Each month, subscribers to *The Formulary Monograph Service* receive 5 to 6 well-documented monographs on drugs that are newly released or are in late phase 3 trials. The monographs are targeted to Pharmacy & Therapeutics Committees. Subscribers also receive monthly 1-page summary monographs on agents that are useful for agendas and pharmacy/nursing in-services. A comprehensive target drug utilization evaluation/medication use evaluation (DUE/MUE) is also provided each month. With a subscription, the monographs are sent in print and are also available on-line. Monographs can be customized to meet the needs of a facility. A drug class review is now published monthly with *The Formulary Monograph Service*. Through the cooperation of *The Formulary, Hospital Pharmacy* publishes selected reviews in this column. For more information about *The Formulary Monograph Service*, call *The Formulary* at 800-322-4349. The February 2015 monograph topics are netupitant/palonosetron, naltrxone SR/bupropion SR, nintedanib, pirfenidone, and ivabradine. The Safety MUE is on netupitant/palonosetron.

### Generic Name:
Ferric citrate

### Proprietary Name:
Auryxia (Keryx Biopharmaceuticals)

### Approval Rating:
5 (new formulation or new manufacturer)

### Therapeutic Class:
Phosphate binders

### Similar Drugs:
Calcium acetate, calcium carbonate, lanthanum carbonate, sevelamer hydrochloride, sevelamer carbonate, sucro-ferric oxyhydroxide

### Sound-or Look-Alike Names:
Ferric gluconate, ferric sulfate, ferric carboxymaltose

### INDICATIONS
Ferric citrate (KRX-0502) is indicated for the reduction of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis.

Absorption of dietary phosphate occurs in the gastrointestinal (GI) tract and excess phosphorus is normally excreted in the urine. Additional phosphate regulatory mechanisms include increases in parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23) to inhibit renal absorption of phosphate. Patients with end-stage renal disease (ESRD) have a decreased ability to excrete phosphate, which can result in hyperphosphatemia. Decreased 1,25-dihydroxycholecalciferol production and dietary calcium absorption can also occur with decreased renal function. Potential complications as a result of these events include the development of CKD-associated mineral and bone disorders (CKD-MBD), extraskeletal calcification of soft tissue, and increased risk of mortality.

In addition to dietary phosphate restriction and dialysis, current therapies to lower serum phosphate act by binding phosphate in the gut prior to absorption. Such products include aluminum hydroxide, calcium-based binders, lanthanum and sevelamer products, and iron-based phosphate binders. However, each of these products has specific disadvantages. Long-term aluminum hydroxide therapy can result in accumulation and aluminum toxicity. Calcium-based...
binders, such as calcium carbonate, calcium acetate, and calcium citrate, can lead to hypercalcemia and metastatic calcification. Noncalcium-based binders, such as lanthanum and sevelamer products, may bind to other medication and increase patient medication costs. Sucroferric oxyhydroxide is a recently approved iron-based phosphate binder in the United States.\textsuperscript{3,5,6-8} Iron deficiency may also be present with CKD due to factors such as use of erythropoiesis-stimulating agents (ESA), repeated blood sampling, or hemodialysis. As a result, iron supplementation is used to reduce the severity of anemia in patients with CKD. The intravenous (IV) route is preferred for patients, especially those on hemodialysis, with oral iron as an alternative option in nondialysis patients.\textsuperscript{3}

As per their special protocol assessment, Keryx Biopharmaceuticals has completed 2 phase 3 clinical trials designed to support regulatory submission for drug approval.\textsuperscript{9} Outside of ESRD dialysis patients, a phase 2 trial reviewing ferric citrate for serum phosphate reduction and iron-deficiency anemia in patients with nondialysis-dependent CKD has been completed.\textsuperscript{10-12} A phase 2 pilot study, expected to be completed in October 2014, is evaluating the efficacy and safety of ferric citrate for iron deficiency anemia in stages 3 to 5 nondialysis-dependent CKD patients.\textsuperscript{13} Under a sublicense from Keryx Biopharmaceuticals, a separate product in Japan designated ferric citrate hydrate has been developed by Japan Tobacco, Inc. and Torii Pharmaceuticals, Co.\textsuperscript{4,8,14-17}

**CLINICAL PHARMACOLOGY**

Iron-based phosphate binder complex binds with phosphate within the GI tract over a wide pH range, which leads to increased phosphate excretion in the feces and decreased phosphate absorption.\textsuperscript{3} In normal and azotemic rats, ferric citrate increased fecal phosphate excretion and decreased intestinal phosphate absorption. Table 1 provides a comparison of mechanisms of action and elemental content of select phosphate binders.

The phosphorus-binding capacity of ferric citrate was estimated to be approximately 84.8 to 87.9 mg of phosphorus per gram of elemental ferric iron and 19.1 to 19.8 mg of phosphorus per gram of ferric citrate.\textsuperscript{18} In comparison, 180 mg of phosphate is estimated to be bound by 1 g of aluminum, 40 mg of phosphate bound by 1 g of elemental calcium (as calcium carbonate), and 100 mg of phosphate bound by 1 g of elemental calcium (as calcium acetate).\textsuperscript{18} Studies in human subjects have observed similar reductions in serum phosphate with ferric citrate as calcium carbonate, calcium acetate, and sevelamer carbonate.\textsuperscript{19-21}

As an iron-containing product, several trials have suggested ferric citrate has a potential to increase iron-related parameters, including serum iron, ferritin, hemoglobin, transferrin saturation (TSAT), and

| Table 1. Comparative mechanism of action and elemental content of phosphate binders used to treat hyperphosphatemia\textsuperscript{6,7,18,45,49} |
|-------|-----------------------------------------------|-----------------------------------------------|
| **Drug** | **Mechanism of action** | **Elemental content** |
| Calcium acetate | Forms insoluble calcium phosphate by binding to dietary phosphate | 169 mg of elemental calcium per 667 mg of calcium acetate |
| Calcium carbonate | Forms insoluble calcium phosphate by binding to dietary phosphate | 400 mg of elemental calcium per 1,000 mg of calcium carbonate |
| Ferric citrate | Binds to dietary phosphorus to increase fecal excretion and decrease intestinal absorption | 210 mg of elemental ferric iron per 1,000 mg of ferric citrate |
| Ferric citrate hydrate | Binds to dietary phosphorus to increase fecal excretion and decrease intestinal absorption | 62 mg of iron as an anhydride per 250 mg of ferric citrate hydrate |
| Sucroferric oxyhydroxide | Exchange of ligands between dietary phosphate and hydroxyl groups and/or water from sucroferric oxyhydroxide | 500 mg of iron per 2,500 mg of sucroferric oxyhydroxide |
| Lanthanum carbonate | Forms insoluble lanthanum phosphate by binding to dietary phosphate | |
| Sevelamer carbonate | Interacts with intestinal phosphate through ionic and hydrogen bonding to decrease absorption | |
| Sevelamer hydrochloride | Interacts with intestinal phosphate through ionic and hydrogen bonding to decrease absorption | |
total iron-binding capacity (TIBC), as well as to potentially decrease the dose requirements or usage of IV iron and ESA.\textsuperscript{5,7,20-28}

**PHARMACOKINETICS**

The ferric ion has limited absorption through the GI tract.\textsuperscript{29} Ferric citrate reduces serum phosphorus in a dose-dependent manner. During a 28-day treatment period, ferric citrate at fixed doses of 1, 6, and 8 g/day produced a difference in serum phosphorus from end of therapy to baseline of −0.1, −1.9, and −2.1 mg/dL, respectively. In this study, a dose-response relationship was also observed for other lab parameters, such as calcium phosphorus product, ferritin, and bicarbonate.\textsuperscript{5}

Ferric citrate hydrate is described to have a larger surface area and faster dissolution rate than ferric citrate.\textsuperscript{8,15,16}

**COMPARATIVE EFFICACY**

**Indication: Hyperphosphatemia in End-Stage Renal Disease Patients on Dialysis Three Times Weekly**

**Guidelines**

**Guideline:** Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines for bone metabolism and disease in CKD

**Reference:** National Kidney Foundation, 2003\textsuperscript{30}

**Comments:** Stage 5 CKD patients unable to control serum phosphorus or PTH with dietary phosphate restriction are recommended to start a calcium-based or noncalcium-, nonaluminum-, nonmagnesium-based phosphate binder. Daily limits of elemental calcium provided by calcium-based binders should not exceed 1,500 mg, and elemental calcium from all sources should not exceed 2,000 mg. Calcium-based phosphate binders should be avoided in hypercalcemic patients (eg, corrected serum calcium greater than 10.2 mg/dL) or patients with PTH less than 150 pg/mL. Dialysis patients failing to achieve serum phosphate of less than 5.5 mg/dL with a single calcium-based or noncalcium-, nonaluminum-, nonmagnesium-based phosphate binder may initiate a combined therapy with these 2 agents. Dialysis patients presenting with severe vascular or calcification of soft tissue should initiate therapy with noncalcium-based phosphate binders. Four weeks of aluminum-based phosphate binders followed by other binders thereafter may be considered in patients with serum phosphorus greater than 7 mg/dL. Consideration of increased dialysis time or frequency (4 times weekly or more often) should be given in patients with serum phosphorus greater than 7 mg/dL, uncontrolled on phosphate binders, or unable to tolerate phosphate binders. Ferric citrate is not mentioned in this version of the guidelines.

**Guideline:** Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of CKD-MBD

**Reference:** KDIGO CKD-MBD Work Group, 2009\textsuperscript{31}

**Comments:** Hypophosphatemia treatment in CKD patients stages 3 to 5, including stage 5 requiring dialysis, consists of dietary phosphate restriction, phosphate binders, and increased dialysis. Maintenance of serum phosphorus and calcium within normal range is recommended in CKD stages 3 to 5. Serum phosphorus toward a normal range and calcium within normal range is recommended for stage 5 CKD requiring dialysis. Preference toward a specific phosphate binder is not expressed in these guidelines. The recommendation for selecting a particular agent is based on CKD staging, complications of CKD-MBD, and medication adverse effects. Guidance regarding appropriate use of specific agents includes restriction of calcium-based phosphate binder dose (and potentially calcitriol or vitamin D analogues) in patients with recurrent/persistent hypercalcemia. Reduction of calcium-based binder dose is also recommended in patients with arterial calcification, adynamic bone disease, or persistently low serum PTH. The use of long-term aluminum-based phosphate binders should be avoided during CKD stages 3 to 5. CKD patients requiring dialysis or unable to tolerate phosphate binders are recommended to increase frequency or duration of dialysis to reduce serum phosphate. Additional recommendations regarding dialysis include a dialysate calcium concentration between 2.5 to 3 mEq/L and avoidance of aluminum dialysate contamination. Brief commentary on tolerability of ferric citrate is mentioned in this version of the guideline; however, a place in therapy is not stated.

**Studies**

**Drug:** Ferric citrate

**Reference:** Dwyer JP, et al, 2013\textsuperscript{5}

**Study Design:** Phase 3, randomized, multicenter, open-label trial

**Study Funding:** Keryx Biopharmaceuticals
**Patients:** One hundred fifty-four adult patients randomized (79.2% completed) with ESRD on hemodialysis 3 times a week and taking 3 to 15 pills of a phosphate binder daily (calcium acetate 667 mg or sevelamer 800 mg per pill). Study included patients with a serum ferritin level less than 1,000 mcg/L, TSAT less than 50%, serum phosphate between 3.5 to 8 mg/dL at screening, and serum phosphorus of 6 mg/dL or more after 2 weeks of washout. At baseline, the intent-to-treat (ITT) population ranged from 52.8 to 56.5 years of age and 57.8% to 64% were male; 50% to 60.8% of patients were Black and 13% to 21% were White. Baseline laboratory parameters included mean phosphorus of 7.3 to 7.6 mg/dL, mean ferritin of 515.2 to 558.2 mg/dL, and mean TSAT of 29.8% to 33.8%.

**Intervention:** Patients were randomized 1:1:1 to ferric citrate 1, 6, or 8 g/day. Ferric citrate was provided as 1 g caplets containing ferric iron 210 mg taken at meals or within 1 hour of eating. Following a 1- to 2-week washout of previous phosphate-binder therapy, patients were provided 28 days of therapy. Patients discontinued therapy if serum phosphorus was 2.5 mg/dL or less at day 7 or was outside the range of 2.5 to 9 mg/dL on days 14 or 21. Permitted concurrent therapies included vitamin D, vitamin D analogues, and cinacalcet held at constant doses. Calcium supplements were to be taken at bedtime or 2 hours outside of mealtime. IV iron therapy was allowed for patients with serum ferritin of 1,000 mcg/L or less and TSAT of 50% or less. The ITT cohort included randomized patients with a baseline and postbaseline assessment. The safety cohort included patients receiving at least 1 study medication dose.

**Results**

**Primary Endpoint(s)**
- Regression analysis confirmed a dose-response change in serum phosphorus from baseline ($P < .001$).

**Secondary Endpoint(s)**
- Compared with baseline, ferric citrate 1, 6, and 8 g/day decreased serum phosphate by a mean of $-0.1\, \text{mg/dL}$, $-1.9\, \text{mg/dL}$, and $-2.1\, \text{mg/dL}$, respectively, at day 28 in the ITT population.
- Mean difference in change of serum phosphate from baseline of 1 g/day versus 8 g/day was $1.5\, \text{mg/dL}$ (95% CI, 0.86 to 2.1; $P < .001$).
- Mean difference in change of serum phosphate from baseline of 6 g/day versus 8 g/day was $0.21\, \text{mg/dL}$ (95% CI, $-0.39$ to 0.81; $P = .5$).
- No statistically significant dose response was observed for calcium or TSAT.
- A statistically significant dose response was observed for ferritin. Change in ferritin from baseline to day 28 was $-14.4\, \text{mg/dL}$, $90.1\, \text{mg/dL}$, and $90.2\, \text{mg/dL}$ for ferric citrate 1, 6, and 8 g/day, respectively.

**Comments:** This trial was conducted across 15 sites in the United States. A total of 22 patients (15.1%) were considered treatment failures by day 28 due to serum phosphorus being 2.5 mg/dL or less (7 patients) or serum phosphorus 9 mg/dL or more (15 patients). High serum phosphorus was seen more often in the 6 and 8 g/day cohorts, and low serum phosphorus was seen more often in the 1 g/day cohort.

**Limitations:** This study may have limited applicability in patients with active GI bleeding, inflammatory bowel disease, parathyroidectomy in the past 6 months, hyperphosphatemia of 10 mg/dL or more, and a history of malignancy in the past 5 years since they were excluded from participation.

**Drug:** Ferric citrate versus active control


**Study Design:** Phase 3, randomized, 3-period, international, multicenter trial

**Study Funding:** Keryx Biopharmaceuticals

**Patients:** Four hundred forty-one ESRD patients who were 18 years and older on 3 times weekly hemodialysis or peritoneal dialysis taking 3 to 18 pills of a phosphate binder daily. Study included patients with a serum ferritin level less than 1,000 mcg/L, TSAT less than 50%, and serum phosphate between 2.5 to 8 mg/dL at screening. Baseline characteristics of the ferric citrate and active controls arms in the safety period were similar. The ITT cohort included randomized patients with a baseline and postbaseline assessment. The safety cohort included patients receiving at least 1 study medication dose.

**Results**

**Primary Endpoint(s)**
- Regression analysis confirmed a dose-response change in serum phosphorus from baseline ($P < .001$).

**Secondary Endpoint(s)**
- Compared with baseline, ferric citrate 1, 6, and 8 g/day decreased serum phosphate by a mean of $-0.1\, \text{mg/dL}$, $-1.9\, \text{mg/dL}$, and $-2.1\, \text{mg/dL}$, respectively, at day 28 in the ITT population.
- Mean difference in change of serum phosphate from baseline of 1 g/day versus 8 g/day was $1.5\, \text{mg/dL}$ (95% CI, 0.86 to 2.1; $P < .001$).
- Mean difference in change of serum phosphate from baseline of 6 g/day versus 8 g/day was $0.21\, \text{mg/dL}$ (95% CI, $-0.39$ to 0.81; $P = .5$).
- No statistically significant dose response was observed for calcium or TSAT.
- A statistically significant dose response was observed for ferritin. Change in ferritin from baseline to day 28 was $-14.4\, \text{mg/dL}$, $90.1\, \text{mg/dL}$, and $90.2\, \text{mg/dL}$ for ferric citrate 1, 6, and 8 g/day, respectively.

**Comments:** This trial was conducted across 15 sites in the United States. A total of 22 patients (15.1%) were considered treatment failures by day 28 due to serum phosphorus being 2.5 mg/dL or less (7 patients) or serum phosphorus 9 mg/dL or more (15 patients). High serum phosphorus was seen more often in the 6 and 8 g/day cohorts, and low serum phosphorus was seen more often in the 1 g/day cohort.

**Limitations:** This study may have limited applicability in patients with active GI bleeding, inflammatory bowel disease, parathyroidectomy in the past 6 months, hyperphosphatemia of 10 mg/dL or more, and a history of malignancy in the past 5 years since they were excluded from participation.

**Drug:** Ferric citrate versus active control


**Study Design:** Phase 3, randomized, 3-period, international, multicenter trial

**Study Funding:** Keryx Biopharmaceuticals

**Patients:** Four hundred forty-one ESRD patients who were 18 years and older on 3 times weekly hemodialysis or peritoneal dialysis taking 3 to 18 pills of a phosphate binder daily. Study included patients with a serum ferritin level less than 1,000 mcg/L, TSAT less than 50%, and serum phosphate between 2.5 to 8 mg/dL at screening. Baseline characteristics of the ferric citrate and active controls arms in the safety period were similar. The ITT cohort included randomized patients with a baseline and postbaseline assessment. The safety cohort included patients receiving at least 1 study medication dose.

**Results**

**Primary Endpoint(s)**
- Regression analysis confirmed a dose-response change in serum phosphorus from baseline ($P < .001$).

**Secondary Endpoint(s)**
- Compared with baseline, ferric citrate 1, 6, and 8 g/day decreased serum phosphate by a mean of $-0.1\, \text{mg/dL}$, $-1.9\, \text{mg/dL}$, and $-2.1\, \text{mg/dL}$, respectively, at day 28 in the ITT population.
- Mean difference in change of serum phosphate from baseline of 1 g/day versus 8 g/day was $1.5\, \text{mg/dL}$ (95% CI, 0.86 to 2.1; $P < .001$).
- Mean difference in change of serum phosphate from baseline of 6 g/day versus 8 g/day was $0.21\, \text{mg/dL}$ (95% CI, $-0.39$ to 0.81; $P = .5$).
- No statistically significant dose response was observed for calcium or TSAT.
- A statistically significant dose response was observed for ferritin. Change in ferritin from baseline to day 28 was $-14.4\, \text{mg/dL}$, $90.1\, \text{mg/dL}$, and $90.2\, \text{mg/dL}$ for ferric citrate 1, 6, and 8 g/day, respectively.

**Comments:** This trial was conducted across 15 sites in the United States. A total of 22 patients (15.1%) were considered treatment failures by day 28 due to serum phosphorus being 2.5 mg/dL or less (7 patients) or serum phosphorus 9 mg/dL or more (15 patients). High serum phosphorus was seen more often in the 6 and 8 g/day cohorts, and low serum phosphorus was seen more often in the 1 g/day cohort.

**Limitations:** This study may have limited applicability in patients with active GI bleeding, inflammatory bowel disease, parathyroidectomy in the past 6 months, hyperphosphatemia of 10 mg/dL or more, and a history of malignancy in the past 5 years since they were excluded from participation.
(calcium acetate 667 mg and/or sevelamer carbonate 800 mg) in a 52-week, open-label, safety assessment period. Ferric citrate was provided as 1 g caplets containing ferric iron 210 mg, and patients were started on 6 g/day titrated up to 12 g/day. Active control was provided at the dose used prior to washout and titrated to a maximum of 12 pills daily. Doses were titrated to achieve a normal serum phosphorus level of 3.5 to 5.5 mg/dL. Compliant patients taking 12 pills/caplets of assigned phosphate binder and serum phosphorus greater than 9 mg/dL were discontinued as treatment failures. In the safety period, 192 ferric citrate patients were re-randomized 1:1 ferric citrate or placebo in a 4-week, open-label, efficacy assessment period. Patients with serum phosphorus of 9 mg/dL or more during this period were considered treatment failures. Allowed concurrent therapies included IV iron preparations (for ferritin 1,000 ng/mL or lower and TSAT of 30% or lower), vitamin D, vitamin D analogues, cinacalcet, dialysate calcium concentrations, and ESA according to the treating physician. Calcium supplements were allowed if not taken with food.

Results

Primary Endpoint(s)

- Ferric citrate decreased mean serum phosphorus from 5.1 mg/dL at week 52 to 4.9 mg/dL at week 56 (end of efficacy period) compared with 5.4 mg/dL at week 52 to 7.2 mg/dL at week 56 with placebo. The least squares mean treatment difference was -2.18 mg/dL (95% CI, -2.59 to -1.77; P < .001).

Secondary Endpoint(s)

- During the 52-week safety period, mean serum phosphorus decreased from 7.4 mg/dL at baseline to 5.4 mg/dL at week 52 with ferric citrate and from 7.6 mg/dL at baseline to 5.4 mg/dL at week 52 with active control. At week 52 of the safety period, 63% of 281 ferric citrate patients compared with 63.7% of patients achieved serum phosphorus of 5.5 mg/dL or less.
- During the safety period, ferric citrate increased serum iron from 72.6 mcg/dL at baseline to 88.4 mcg/dL at week 52 compared with serum iron remaining at approximately 69 mcg/dL throughout the safety period in active control (P < .001).
- During the safety period, ferric citrate increased mean serum ferritin from 593 ng/mL at baseline to 899 ng/mL at week 52 compared with 609 ng/mL at baseline to 628 ng/mL at week 52 for active control (P < .001).
- During the safety period, ferric citrate changed the mean TSAT from 31.3% at baseline to 39.3% at week 52 with ferric citrate compared with 30.9% at baseline to 29.7% active control (P < .001).
- During the safety period, TIBC changed from 233 mcg/dL at baseline to 227 mcg/dL at week 52 with ferric citrate compared with 225 mcg/dL at baseline to 235 mcg/dL at week 52 (P < .001).
- Median elemental IV iron use was 12.9 mg/week with ferric citrate compared with 26.8 mg/week with active control for a treatment difference of -52% (P < .001). In the last 9 months of the study, 42% of patients were off IV iron compared with 11% in active control.
- Median ESA use was 5,303 epoetin equivalent units per week with ferric citrate compared with 6,954 epoetin equivalent units per week with active control for a treatment difference of -24% (P < .04).

Endpoint(s)

- Mean hemoglobin during the safety period decreased from 11.6 g/dL at baseline to 11.4 g/dL at week 52 with ferric citrate compared with 11.7 g/dL at baseline to 11.1 g/dL at week 52 with active control (P < .05).
- During the safety period, serum calcium increased from 8.9 mg/dL at baseline to 9.1 mg/dL at week 52 with ferric citrate compared with 9 mg/dL at baseline to 9.3 mg/dL at week 52 with active control.
- In a subgroup analysis of the safety period, 74 patients taking ferric citrate who were not given IV iron over the 52-week period saw improvement in serum iron, ferritin, and TSAT at week 52 compared with baseline. In 207 patients provided IV iron, improvements were seen in serum iron, ferritin, TSAT, and hemoglobin at week 52 compared with baseline. Between group differences (IV iron vs no IV iron) at week 52 were not statistically significant.

Comments: This trial was conducted at 60 sites across the United States and Israel. In the safety period, 35 of 98 patients discontinued ferric citrate and 8 of 34 patients discontinued active control due to adverse events. In the efficacy period, 2 of 5 patients discontinued ferric citrate and 2 of 10 patients discontinued placebo due to adverse events.
An open-label extension trial exposed 168 patients, who successfully completed the original 58-week study, to ferric citrate for an additional 48 weeks. Preliminary data over the 48-week period reported serum phosphorus ranging from 5.2 to 5.5 mg/dL (baseline, 5.7 mg/dL), TSAT ranging from 36% to 38% (baseline 32%), and hemoglobin ranging from 11.1 to 11.6 g/dL (baseline, 11.1 g/dL) over 48 weeks. Ferritin increased from 700 ng/mL at baseline to a maximum of 848 ng/mL at week 24 and dropped to 717 ng/mL at week 48. Mean monthly IV iron dose per patient was 32 mg/month, and weekly mean ESA dose per patient was 4,500 units per week. Approximately 69% of patients in this period did not require IV iron. Pharmacoeconomic analysis of similar data concluded that the use of ferric citrate may reduce the cost associated with anemia-management drugs, and total health care cost of these patients may be reduced.

Limitations: This study may have limited applicability in patients with active GI bleeding or inflammatory bowel disease, parathyroidectomy in the past 6 months, serum phosphorus 10 mg/dL or more 3 months prior to screening, and a history of malignancy in the past 5 years since they were excluded from participation.

Drug: Ferric citrate versus placebo

Reference: Lee CT, et al, 2014

Study Design: Phase 3, randomized, multicenter, double-blind, placebo-controlled study

Study Funding: Panion and BF Biotech Inc.

Patients: One hundred eighty-three randomized patients (36 received placebo; 75 received ferric citrate 4 g/day; 72 received ferric citrate 6 g/day) who were 18 years and older on 3 times weekly hemodialysis and a stable dose of a phosphate binder. Included patients also had a urea reduction ratio greater than 65%, hematocrit greater than 20%, and serum calcium between 8.5 to 10.5 mg/dL. Baseline characteristics of placebo and both ferric citrate groups were similar. At baseline in the ferric citrate groups, mean age ranged from 53.4 to 56.4 years, 56.9% to 62.7% were male, baseline serum phosphorus was 7 mg/dL, and average dietary phosphorus intake was 1,165 to 1,240 mg.

Intervention: Patients with serum phosphorus between 5.5 and 10 mg/dL following a washout of previous phosphate binders for up to 2 weeks were randomized 1:2:2 to 8 weeks of placebo, ferric citrate 4 g/day, and ferric citrate 6 g/day. Ferric citrate was provided as 500 mg capsules containing ferric iron 105 mg. Patients were withdrawn from the study if they developed serum phosphorus of 9 mg/dL or more or TSAT of 55% or more. Stables doses of vitamin D analogues were allowed during the study, while iron-containing medications and oral and IV iron were prohibited. The efficacy cohort (166 patients) included patients with serum phosphorus measurement baseline and at day 14 or later. The safety cohort received at least 1 dose of study medication.

Results

Primary Endpoint(s)
- Change of serum phosphorus from baseline to week 8 was 0.08 with placebo and −1.6 and −2.27 with ferric citrate 4 and 6 g/day, respectively. Changes in serum phosphorus with the ferric citrate 4 and 6 g/day groups were both significantly greater than placebo. Change in serum phosphorus between the ferric citrate 4 and 6 g/day groups was also significantly different (P < .001).

Secondary Endpoint(s)
- Percentage of patients achieving serum phosphorus of 5.5 mg/dL or less at week 8 was 16.7%, 57.6%, and 74.1% with the placebo, ferric citrate 4 g/day, and ferric citrate 6 g/day groups, respectively.
- Change in serum ferritin from baseline to week 8 was −41.75 ng/mL in the placebo group, 73.9 ng/mL (P = .008 vs placebo) in the ferric citrate 4 g/day group, and 103.4 ng/mL (P = .003) in the ferric citrate 6 g/day group.
- Change in TSAT from baseline to week 8 was −1.15%, 5.35%, and 4.95% in the placebo, ferric citrate 4 g/day, and ferric citrate 6 g/day groups, respectively. Change in TSAT was not significantly different at either ferric citrate doses compared with placebo.
- Change in hemoglobin from baseline to week 8 was 0.35, 0.3, and 0.6 g/dL in the placebo, ferric citrate 4 g/day, and ferric citrate 6 g/day groups, respectively. Change in hemoglobin was not significantly different at either ferric citrate doses compared with placebo.
- Change in bicarbonate from baseline to week 8 was −0.15, −0.6, and 0.45 mmol/L in the placebo, ferric citrate 4 g/day, and ferric citrate 6 g/day groups, respectively. Change in bicarbonate was not significantly different at either ferric citrate doses compared with placebo.
• Change in serum calcium from baseline to week 8 was 0.17, 0.15, and 0.18 mg/dL with placebo, ferric citrate 4 g/day, and ferric citrate 6 g/day, respectively.

Comments: Twenty-four placebo patients discontinued the study; most cases were voluntary withdrawal. Three cases were due to adverse events and 1 case was due to serum phosphorus greater than 9 mg/dL. Nine patients given ferric citrate 4 g/day discontinued treatment, with 2 cases due to adverse events and 1 case due to serum phosphorus greater than 9 mg/dL. Eighteen patients given ferric citrate 6 g/day discontinued treatment, with 7 cases due to adverse events.

Limitations: This study was conducted in 5 medical centers in Taiwan; it was unspecified if this was the KRX-0502 formulation of ferric citrate. This study may have limited applicability in patients with GI abnormality, tertiary hyperparathyroidism, heart failure, diabetes mellitus with clinically relevant gastroparesis, unstable medical or psychiatric conditions, clinically significant electrocardiogram abnormalities, serum ferritin greater than 800 ng/mL, history of hemochromatosis, or active malignancy, except basal/squamous cell carcinoma, as these patients were excluded from participation.

Indication: Hyperphosphatemia and Iron Deficiency Anemia in Stages 3 to 5 Nondialysis-Dependent Chronic Kidney Disease Patients

Guidelines
Guideline: KDOQI clinical practice guidelines for bone metabolism and disease in CKD
Comments: In patients with stage 3 or 4 CKD, these guidelines recommend phosphate binders if serum phosphorus or intact PTH cannot be controlled with dietary phosphate restrictions with or without vitamin D therapy. Calcium-based binders are mentioned as a potential first-line agent. Ferric citrate is not mentioned in this version of the guidelines.

Studies
Drug: Ferric citrate versus placebo
Study Design: Phase 2 randomized, multicenter, double-blind, placebo-controlled trial
Study Funding: Keryx Biopharmaceuticals
Patients: One hundred forty-nine randomized adult patients (141 included in ITT cohort) with an estimated glomerular filtration rate less than 60 mL/min/1.73 m², serum ferritin 300 ng/mL or less, TSAT 30% or less, hemoglobin between 9 to 12 g/dL, and serum phosphorus between 4 and 6 mg/dL. Baseline demographics between ferric citrate and placebo groups appeared similar. The ferric citrate cohort at baseline was a mean age of 66 years, 31% were male, and 79% were White. Stage 4 CKD was the most prevalent (53%), followed by stage 5 (28%) and stage 3 (18%). Baseline laboratory values of this cohort included mean phosphate of 4.5 mg/dL, iron saturation of 22%, hemoglobin of 10.5 g/dL, ferritin of 116 ng/mL, intact FGF-23 of 159 pg/mL, 24-hour urine phosphate of 730 mg/day, and estimated glomerular filtration rate of 26 mL/min/1.73 m².

Intervention: Following a 2-week washout of phosphate binders, patients were randomized 1:1 to ferric citrate or placebo for a 12-week treatment period. Ferric citrate was provided as tablets (elemental iron 210 mg each) 3 times daily with meals and titrated to 12 tablets daily for achievement of serum phosphorus less than 3.5 mg/dL. Results were analyzed in the modified ITT cohort consisting of patients receiving 1 study drug and at minimum 1 baseline value with last observation carried forward for missing values. IV iron and ESA use were prohibited in the period leading up to and during the trial.

Results
Primary Endpoint(s)
• Ferric citrate decreased mean serum phosphate from 4.5 mg/dL at baseline to 3.9 mg/dL at week 12 compared with 4.7 mg/dL at baseline to 4.4 mg/dL at week 12 with placebo (P < .001).
• Ferric citrate increased TSAT from 22% at baseline to 32% at week 12, whereas TSAT remained unchanged at approximately 20% with placebo (P < .001).

Secondary Endpoint(s)
• Mean hemoglobin increased from 10.5 g/dL at baseline to 11 g/dL at week 12 with ferric citrate compared with 10.6 g/dL at baseline to 10.4 g/dL with placebo (P < .001).
• Mean ferritin increased from 116 ng/mL at baseline to 189 ng/mL at week 12 with ferric citrate compared with 110 ng/mL at baseline to 106 ng/mL with placebo (P < .001).
• Mean intact FGF-23 changed from 319 pg/mL at baseline to 200 pg/mL at week 12 with ferric citrate compared with 263 to 293 pg/mL with placebo (P = .017).
• Mean C-terminal FGF-23 changed from 468 pg/mL at baseline to 316 pg/mL at week 12 with ferric citrate compared with 511 to 579 pg/mL with placebo (P < .001).

Comments: This study was conducted in 20 sites across the United States. Statistically significant findings in both primary endpoints were prespecified to consider the trial results as positive. Discontinuation of ferric citrate occurred in 14 of 75 (19%) patients, with 1 case due to a hemoglobin less than 9 g/dL and 6 cases due to adverse events. Discontinuation of placebo occurred in 24 of 74 (32%) patients, with 9 cases due to hemoglobin less than 9 g/dL and 3 cases due to adverse effects.

Limitations: Study results were only available as posters, meeting abstracts, and press releases from the manufacturer. This study may have limited applicability in patients with active GI bleeding, inflammatory bowel disease, parathyroidectomy in the last 24 weeks, history of hemochromatosis, history of malignancy in the past 5 years, recent need for dialysis, or anemia due to causes other than CKD or iron deficiency anemia, as they were excluded from participation.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications
Ferric citrate is contraindicated in patients with known iron overload syndromes (eg, hemochromatosis). Ferric citrate should be used cautiously in patients at risk of or presenting with hemochromatosis. Part of the inclusion criteria used in ferric citrate studies included a serum ferritin less than 1,000 mcg/L and TSAT less than 50%. In 1 study, patients with a history of hemochromatosis or a serum ferritin greater than 800 ng/mL were excluded from participation.

Warnings and Precautions
Iron absorption from ferric citrate may lead to excessive elevations in iron stores, as reflected by increases in serum ferritin and transferrin saturation levels. Additionally, clinical studies have reflected the potential of ferric citrate and ferric citrate hydrate to increase iron-related parameters following ferric citrate administration. A phase 3 clinical trial administering ferric citrate at 1, 6, or 8 g/day for 4 weeks noted significant dose response with ferritin. Compared with baseline, serum ferritin at day 28 with 1, 6, and 8 g/day of ferric citrate changed by -14.4, 90.1, and 90.2 mg/dL, respectively. A 52-week safety period of a phase 3 study administering 6 to 12 g/day of ferric citrate compared the impact of iron-related parameters with calcium acetate or sevelamer carbonate. During this period, significant treatment differences with ferric citrate compared with active control were observed with serum ferritin, TSAT, hemoglobin, serum iron, and TIBC. A phase 3 study of ferric citrate in Taiwan noted increases in ferritin with 4 and 6 g/day of ferric citrate from baseline to week 8 compared with placebo. Assessment of iron parameters (eg, serum ferritin, TSAT) should occur prior to the start of the ferric citrate and be monitored throughout therapy.

Ferric citrate is an iron-containing product and should be kept out of reach of children. Accidental overdose may occur with any iron-containing product and is the leading cause of fatal poisoning in children younger than 6 years. Patients should be provided counseling regarding the potential of ferric citrate to discolor the stool. Counseling should also convey the information that stool discoloration (dark/tarry stools) may also serve as 1 of the signs and symptoms of potential GI bleeding. Stool discoloration was a common adverse effect of ferric citrate recorded during clinical trials. In a 28-day phase 3 trial with ferric citrate, fecal discoloration was reported in 29 of 151 patients (19%). During the 52-week safety assessment period of a phase 3 trial, fecal discoloration was noted in 17% of 289 patients given ferric citrate compared with 0% of 149 patients given sevelamer carbonate or calcium acetate. In a phase 3 trial of ferric citrate conducted in Taiwan, discoloration of stool was reported in 2 of 36 patients given placebo compared with 28 of 75 patients given ferric citrate 4 g/day and 27 of 72 patients given ferric citrate 6 g/day.

Cautious use may be warranted in patients with a history or current GI disorders. In ferric citrate studies, patients with GI abnormality, active GI bleeding, inflammatory bowel disease, or diabetes mellitus with clinically relevant gastroparesis were excluded from participation. A majority of adverse effects reported in clinical trials with ferric citrate and ferric citrate hydrate involved the GI tract. Some patients discontinued therapy with ferric citrate or ferric citrate hydrate due to treatment-related adverse effects that involved the GI tract.
Not enough information is available regarding the metabolic effects of alkali absorption of citrate.\textsuperscript{3}

In a clinical trial administering ferric citrate at 1, 6, or 8 g/day for 4 weeks, a significant dose response was observed for bicarbonate. Compared with baseline, bicarbonate values at day 28 with 1, 6, and 8 g/day of ferric citrate changed by 0.1, 1.6, and 1.5 mEq/L, respectively.\textsuperscript{5} A phase 3 trial of ferric citrate in Taiwan did not observe a significant change of bicarbonate from baseline to week 8 between placebo, ferric citrate 4 g/day, and ferric citrate 6 g/day groups. However, at week 8, the bicarbonate level was 23.75 mmol/L in the ferric citrate 6 g/day group compared with 21.8 mmol/L in the placebo group ($P = .028$).\textsuperscript{7} In a phase 2 trial providing ferric citrate 4.5 to 11.25 g/day for 4 weeks, an increase in bicarbonate from 22.2 mEq/L at baseline to 23.7 mEq/L at end of study was noted.\textsuperscript{29}

Ferric citrate is classified as Pregnancy Category B; no adequate and well-controlled studies in pregnant women have been conducted.\textsuperscript{1}

Animal studies found some transfer of iron into milk; it may be possible for breast-feeding infants to be exposed to ferric citrate.\textsuperscript{1}

Safety and efficacy have not been established in pediatric patients.\textsuperscript{1}

No known differences have been established between elderly and younger patients treated with ferric citrate.\textsuperscript{1}

### ADVERSE REACTIONS

Treatment-related GI adverse effects (e.g., diarrhea [21\%], discolored feces, constipation [8\%], nausea [11\%], vomiting) were the most commonly reported across several clinical trials with ferric citrate.\textsuperscript{1,5,7,29,33,37}

A phase 3 study administering ferric citrate 1, 6, and 8 g/day for 4 weeks noted the lower rate of adverse events in the 1 g/day cohort and similar rate in the 6 and 8 g/day cohorts. The rate of drug-related adverse events, serious adverse events, or events leading to discontinuation increased with the dose.\textsuperscript{5}

In a phase 3 trial of fixed-dose ferric citrate, 91 of 151 events (60.2\%) were graded as mild to moderate, with 53 of 151 events (35.1\%) determined to be related to the study drug. The most common adverse effects in the study involved the GI tract and included nausea, vomiting, diarrhea, constipation, fecal discoloration, and upper abdominal pain.\textsuperscript{5}

In a 52-week safety period of a phase 3 study, 289 patients were provided with ferric citrate 6 to 12 g/day, and 149 were provided active control (up to 12 tablets of calcium acetate 667 mg or sevelamer carbonate 800 mg) over 52 weeks. Treatment-emergent adverse events were reported in 90.7\% of patients taking ferric citrate and 89.3\% of active control patients. The GI tract was the most common system organ class reported with treatment-emergent adverse effects, which affected 56.4\% of patients with ferric citrate and 46.3\% of active control patients. Most of the GI treatment-emergent adverse effects were nonserious and occurred in 49.4\% of ferric citrate patients compared with 34.2\% of active control patients. Event rates of select GI adverse effects are shown in Table 2. Serious adverse effects occurred in 39.4\% of patients taking ferric citrate and 49\% of active control patients (Table 3). A total of 19.1\% of patients taking ferric citrate had a serum ferritin greater than 1,500 ng/mL compared with 10.1\% of patients with active control. In both groups, IV iron administration was most frequently determined to be the causative factor, with 7.6\% of the ferric citrate group compared with 4.7\% in the active control group.\textsuperscript{33}

Treatment-emergent adverse events leading to study drug discontinuation occurred in 21\% of patients with ferric citrate compared with 14\% with active control. The most common reasons for treatment discontinuation in both groups were renal transplant and GI events.\textsuperscript{1,33}

### Table 2. Select gastrointestinal adverse effects during a 52-week safety assessment period of a phase 3 trial\textsuperscript{33}

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Ferric citrate ($n = 289$)</th>
<th>Active control ($n = 149$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>25.6%</td>
<td>14.1%</td>
</tr>
<tr>
<td>Fecal discoloration</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>14.2%</td>
<td>14.1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9%</td>
<td>14.8%</td>
</tr>
<tr>
<td>Constipation</td>
<td>8%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6.2%</td>
<td>6%</td>
</tr>
</tbody>
</table>
The most common adverse events in a phase 3 trial of 166 patients in Taiwan were related to the GI tract and were reported at 27.8%, 61.3%, and 58.3% of placebo, ferric citrate 4 g/day, and ferric citrate 6 g/day arms, respectively. The 2 most commonly treated related adverse effects across all cohorts were fecal discoloration and diarrhea. Fecal discoloration occurred in 2 patients with placebo and in 28 and 27 patients taking ferric citrate 4 and 6 g/day, respectively. Diarrhea occurred in 2 patients with placebo and in 5 patients and 3 patients taking ferric citrate 4 and 6 g/day, respectively. Adverse effects led to study discontinuation in 3 patients with placebo, 2 patients with ferric citrate 4 g/ day, and 7 patients with ferric citrate 6 g/day.

**DRUG INTERACTIONS**

Ferric citrate is an iron-containing product. Medications that may interact with iron, including, but not limited to, antacids, ascorbic acid, calcium salts, levodopa, levothyroxine, fluoroquinolones, tetracyclines, and doxycycline, should be appropriately administered separately or avoided with ferric citrate. Most drugs should not be administered at the same time as the ferric citrate dose. Medications that can be coadministered with ferric citrate include amlodipine, aspirin, atorvastatin, calcitriol, clopidogrel, digoxin, doxycycline, eralapril, fluvastatin, levofloxacin, metoprolol, pravastatin, propranolol, sitagliptin, and warfarin.

**RECOMMENDED MONITORING**

Serum phosphorus should be assessed at baseline and monitored as often as clinically indicated throughout therapy with ferric citrate. In clinical trials with ferric citrate, serum phosphorus was evaluated at various intervals that included weekly assessments; weekly assessment for the first 2 weeks, then every other week thereafter; or assessment every other week for 12 weeks followed by monthly thereafter. Various criteria were utilized in clinical trials to determine discontinuation of therapy with ferric citrate. In 2 clinical trials, patients discontinued therapy or were considered treatment failures with ferric citrate if they had 2 consecutive serum phosphorus measurements above 8 to 9 mg/dL. A third clinical trial discontinued ferric citrate therapy if patients had a serum phosphorus of 2.5 mg/dL or less on day 7 and a reading of 2.5 mg/dL or less or 9 mg/dL or higher on day 14 or 21.

It may be advisable to assess baseline iron-related parameters and monitor them as often as clinically indicated with ferric citrate therapy. In 1 clinical trial, iron parameters were monitored at a minimum of every 12 weeks. Clinical studies have shown the potential of ferric citrate and ferric citrate hydrate to improve iron-related parameters, such as serum iron, ferritin, hemoglobin, TSAT, and TIBC, following ferric citrate administration.

**Table 3. Summary of the most common severe adverse effects occurring in 5% or more of patients during a 52-week safety assessment period of a phase 3 trial**

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Ferric citrate (n = 289)</th>
<th>Active control (n = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>12.5%</td>
<td>18.1%</td>
</tr>
<tr>
<td>Surgical and medical procedures</td>
<td>7.6%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Vascular</td>
<td>7.6%</td>
<td>9.4%</td>
</tr>
<tr>
<td>General disorders and administration site</td>
<td>7.3%</td>
<td>8.1%</td>
</tr>
<tr>
<td>Cardiac</td>
<td>6.9%</td>
<td>11.4%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>6.9%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal</td>
<td>6.6%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural</td>
<td>5.2%</td>
<td>6%</td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td>5.2%</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

The recommended dose by the manufacturer is 2 tablets (ferric iron 210 mg per tablet; equivalent to ferric citrate 1 g per tablet) orally 3 times per day with meals. Patients should be instructed to take their other medications at a different time. The dose of ferric citrate should be adjusted based on the patient's serum phosphorus levels. Decrements or increments
of 1 to 2 tablets per day, done at intervals of 1 week or longer, should be used to maintain the serum phosphorus at target levels. The daily maximum dose is 12 tablets. The average dose required in the clinical trials to achieve the target serum phosphorus level was 8 to 9 tablets per day.

**PRODUCT AVAILABILITY**

A special protocol agreement was arranged with the US Food and Drug Administration (FDA) to aid with phase 3 trials for regulatory approval of ferric citrate. The filing of a new drug application for ferric citrate was accepted by the FDA in October 2013. The initial Prescription Drug User Fee Act date was extended by 3 months in May 2014. Ferric citrate was approved by the FDA on September 5, 2014.

The product is available as a film-coated tablet containing ferric iron 210 mg (equivalent to ferric citrate 1 g) in 200-count polyethylene bottles. The product should be stored at controlled room temperature 68°F to 77°F (20°C to 25°C) and protected from moisture.

**DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

No REMS is required for ferric citrate.

**CONCLUSION**

Ferric citrate is indicated for phosphate reduction in ESRD patients on hemodialysis with hyperphosphatemia. As part of the special protocol assessment with the FDA, Keryx Biopharmaceuticals completed 2 phase 3 trials to support the approval of this indication. Two additional clinical trials with ferric citrate are currently being conducted in slightly different populations: hyperphosphatemia with iron deficiency anemia in nondialysis-dependent CKD patients, and iron deficiency anemia in CKD patients. In clinical trials funded by Keryx Biopharmaceuticals, 1 g of ferric citrate is estimated to provide approximately 210 mg of elemental iron. It is estimated that 85 g of phosphate is bound per gram of elemental iron. In addition to ferric citrate’s dose-dependent effect of serum phosphate reduction, secondary endpoints in clinical trials hint at an additional benefit of an increase in iron-related parameters as well as a potential decrease in the need for parenteral iron or ESA. However, because of these potential effects on iron-related parameters, it may be advisable to appropriately monitor patients for prevention of iron overload. GI adverse effects were the most commonly reported treatment-related adverse effects. Despite the results shown with ferric citrate thus far, most studies evaluated surrogate endpoints (eg, change in phosphate level) rather than hard endpoints (eg, vascular calcification, left ventricular hypertrophy, cardiovascular mortality, CKD progression, mortality in CKD).

**REFERENCES**


33. Sika M, Umanath K, Goral S, et al. Keryx FC phase III safety thumbnail ferric citrate as a phosphate binder has a safety profile similar to sevelamer carbonate and calcium

150 Volume 50, February 2015
acetate [poster]. Presented at: 2013 ASN Kidney Week Meeting; November 5-10, 2013; Atlanta, GA. Abstract SA-PO540.


46. Levothroid (levothyroxine sodium) [prescribing information]. Shenandoah, IA: Lloyd Pharmaceutical; September 2005.


49. Velphoro (sucroferric oxyhydroxide) [prescribing information]. Waltham, MA: Fresenius Medical Care; December 2013.
Continuing Education Case Study Quiz

**Goal**—The goal of this activity is to educate pharmacists about the use of ferric citrate for the treatment of patients with chronic kidney disease.

**Objectives**—At the completion of this activity, the reader will be able to:
1. Describe the pharmacology and pharmacokinetics of ferric citrate.
2. Discuss the risks associated with the use of ferric citrate.
3. Discuss the potential benefit of ferric citrate for an individual patient.
4. Apply the information on the use of ferric citrate to a case study.

**Key Words**—ferric citrate, new drugs, chronic kidney disease, dialysis

---

1. The US Food and Drug Administration (FDA)—approved indication for ferric citrate is for the treatment of:
   a. Adult and pediatric patients with iron deficiency anemia.
   b. Adult patients with macrocytic anemia.
   c. Adult patients with elevated serum phosphorus associated with chronic kidney disease (CKD) requiring dialysis.
   d. Adult and pediatric patients with elevated serum phosphorus associated with CKD not requiring dialysis.

2. Ferric citrate produces its serum phosphorous lowering effects by:
   a. Binding dietary phosphorous to increase fecal excretion.
   b. Forming insoluble calcium phosphate complex.
   c. Exchanging ligands between dietary phosphate and hydroxyl groups.
   d. Forming ionic and hydrogen bonds with intestinal phosphate.
3. Ferric citrate contains how many milligrams of elemental ferric iron per 1 g of ferric citrate?
   a. 210 mg
   b. 248 mg
   c. 400 mg
   d. 500 mg

4. Which of the following is a contraindication to therapy with ferric citrate?
   a. Low serum ferritin
   b. History of gastrointestinal disorders
   c. Known iron overload syndrome
   d. Concomitant acid-reducing medications (eg, H2-blockers, protein pump inhibitors)

5. Ferric citrate is in Pregnancy Category:
   a. A.
   b. B.
   c. C.
   d. X.

Case History
B.B. is a 62-year-old obese female patient with hypertension, diabetes, chronic kidney disease, and major depressive disorder. Her current medications include lisinopril, diltiazem, sitagliptin, glipizide, and paroxetine. Her physician has just diagnosed her with end-stage renal disease and has decided to start her on dialysis. Her current laboratory values of note include phosphorous of 7.5 mg/dL, ferritin 180 mg/dL, and transferrin saturation of 35%. Her physician thinks she may benefit from the use of ferric citrate.

6. The recommended initial dose of ferric citrate for B.B. would be:
   a. 1 g three times daily.
   b. 4 g per day in divided doses.
   c. 2 g twice daily.
   d. 2 g three times daily.

7. How many tablets make up the maximum recommended dose of ferric citrate for B.B.?
   a. 6 tablets
   b. 8 tablets
   c. 9 tablets
   d. 12 tablets

8. B.B. should be instructed to take ferric citrate:
   a. On an empty stomach.
   b. With meals.
   c. Three times daily with or without food.
   d. Every 3 days, after dialysis.

9. Which of B.B.'s medications can be taken concomitantly with the ferric citrate?
   a. Lisinopril
   b. Sitagliptin
   c. Diltiazem
   d. None of the above

10. Which of the following potential options for the treatment of urinary tract infection may be administered with ferric citrate?
    a. Ciprofloxacin
    b. Levofoxacin
    c. Doxycycline
    d. None of the above

11. What baseline and periodic monitoring would you recommend for B.B.'s ferric citrate therapy?
    a. Serum phosphorous and iron parameters
    b. Serum phosphorous and corrected calcium
    c. Serum creatinine and corrected calcium
    d. Serum creatinine and serum uric acid

12. The most common side effects associated with ferric citrate include:
    a. Nausea, headache, and pruritus.
    b. Nausea, headache, and diarrhea.
    c. Diarrhea, nausea, and constipation.
    d. Vomiting, rash, and abnormal liver function tests.

13. At what interval should you adjust B.B.'s dose of ferric citrate?
    a. Every 3 days as needed
    b. No more frequently than every week
    c. No more frequently than every 2 weeks
    d. Daily until at the maximum dose.

14. B.B. has been taking ferric citrate for 6 months and has recently been experiencing postprandial fullness and bloating. Her physician has diagnosed her with diabetic gastroparesis. What action is recommended?
    a. Reduce the dose of ferric citrate by half.
    b. Reduce the dose by one fourth.
    c. Monitor her more closely.
    d. Increase the dose by one fourth.

15. Ferric citrate should be stored:
    a. Only in the original container.
    b. In the refrigerator and protected from moisture.
    c. In the freezer and protected from light.
    d. At controlled room temperature and protected from moisture.

Hospital Pharmacy 153