CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205874Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	August 8, 2014
From	Aliza Thompson
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 205874
Applicant	Keryx Biopharmaceuticals, Inc
Date of Submission	August 7, 2013 (receipt date)
PDUFA Goal Date	Initially June 7, 2014; extended to September 7, 2014 because of a major amendment
Proprietary Name / Established (USAN) names	Proprietary name to be determined/ferric citrate
Dosage forms / Strength	Tablets / 210 mg of iron (equivalent to 1 g ferric citrate)
Proposed Indication(s)	1. control of serum phosphorus levels in patients with chronic kidney disease on dialysis 2. (b) (4)
Recommended:	Approval for control of serum phosphorus levels in patients with chronic kidney disease on dialysis

Material Reviewed/Consulted	
Product Quality Microbiology Review (8/8/13)	Stephen E. Langille
Chemistry Review (3/31/14 and 7/29/14)	Monica D. Cooper (Drug Substance) Thomas Wong (Drug Product)
Biopharmaceutics Review (4/2/14)	Elsbeth Chikhale
Pharmacology Toxicology Review (1/16/14)	Rama Dwivedi
Clinical Pharmacology Review (6/10/14 and 7/23/14)	Ju-Ping Lai
Clinical Review (4/28/14)	Nancy Xu
Statistical Review (4/22/14)	John Lawrence
Divison of Hematology Products Review (3/14/14)	Andrew Dmytrijuk
Division of Medication Error Prevention and Analysis Review (initial review 2/7/14, revised review pending)	Jean Olumba
Office of Scientific Investigations Clinical Inspection Summary (4/2/14)	Sharon Gershon

1. Introduction

Keryx has submitted a 505(b)(2) application for ferric citrate tablets for the control of serum phosphorus levels (b) (4) The submitted data provide substantial evidence of the drug's effectiveness in lowering serum phosphorus levels, but are not adequate to support a claim related to (b) (4) They are no safety concerns that would preclude approval. According to DMEPA, the currently proposed tradename is not acceptable; however, from a CMC, pharmacology-toxicology, clinical pharmacology, clinical and statistical perspective, the application can be approved once agreement is reached on labeling.

2. Background

Proposed Indication: control of serum phosphorus levels in patients with chronic kidney disease on dialysis

Ferric citrate was developed as a phosphate binder under IND 052868. The principal studies supporting effectiveness were conducted under Special Protocol Assessment and sought to establish the product's effectiveness in lowering serum phosphorus levels in patients with end-stage renal disease on dialysis.

Hyperphosphatemia is common in end-stage renal disease patients on dialysis and, as noted in Dr. Xu's review, a number of phosphate binders are approved for use in this population. Like ferric citrate, these products bind phosphate in the gastrointestinal tract, thereby decreasing absorption and lowering serum levels.

All of the marketed products were approved based on effects on serum phosphorus levels. In epidemiologic studies, elevated serum phosphorus levels have been associated with an increased risk of secondary hyperparathyroidism, vascular, valvular, and other soft tissue calcification and cardiovascular disease in patients with chronic kidney disease. In patients on dialysis, higher serum phosphorus levels have also been associated with an increased risk of mortality. To date, however, there are no data from outcome studies demonstrating that a treatment's effect on serum phosphorus levels predicts its effect on clinical outcomes such as cardiovascular events or mortality. Nevertheless, the Division of Cardiovascular and Renal Products, following the precedent set by the Division of Metabolism and Endocrinology Products, treats serum phosphorus reduction as a valid surrogate in patients with end-stage renal disease.

In January 2014, ferric citrate (Riona® Tablets 250 mg) was approved in Japan for the improvement of hyperphosphatemia in patients with chronic kidney disease. Ferric citrate is being marketed in Japan by Torii Pharmaceutical Co., Ltd, a subsidiary of Japan Tobacco Inc.

Proposed Indication: [redacted]

This claim was not discussed during the product's development. The Division of Hematology Products [redacted] and hence was consulted regarding this claim.

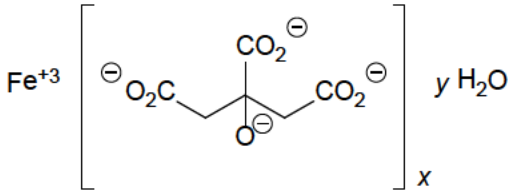
3. CMC

According to Drs. Cooper and Wong, the NDA is recommended for approval from a CMC perspective. According to Dr. Chikhale, the NDA is also recommended for approval from a Biopharmaceutics perspective.

In their initial review dated March 31, 2014, Drs. Cooper and Wong recommended a complete response action. A key concern was that the drug substance was not adequately controlled, resulting in significant variability in drug substance batches and [redacted] effects on the drug product. A discipline review letter was sent to the applicant on April 9, 2014. In response, the applicant submitted new information, including substantial revisions to the CMC section of the application; a major amendment was issued in order to allow sufficient time for review.

According to the CMC review dated July 29, 2014, the applicant provided adequate information to allow a satisfactory evaluation of the quality of both the drug substance and drug product. The data indicate that the drug substance and drug product are manufactured and packaged in accordance with procedures and proposed specifications to assure quality throughout the shelf-life. In particular, the submitted information confirms that a consistent amount of ferric iron is present in each tablet.

Drug Substance: The chemical name of ferric citrate is iron (+3), *x* (1,2,3-propanetricarboxylic acid, 2-hydroxy-), *y* (H2O); the chemical structure is shown below.



The drug substance is an [redacted] that is [redacted] It is [redacted]

The applicant claims that the drug substance is a coordination complex [redacted]. However, according to Drs. Cooper and Wong, it is unclear if the coordination complex is present [redacted] and no data were provided demonstrating that these species [redacted] are responsible for the drug's effect on serum phosphorus.

Although the applicant has proposed a drug substance retest date of (b) (4) months, based on stability data from eleven batches, a (b) (4)-month retest date is being granted for the drug substance (b) (4)

Drug Product: The drug product is an immediate release, film-coated, peach-colored and oval-shaped tablet embossed with KX52 (b) (4) Each tablet contains 210 mg of ferric iron equivalent to 1000 mg of ferric citrate [1]; excipients include pregelatinized starch and calcium stearate and inactive ingredients include hypromellose, titanium dioxide, triacetin, FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake, FD&C Red #40/Allura Red AC Aluminum Lake, and FD&C Blue #2/Indigo Carmine Aluminum Lake. Tablets are supplied in (b) (4) (b) (4) high density polyethylene bottles (b) (4); bottles contain 200 tablets. Tablets should be protected from moisture and are to be stored at room temperature (20 to 25° C with excursions permitted to 15 to 30° C). With regard to shelf-life, two of the three tested batches failed dissolution acceptance criterion at the 24-month time point and the third batch barely met the acceptance criterion at the 24-month time point. The applicant has proposed a shelf-life of 18 months and according to the CMC review, an 18 month shelf-life is being granted for the tablets packaged in the proposed commercial package and stored under the aforementioned storage conditions.

Biopharmaceutics: According to Dr. Chikhale, the applicant's dissolution method is acceptable. Based on the overall dissolution data from the clinical and registration batches a dissolution acceptance criterion of Q= (b) (4)% at 45 minutes was recommended; the Applicant has agreed to this recommendation.

Facilities inspections: Facilities inspections have been completed. The Offices of Compliance and New Drug Quality Assessment have determined that the facilities are acceptable.

4. Nonclinical Pharmacology/Toxicology

According to Dr. Dwivedi's review, the application can be approved from a pharmacology and toxicology perspective. Ferric citrate for use as a food supplement is listed as Generally Regarded As Safe (GRAS) in the Code of Federal Regulations. The application references the published literature for data on primary pharmacology, safety pharmacology, pharmacokinetics, acute toxicity, nonclinical reproductive toxicology, carcinogenicity, and mutagenicity.

Pharmacology: Ferric iron forms an insoluble complex with phosphate in the gastrointestinal tract, thus preventing the systemic absorption of phosphate. The insoluble ferric-phosphate complex is excreted in the stool, while the citrate component is either metabolized to carbon dioxide via the citric acid cycle or converted to bicarbonate. Free ferric iron (Fe^{3+}) is either excreted or is converted to ferrous iron (Fe^{2+}) and transported into enterocytes where it is stored as ferritin or exported into the blood by ferroportin.

[1] Some reviews refer to tablets containing (b) (4) mg of ferric citrate. Data submitted by the applicant in response to the CMC discipline letter indicate that each tablet contains 210 mg of ferric iron equivalent to 1 g of ferric citrate.

Toxicity: According to the published literature, animals exposed to lethal doses of iron compounds have shown congestion and hemorrhagic necrosis of the gastrointestinal tract, gastroenteritis (including diarrhea and vomiting leading to dehydration, and electrolyte imbalance), bowel obstruction, decreased activity, weakness, decreased muscular control, prostration, decreased urination, rapid and shallow respiration, convulsions, coma, respiratory failure, and cardiac arrest. The gastrointestinal tract is one of the most common sites of iron toxicity, but other organ systems can also be affected by iron deposition and overload.

Because of the relatively high doses of iron and citrate proposed for clinical use, repeat-dose toxicity studies of ferric citrate were conducted in the rat and dog. According to Dr. Dwivedi,

- A Keryx-sponsored 28-day repeat-dose oral toxicology study in rats showed reduced systemic bioavailability of iron when complexed with citrate.
- Target organs for toxicity and iron deposition in repeat-dose toxicity studies included the gastrointestinal tract, liver and spleen. Increased liver weight, bile duct hyperplasia, and gastrointestinal tract and liver injury were seen at high doses and were attributed to iron overload. There were no treatment related deaths in these studies; however, in a 42-week toxicity study in dogs, there was one unscheduled death of a dog in a high dose group (2000 mg/kg/day ferric citrate) at week 40 because of liver injury attributed to iron overload.
- At the proposed maximum dose in humans (12 g/day, equivalent to 200 mg ferric citrate/kg or 42 mg ferric iron/kg in a 60-kg human), there is essentially no safety margin over the NOAEL in the most sensitive species, the dog. However, based on more overt toxicology and persistent histopathology changes (e.g., inflammatory liver foci), the safety margin is 5-10 times on a mg/kg basis.

Carcinogenicity: There was no evidence of carcinogenicity in a lifetime carcinogenicity study of ferric citrate in mice at doses equivalent to 0.8 times the maximum human recommended dose (MHRD) on a milligram-per-kilogram basis or 0.06 times the MHRD on a body-surface-area basis. Ferric citrate was not mutagenic in the Ames test or clastogenic in the chromosomal aberration test.

Reproductive and developmental toxicity: No reproductive or developmental toxicity studies have been conducted with ferric citrate. Studies of other iron-containing compounds and citric acid in animals have not raised significant safety concerns.

5. Clinical Pharmacology/Biopharmaceutics

According to Dr. Lai's review, the application can be approved from a clinical pharmacology perspective. As previously noted, ferric iron reacts with dietary phosphate in the GI tract, forming an insoluble complex that is excreted in the stool. Clinical and preclinical data indicate that there is systemic absorption of iron from ferric citrate; however the extent of absorption was not quantified in a mass balance study.

Dosage and Administration: Because of its mechanism of action, ferric citrate is taken with or proximate to meals.[2]

- In the 58-week safety and efficacy trial, subjects were initiated on 6 caplets/day of ferric citrate and could be titrated up to a maximum of 12 caplets per day as needed to achieve a phosphorus level between 3.5 and 5.5. According to Dr. Lai's review, the overall mean ferric citrate dose at the end of the pivotal trial, which was conducted largely in the U.S., was 8.8 caplets/day (median=9.0 g/day; range of 0 to 12 g/day); her review also states that "very few subjects (n<20)" required down titration in this trial.
- Per Dr. Lai, in clinical trials, near maximum serum phosphate lowering effects were seen within 1 week on all doses of ferric citrate that showed an effect.

Of note, the applicant has proposed that labeling recommend a starting dose of (b) (4) 2 tablets orally three times per day with meals. However, according to Dr. Lai's review, data from the applicant's pivotal safety and efficacy trial, KRX-0502-304, suggest that most patients will likely require (b) (4) tablet three times per day with meals.[3] Her review also notes that there was no clear dose-response relationship for safety/tolerability at ferric citrate doses of 6 g per day and below (see pages 8-9 of her review). Given this experience, the utility of starting the average patient in the U.S. on (b) (4) tablet three times per day with meals is unclear. Unless the applicant can provide a compelling rationale for recommending the proposed starting dose, I think labeling should recommend a starting dose of 2 tablets orally three times per day with meals and state that therapy should be increased or decreased as needed to achieve target levels.

Drug-Drug Interaction: Potential drug-drug interactions with medication classes/medications commonly administered in the intended population were explored in *in vitro* studies. Of the drugs that were tested, only doxycycline was found to show extensive binding with ferric citrate. The following drugs did not show an interaction potential: digoxin, clopidogrel, warfarin, aspirin, levofloxacin, propranolol, metoprolol, enalapril, amlodipine, calcitriol, doxercalciferol, atorvastatin, fluvastatin, pravastatin, and sitagliptin.

6. Clinical Microbiology

According to Dr. Langille, the microbial limits specification for ferric citrate is acceptable from a Product Quality Microbiology perspective.

[2] In the pivotal trials supporting efficacy, subjects were advised to take study medication during or within one hour of meals or snacks. Subjects were allowed to take their study medication in any distribution with meals since it was felt that subjects would require a different distribution in a given day due to snacks or missed meals.

[3] As discussed in Dr. Lai's review, a study conducted in Japan showed a steeper dose-response (phosphate-lowering) relationship than that seen in studies conducted exclusively or in part in the U.S. Based on Dr. Lai's analyses, the difference may be explained in part by differences in body weight and dietary phosphate intake.

7. Clinical/Statistical- Efficacy

Principal support for efficacy comes from studies KRX-0502-305 and KRX-0502-304. Both trials were conducted under Special Protocol Assessment and had primary endpoints that assessed effects on serum phosphorus levels. Both trials were successful in meeting their primary endpoint and Drs. Xu and Lawrence agree that the trials provide substantial evidence of effectiveness in lowering serum phosphorus levels.

KRX-0502-305

Design: KRX-0502-305 was a multicenter, randomized, open-label, dose-ranging and efficacy study conducted in patients with end-stage renal disease on thrice-weekly hemodialysis in the United States. Patients who had a serum phosphorus concentration ≥ 6 mg/dL by the end of an approximately 2-week washout period were randomized in a 1:1:1 ratio to 4 weeks of treatment with one of three fixed doses of ferric citrate (1, 6, or 8 g). The use of other phosphate binders was not permitted while on study drug and the dose of ferric citrate was not to be altered. Treatment failures (serum phosphorus > 9.0 mg/day or < 2.5 mg/dL) were discontinued from study drug.

The primary endpoint was the change in serum phosphorous at day 28 or last value on treatment. The primary analysis used a linear regression model with dose effect. If the null hypothesis of slope= 0 was rejected at a significance level of 0.05, then each pairwise comparison was to be tested sequentially starting with 8 g vs. 1 g, then 6 g vs 1 g, followed by 8 g vs. 6 g.

There were numerous secondary endpoints (see page 25 of 84 of Dr. Xu's review). These endpoints assessed effects on serum phosphorus and other laboratory parameters. According to Dr. Lawrence's review, there was no plan to control the overall type 1 error rate in testing these secondary endpoints.

Subject Disposition: The trial randomized 154 subjects; of these, 151 were treated. According to Dr. Xu's review (Table 10, page 34), 23% of subjects discontinued treatment in the 1 g/day arm, 10 % in the 6 g/day arm, and 24% in the 8 g/day arm. The most common reason for discontinuing treatment in the 8 g/day group was an adverse event (16%). The most common reason for discontinuing treatment in the 1 g/day group was treatment failure (17%).

Efficacy Findings: The mean reduction in serum phosphorus at week 4 was 0.1 mg/dL in the 1 g arm, 1.9 mg/dL in the 6 g arm and 2.1 mg/dL in the 8 g arm (see Figure 6 of Dr. Lawrence's review for the cumulative distribution function of the change from baseline). The null-hypothesis of slope=0 was rejected at a significance level of 0.0001. The change from baseline was statistically significantly different in the 8 g vs. 1 g and 6 g vs 1 g pairwise comparison but not the 8 g vs. 6 g comparison.

The primary endpoint analysis used LOCF for subjects with no final value, and, according to Dr. Lawrence's review, the mean change from baseline in LOCF subjects was somewhat different from the mean change from baseline in completers. In the 1 g/day arm, the mean change from baseline for the LOCF values was +0.5 mg/dL compared to -0.1 mg/dL for the

completer values. In both higher dose groups, the mean change for the LOCF values was a larger negative number than the mean change for completers. On face, the findings seem consistent with the practice of discontinuing treatment failures (serum phosphorus > 9 or < 2.5 mg/dL) and possibly a greater efficacy response in subjects discontinuing treatment because of an AE in the higher dose groups.

KRX-0502-304

Design: KRX-0502-304 was a three-period, randomized, open-label, 58-week safety and efficacy trial of ferric citrate in patients with end-stage renal disease on dialysis. Fifty-six out of 58 sites were in the United States; two were in Israel.

Following a 2-week washout period, subjects were randomized in a 2:1 ratio to ferric citrate or active control (calcium acetate or sevelamer carbonate or any combination of calcium acetate and sevelamer) for 52 weeks of treatment (the "safety assessment period"). Subjects in the ferric citrate arm were initiated on 6 caplets/day, with dose titrated to achieve a target phosphorus of 3.5 - 5.5 mg/dL. Subjects completing the 52-week safety assessment period on ferric citrate were re-randomized in a 1:1 ratio to continue treatment with ferric citrate or to receive placebo for an additional 4 weeks.

The trial's primary endpoint was the change in serum phosphorus from the beginning of the efficacy period (the end of the 52-week safety assessment period) to the end of the 4-week efficacy period (week 56 of the trial). The primary endpoint analysis used an analysis of covariance (ANCOVA) model with treatment as a fixed class effect and study baseline (week 52) as a covariate. The efficacy analysis population included patients who took at least one dose of study medication and provided baseline and at least one post-baseline efficacy assessment; missing efficacy values were imputed using last observation carried forward.

Subject Disposition in the Efficacy Assessment Period: In the efficacy assessment period, 96 subjects were randomized to KRX-0502 and 96 to placebo; all but two subjects received study drug. Per Dr. Xu's review (Table 7, page 28), 94% of subjects randomized to ferric citrate completed the efficacy assessment period on study drug, compared to 73% in the placebo arm. The most common reason for discontinuing treatment in the placebo arm is listed as "Other"; according to Dr. Xu, the majority of these events were discontinuations for a serum phosphorus level ≥9 mg/dL.

Efficacy Findings: The mean change in serum phosphorus from week 52 to the end of the 4-week efficacy period was 1.8 mg/dL (95% CI 1.6, 2.2) in the placebo arm and -0.2 mg/dL (95% CI -0.6, -0.03) in the ferric citrate arm; the LS mean treatment difference for the change in serum phosphorus was -2.2 mg/dL (95% CI -2.6, -1.8; p-value < 0.0001). The cumulative distribution function for the change in each arm is shown below; the y-axis represents the proportion of subjects with a change from baseline less than X.

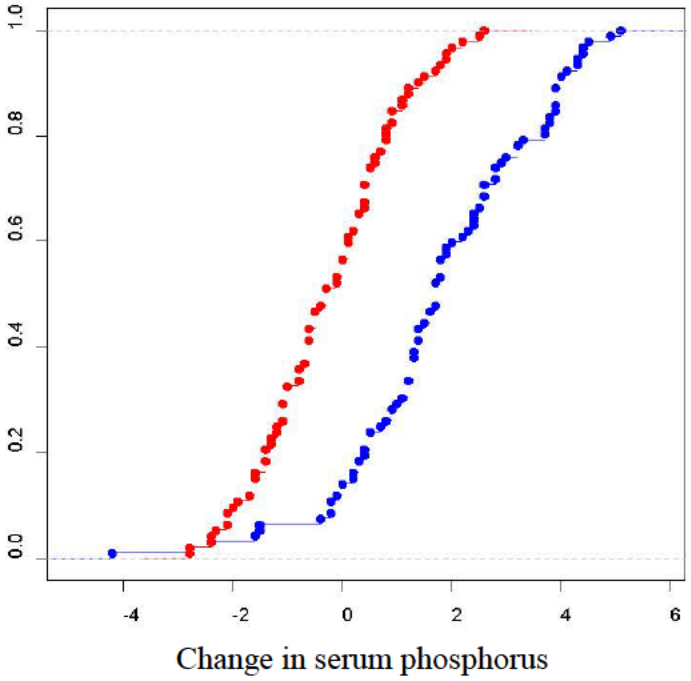


Figure 1. Empirical cumulative distribution function for the change in each arm in KRX-0502-304
Source: Figure 3, Dr. Lawrence's review; blue=placebo, red=ferric citrate; the y-axis represents the proportion of subjects with a change from baseline less than X

KRX-0502-304 included 4 secondary endpoints which were to be tested using a sequential testing procedure. The results, as reported by the applicant, are shown in the table below; Dr. Lawrence reports that he was unable to replicate these analyses. The Division of Hematology Products was consulted regarding the clinical significance of these findings. (b) (4)

(b) (4)

8. Safety

Principal support for safety at the doses proposed for clinical use is provided by the 52-week active-control phase ("safety assessment period") of KRX-0502-304. During the safety assessment period, 289 subjects were treated with ferric citrate and 149 subjects were treated with active control (calcium acetate or sevelamer carbonate or any combination of calcium acetate and sevelamer).

Deaths and serious adverse events
Deaths within 30 days of discontinuation of therapy where similar in the two arms (~5.0%) and serious treatment emergent adverse events were reported in 39% of ferric citrate subjects compared with 49% of active control subjects.

Discontinuation due to adverse events
Discontinuations due to adverse events were more common in the ferric citrate arm than in the active control arm. During the 52-week, active-control period, 60 subjects (21%) on ferric citrate discontinued study drug because of an adverse reaction, as compared to 21 subjects (14%) in the active control arm. Gastrointestinal adverse events were the most common reasons for discontinuing ferric citrate and led to more discontinuations in the ferric citrate arm than in the active control arm (14% and 4%, respectively). Gastrointestinal adverse events that led to more discontinuations in the ferric citrate arm than in the control arm included diarrhea (8% vs. 1%), discolored feces (3.5% vs. 0) and abdominal pain (3% vs. 1%).

Common adverse events
Among patients treated with ferric citrate in the 52-week, active control period, the most frequently reported adverse reactions were diarrhea (25.6%) discolored feces (17%), nausea (14.2%), cough (9.7%), vomiting (9.0%) and constipation (8%). Events that were reported in at least 5% of subjects on ferric citrate and more frequently (> 2%) than in patients on active control included diarrhea, feces discolored and constipation (see table below). As noted in Dr. Xu's review, in the majority of subjects with treatment emergent diarrhea, the adverse event resolved without dose reduction or discontinuation of therapy.

Table 2. Adverse events reported in at least 5% of patients on ferric citrate and more frequently (>2%) than in patients on active control in KRX-0502-304

	Ferric Citrate n (%)	Active Control n (%)
	N=298	N=149
Diarrhea	74 (26%)	21 (14%)
Feces discolored	49 (17%)	0
Constipation	23 (8%)	8 (5%)

Of note, although treatment emergent gastrointestinal adverse events were reported in a greater proportion of subjects in the ferric citrate than active control arm (57% and 47%, respectively), serious treatment emergent gastrointestinal adverse events were not (6.9% of subjects on ferric citrate vs. 12.1% of subjects on active control).

Iron absorption and overload
Because iron is absorbed from ferric citrate, iron deposition in tissues and iron overload is a potential safety concern. The protocol for KRX-0502-304 included several measures to mitigate risk to study subjects.

- Although hemochromatosis was not explicitly stated as an exclusion criteria, trial entry criteria included a serum ferritin <1000 micrograms/L and TSAT <50% at the Screening Visit.
- During the trial, iron parameters were monitored at regular intervals (initially ~ every 12 weeks; the protocol was later amended to increase the frequency to ~ every four weeks).[4]
- The protocol included rules for stopping concomitant IV iron therapy. Absent approval by the Clinical Coordinating Center, IV iron therapy was not permitted if the serum ferritin was >1000 mcg/L or the TSAT was > 30% based on central laboratory values. Oral iron and vitamin C supplements were not permitted.[5]

With these measures, 55 (19%) of patients treated with ferric citrate had a ferritin level > 1500 ng/mL as compared with 13 (9%) of patients treated with active control (see page 64 of 84 of

[4] According to the protocol, the change was made in response to a request from the EMA and not because of a safety signal.
[5] Subjects could take daily water soluble vitamins that include a "small amount of Vitamin C (e.g., Centrum, Nephrocaps, Renaphro)," but were to be instructed to take them two hours or more prior to or following food ingestion or at bedtime.

Dr. Xu's review). There was one case of iron overload as confirmed by liver biopsy in a patient administered IV iron and ferric citrate; otherwise analyses of adverse event data did not indicate a higher incidence of adverse events suggestive of iron overload in the ferric citrate arm. There was no obvious signal indicating an increased risk of systemic infections with ferric citrate, a theoretical risk given the drug's effect on iron parameters.

Reviewer's comment: The data indicate that marked elevations in ferritin level were more common in the ferric citrate arm, which suggests that the applicant has yet to identify a strategy for using these agents with or without concomitant IV iron that avoids excessive iron administration. According to clinical practice guidelines, available methods for estimating iron stores, such as TSAT and serum ferritin, are poor measures of actual iron stores, and, the relationship between these measures and iron deposition in patients with end-stage renal disease is not well understood. Nonetheless, the ability to monitor iron parameters and adjust therapy as needed should mitigate risk to patients.

Aluminum absorption and aluminum toxicity

Because oral citrate solubilizes aluminum that is present in the diet, there is a theoretical concern that ferric citrate could increase aluminum absorption in patients, possibly leading to aluminum overload and toxicity. In trial 304, serum aluminum levels were measured at baseline and at week 52. As shown in the table below, among subjects with a baseline and follow-up measurement at week 52, the median change from baseline at week 52 was zero in both treatment arms; the mean change was zero in the active control arm and 0.2 mcg/L in the ferric citrate arm.

Table 3. Mean baseline aluminum levels (mcg/L) and mean change from baseline to week 52 in KRX-0502-304

	Ferric Citrate N=110	Active Control N=77
Mean baseline value (SD)	8.4 (3.4)	7.4 (2.3)
Mean change from baseline (SD)	0.2 (4.5)	0 (2.9)
Median (range)	0 (-17, 14)	0 (-6, 9)

Source: Reviewer's analysis[6]

As shown in the figures below, in both treatment arms, the proportion of subjects with an increase in aluminum levels was similar to the proportion with a decrease in levels. No clear treatment effect on aluminum levels is discerned.

[6] The analysis uses subjects in the safety population with post-treatment value ≥ 90 days from baseline value; CSR, Table 14.3.2.1. gives the same values for an analysis based on the "safety population" but reports somewhat different n's (n=111 ferric citrate and N=74 active control)

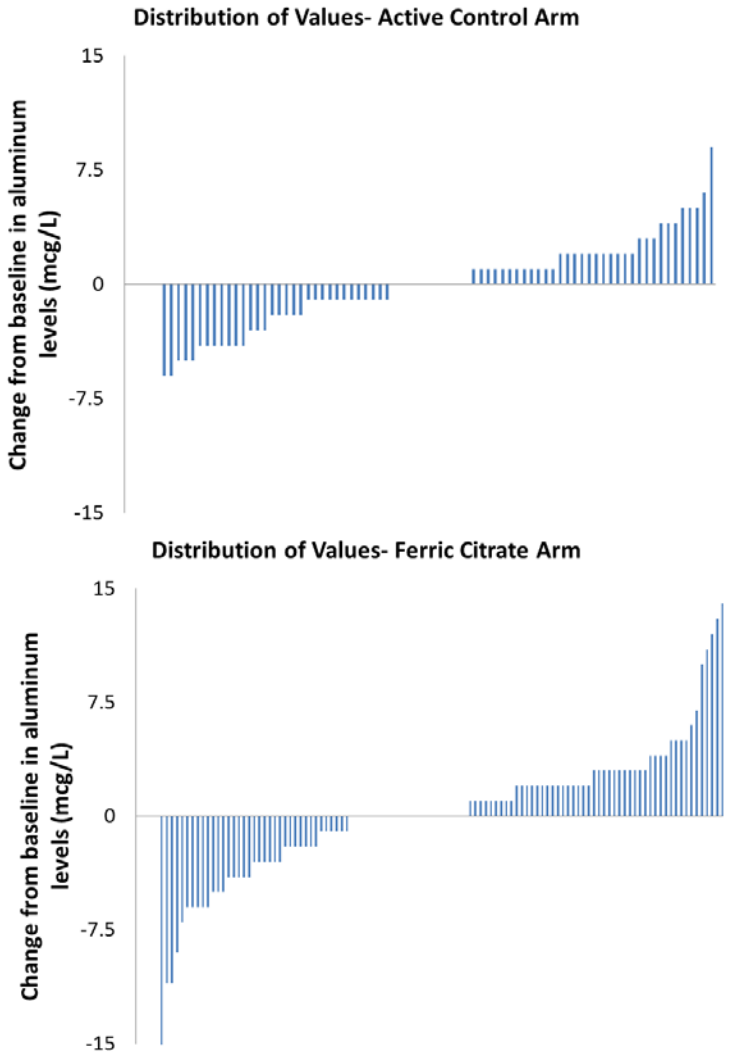


Figure 2. Change from baseline in aluminum levels- distribution of values in KRX-0502-304
Source: Reviewer's analysis

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. Ferric citrate is not an NME and the application does not raise significant issues regarding safety or effectiveness.

10. Pediatrics

The applicant requested a deferral of pediatric studies in patients 6 months to less than 18 years of age and a waiver in patients less than 6 months of age. According to the applicant, greater gastrointestinal toxicity was observed in dogs when KRX-0502 was administered by gavage (including vomiting, watery or unformed stool, red exudate in the stool, black-colored stool, and ulceration/hemorrhage in the colon), and less toxicity was observed when KRX-

0502 was administered with solid food. Since patients under 6 months of age are unlikely to be eating solid food, they may be at greater risk of gastrointestinal toxicity.

The Division and PeRC agreed to grant a deferral for pediatric patients 6 months to less than 18 years of age because the product is ready for approval for use in adults. The Division and PeRC also agreed to grant a waiver in patients less than 6 months of age because the product is likely to be unsafe.[7] The age for waiving pediatric studies may need to be modified based on the findings in animal studies and/or data obtained in older children.

11. Other Relevant Regulatory Issues

- The applicant has requested (b) (4); the Agency's determination is pending. As noted in the CMC review, although the applicant claims that the drug exists as a (b) (4) hat is thought to be critical for the drug's mechanism of action.
- According to Dr. Olumba (email correspondence dated July 18, 2014), the Division of Medication Error Prevention and Analysis (DMEPA) has concluded that the proposed proprietary name, Zerenex, is not acceptable. Based on orthographic and phonetic similarities, shared product characteristics, as well as post marketing experience with other drug products, DMEPA is concerned that that there may be proprietary name confusion with (b) (4) resulting in medication errors.
- Three domestic clinical investigator sites were inspected. No regulatory violations were found at two sites; one site (Schulman) was classified as VAI based on the large number of violations identified for subject records reviewed for Study KRX-0502-304. Although these violations were found, OSI does not consider them significant. OSI's Clinical Inspection Summary indicates that the data from the Schulman site, as well as the data from the other sites, may be considered reliable.

12. Labeling

- Claims related to the product's ability to (b) (4) should be removed from the label.
- Use in patients with hemochromatosis or evidence of iron overload should be contraindicated. The label should also include a *Warning and Precaution* on the risk of iron overload, the importance of assessing iron parameters, and the potential need to adjust the dose of parenteral iron in patients being administered such therapy.

[7] In June 2013, the EMA's Paediatric Committee also recommended a waiver in pediatric patients less than 6 months of age because of safety concerns.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

1. Approval for the proposed indication for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis

(b) (4)

Risk Benefit Assessment

1. *Proposed Indication: control of serum phosphorus levels in patients with chronic kidney disease on dialysis*

The submitted data provide substantial evidence of ferric citrate's effectiveness in lowering serum phosphorus levels. Principal support for efficacy comes from studies KRX-0502-305 and KRX-0502-304. In the randomized withdrawal period of KRX-0502-304, the mean change from baseline in serum phosphorus (week 56 minus week 52) was -0.2 mg/dL in the ferric citrate arm compared with 1.8 mg/dL in the placebo arm, corresponding to a treatment difference of -2.2 mg/dL (95% CI -2.6 to -1.8, p-value <0.0001). During the 52-week open-label safety assessment period, the change in serum phosphorus levels was similar in the ferric citrate and active control arms. In trial KRX-0502-305, the mean reduction in serum phosphorus at week 4 was 0.1 mg/dL in the 1 g arm, 1.9 mg/dL in the 6 g arm and 2.1 mg/dL in the 8 g arm. The change from baseline was statistically significantly different in the 8 g vs. 1 g and 6 g vs 1 g pairwise comparison but not the 8 g vs. 6 g comparison. Of note, the effect size reported in these trials is similar to what has been observed in trials of approved phosphate binders.

There were no safety findings that would preclude approval.

- GI tolerability appears to be an issue. GI adverse events were the most common reason for discontinuing ferric citrate and led to more discontinuations in the ferric citrate arm as compared to the active control arm (13.8% and 4.0%, respectively) during the 52-week safety assessment period of study KRX-0502-304. Common GI adverse events in subjects treated with ferric citrate included diarrhea (25.6%), discolored feces (17%), nausea (14.2%), vomiting (9.0%), and constipation (8%).
- Because iron is absorbed from ferric citrate, iron absorption leading to iron deposition in tissues and iron overload is a potential risk. In study KRX-0502-304, marked elevations in iron parameters (i.e., serum ferritin levels > 1500 ng/mL) were more common in the ferric citrate arm than in the active control arm. Other analyses to determine whether adverse events indicative of iron overload were more common in the ferric citrate arm did not suggest a higher incidence of such adverse events in subjects treated with ferric citrate; however, the ability to detect such complications may have been limited because of the trial's size and duration. There was no obvious

signal indicating an increased risk of systemic infections with ferric citrate, a possible risk given the drug's effects on iron levels.

- High pill burden is reported to be problem in dialysis patients. In this regard, ferric citrate does not appear to offer an advantage over other phosphate binders; in the pivotal trial conducted in the United States, the mean and median dose was approximately 9 tablets per day.

(b) (4)

According to Dr. Dmytrijuk's consult, the submitted data are not adequate to support a claim related to (b) (4)

(b) (4)

Recommendation for Postmarketing Risk Evaluation and Management Strategies
None.

Recommendation for other Postmarketing Requirements and Commitments
Pediatric studies under PREA in pediatric patients age 6 months to < 18 years.

Recommended Comments to Applicant
According to Drs. Cooper and Wong, the following comment should be included in the approval letter:
Note that the dissolution results of two out of three registration batches significantly failed the dissolution acceptance criteria at the 24-month stability time point. In the future, if a request for a shelf-life extension for the tablets beyond 18 months is received, the request should be submitted as a supplement, not an annual report.

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD–MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD–MBD). Kidney International 2009; 76 (Suppl 113): S1–S130.

2. Chiu YW, Teitelbaum I, Misra M, de Leon EM, Adzize T, Mehrotra R. Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients. Clin J Am Soc Nephrol. 2009 Jun; 4(6): 1089-96.

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/s/

ALIZA M THOMPSON
08/08/2014