 months prior · severe hyperphos · intolerance to calcium acetate and sevelamer	Efficacy period ITT: 1. 95 2. 95 mITT: 1. 91 2. 91 Efficacy period attrition: 1. FC: 5/95 (5%) 2. PC: 25/95 (26%) Safety population: 1. FC: 289 2. AC: 149 Safety period attrition: 1. FC: 96 (33%) 2. AC: 38 (26%)	Mean change from baseline in serum phosphorus (mg/dL): 1. FC: -0.26 2. AC: +1.77 Adjusted mean difference FC vs PLA: -2.18 (CI: -2.59 to -1.77), p<0.001	NA	TEAE (safety period): Infections and infestations: 1. FC: 12.8% 2. AC: 20.1% GI disorders: 1. FC: 6.9% 2. AC: 12.1% Respiratory, thoracic, mediastinal disorders: 1. FC: 6.9% 2. AC: 10.1% Nervous system disorders: 1. FC: 4.8% 2. AC: 4% Hepatobiliary disorders: 1. FC: 0.7% 2. AC: 1.3% D/C due to TEAE (safety period): 1. FC: 20.8% 2. AC: 14.1% All SAEs any time after drug initiation: 1. FC: 41.9% 2. AC 51% D/C due to AE during efficacy period: 1. FC: 2% 2. PC: 3%	 -7.3/-14 -5.2/-19 -3.2/-31 -0.8/2 -0.6/2 6.4/16 -9.1/-11 -1/-100	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Sex, ferritin, and hemoglobin were imbalanced between the study arms, but sensitivity analysis was performed and showed the mean treatment difference persisted. Performance Bias: Low. The study was open-label, but the study outcomes were objectively defined. Detection Bias: Unclear. The study was unclear as to whether outcome assessors were blinded. The FDA Medical Review makes a statement that laboratory staff were blinded but the published study and design do not. Attrition Bias: High. The study used LOCF. During the efficacy period there was greater attrition in the PLA arm, while the FC and PLA arms both had the same withdrawal rates for AE and consent. Reporting Bias: High. The statistical plan was finalized after the trial finished. **Applicability**: Patient: The 52-week safety period resulted in the exclusion of 39% of subjects entering the efficacy phase, with 13% and 8% excluded for AE and "other," respectively. Patients intolerant to phosphate binders were excluded. Intervention: The 4-week efficacy period was short in duration, but the overall treatment period was 56 weeks. Comparator: The efficacy period comparator was placebo. Outcomes: Serum phosphorus level is a surrogate outcome, but it is an accepted one. Setting: The effectiveness of FC in a general population of CKD dialysis patients with hyperphosphatemia is unclear because only subjects tolerant to phosphate binders were included in the study.

2. Dwyer 2013 15 sites in US Phase 3, randomized, uncontrolled, open-label, dose-ranging and efficacy trial	1. FC 1-g 2. FC 6-g 3. FC 8-g Duration: 4 weeks	<u>Demographics</u>: (FC 1-g, 6-g, 8-g) · Age (y) 56, 57, 53 · Male (%) 64, 59, 58 · Race (%) Black 50, 61, 60 White 42, 33, 29 · Serum phosphorus (mg/dL) 7.3, 7.6, 7.5 · Calcium (mg/dL) 9, 8.9, 8.9 · Ca x P (mg^2/dL^2) 66, 67, 66 · Ferritin (mg/dL) 558, 515, 527 · TSAT (%) 32, 34, 30 <u>Key Inclusion Criteria</u>: · adults with ESRD · 3x-week HD/PD for ≥3 months · 3–15 doses phosphate binder daily · ferritin <1000 ng/mL · TSAT <50% · phosphorus ≥3.5 and ≤8 mg/dL <u>Key Exclusion Criteria</u>: Same as above	<u>ITT</u>: 1. 51 2. 52 3. 48 <u>Attrition</u>: 1. 23% 2. 10% 3. 24%	<u>Mean change in serum phosphorus (mg/dL±SD):</u> 1. -0.1 ± 1.3 2. -1.9 ± 1.7 3. -2.1 ± 2 Pairwise comparison: 6-g vs 1-g: 1.3 (CI: 0.69 to 1.9), p<0.001 1-g vs 8-g: 1.5 (CI: 0.86 to 2.1), p<0.001 6-g vs 8-g: 0.21 (CI: -0.39 to 0.81), p=0.5	NA	<u>GI AE</u>: 1. 43.1% 2. 42.3% 3. 52.1% <u>All SAEs</u>: 1. 11.8% 2. 13.5% 3. 18.8% <u>D/C due to AE</u>: 1. 3.9% 2. 5.8% 3. 16.7%	NA NA NA	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: Unclear. The method of randomization was unclear. <u>Performance Bias</u>: Low. The study was open-label, but the study outcomes were objectively defined. <u>Detection Bias</u>: Unclear. The study was unclear as to whether outcome assessors were blinded. <u>Attrition Bias</u>: High. The study used LOCF. The attrition rates were high, driven by treatment failure for the 1-g arm and AE in 8-g arm. <u>Reporting Bias</u>: Low. No reporting bias apparent **Applicability**: <u>Patient</u>: Patients intolerant to phosphate binders were excluded. <u>Intervention</u>: The study was only 4 weeks in duration. <u>Comparator</u>: No comparator was used. <u>Outcomes</u>: Serum phosphorus level is a surrogate outcome, but it is an accepted one. <u>Setting</u>: The effectiveness of FC in a general population of CKD dialysis patients with hyperphosphatemia is unclear because only subjects tolerant to phosphate binders were included in the study.

<u>Abbreviations</u> [alphabetical order]: AC = active control (median 7.7 tabs daily calcium acetate 667-mg capsules; median 9 tabs daily sevelamer carbonate 800-mg tablets; or both titrated according to prescribing information); AE = adverse events; ARR = absolute risk reduction; CI = confidence interval; D/C = discontinuations; FC = ferric citrate (1-g tablets contained 210 mg ferric iron); GI = gastrointestinal; HD = hemodialysis; IBD = inflammatory bowel disease; ITT = intention to treat; LOCF = last observation carried forward; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PD = peritoneal dialysis; PLA = placebo; PP = per protocol; TEAE = treatment emergent adverse events.

References:

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Appendix 1: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AURYXIA safely and effectively. See full prescribing information for AURYXIA.

AURYXIA (ferric citrate) tablets , for oral use
Initial U.S. Approval: 2014

---------- **INDICATIONS AND USAGE** ----------

Auryxia™ is a phosphate binder indicated for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis (1)

----------**DOSAGE AND ADMINISTRATION**----------

- Starting dose is 2 tablets orally 3 times per day with meals (2)
- Adjust dose by 1 to 2 tablets as needed to maintain serum phosphorus at target levels, up to a maximum of 12 tablets daily. Dose can be titrated at 1-week or longer intervals. (2)

---------- **DOSAGE FORMS AND STRENGTHS**----------

- Tablets: 210 mg ferric iron, equivalent to 1 g ferric citrate (3)

---------- **CONTRAINDICATIONS** ----------

- Iron overload syndromes (e.g., hemochromatosis) (4)

---------- **WARNINGS AND PRECAUTIONS** ----------

- Iron overload: Monitor ferritin and TSAT. Patients may require a reduction in dose or discontinuation of IV iron. (5.1)
- Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6 years of age. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately. (5.2)
- Patients with gastrointestinal bleeding or inflammation: Safety has not been established. (5.3)

---------- **ADVERSE REACTIONS** ----------

- In clinical trials, likely adverse reactions occurring with Auryxia included diarrhea, discolored feces, constipation, nausea, and vomiting (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Keryx Biopharmaceuticals at 1-844-445-3799 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- **DRUG INTERACTIONS**----------

- When clinically significant drug interactions are expected, consider separation of the timing of administration. Consider monitoring clinical responses or blood levels of the concomitant medication (7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07\2015

From Lewis 2014: [8]

Appendix 4. Adverse events during the 52-week active-control period.

Type of AE	Patients with Treatment Emergent Adverse Events Within 12 Weeks of Randomization[1]		Patients with Treatment Emergent Adverse Events[2]		Patients with Adverse Events Recorded Anytime After Drug Initiation[3]	
	Ferric Citrate	Active Control	Ferric Citrate	Active Control	Ferric Citrate	Active Control
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
All SAEs	46 (15.9%)	26 (17.4%)	113 (39.1%)	73 (49.0%)	121 (41.9%)	76 (51.0%)
All AEs	214 (74.0%)	108 (72.5%)	261 (90.3%)	133 (89.3%)	266 (92.0%)	138 (92.6%)
GI Serious AEs	6 (2.1%)	4 (2.7%)	20 (6.9%)	19 (12.8%)	24 (8.3%)	19 (12.8%)
GI Non-serious AEs[4]	121 (41.8%)	32 (21.5%)	143 (49.5%)	52 (34.9%)	141 (48.8%)	55 (36.9%)
Infection Serious AEs	13 (4.5%)	9 (6.0%)	36 (12.5%)	27 (18.1%)	42 (14.5%)	29 (19.5%)
Infection Non-serious AEs[3]	35 (12.1%)	21 (14.1%)	73 (25.3%)	35 (23.5%)	79 (27.3%)	36 (24.2%)
Cardiac Serious AEs	7 (2.4%)	4 (2.7%)	21 (7.3%)	18 (12.1%)	27 (9.3%)	20 (13.4%)
Cardiac Non-serious AEs[3]	11 (3.8%)	5 (3.3%)	30 (10.4%)	14 (9.4%)	33 (11.4%)	14 (9.4%)

[1] Counts of subjects with treatment emergent adverse events in the indicated categories. Counts for nonserious adverse events include non-serious adverse events occurring after study drug initiation and prior to 12 weeks after randomization or

Phosphate Binders

Goal(s):

- Promote preferred drug products for conditions funded by the OHP.
- Reserve non-calcium acetate binders for second-line therapy.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred phosphate binders and all non-calcium acetate phosphate binders

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org/drugs

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is this an OHP-covered diagnosis?	Yes: Go to #3	No: Go to #5
3. Has the patient tried or contraindicated to calcium acetate?	Yes: Go to #4 Document trial dates and/or intolerance	No: Pass to RPh. Deny for medical appropriateness. Recommend trial of preferred calcium acetate product.
4. Will the prescriber consider a change to a preferred non-calcium acetate product?	Yes: Approve for 1 year and inform provider of preferred alternatives in class.	No: Approve for 1 year or length of prescription, whichever is less.

Approval Criteria

5. RPh only: All other indications need to be evaluated as to whether they are a funded or non-funded condition under the OHP:
   - If funded prescriber provides supporting literature: approve for length of treatment.
   - If non-funded: Deny, (not funded by the OHP).

P&T / DUR Review: *1/16; 11/12; 9/12; 09/10*
Implementation: *2/21/13*