

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205874Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Ferric Citrate tablet containing 210 mg of ferric iron equivalent to 1 g ferric citrate for oral use
Initial U.S. Approval: 2014

-----INDICATIONS AND USAGE-----
Ferric Citrate is a phosphate binder indicated for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis (1)

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

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

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

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

-----CONTRAINDICATIONS-----

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

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

- Iron overload: Monitor ferritin and TSAT. Patients may require a reduction in dose or discontinuation of IV iron. (5.1)

- Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6 years of age. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately. (5.2)

- Patients with gastrointestinal bleeding or inflammation: Safety has not been established. (5.3)

-----ADVERSE REACTIONS-----

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

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

-----DRUG INTERACTIONS-----

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

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

1	INDICATIONS AND USAGE	10	OVERDOSAGE
2	DOSAGE AND ADMINISTRATION	11	DESCRIPTION
2.1	Dosing and Dose Adjustment	12	CLINICAL PHARMACOLOGY
3	DOSAGE FORMS AND STRENGTHS	12.1	Mechanism of Action
4	CONTRAINDICATIONS	12.2	Pharmacodynamics
5	WARNINGS AND PRECAUTIONS	12.3	Pharmacokinetics
5.1	Iron Overload	13	NONCLINICAL TOXICOLOGY
5.2	Accidental Overdose of Iron	13.1	Carcinogenesis, Mutagenesis, and Impairment of Fertility
5.3	Patients with Gastrointestinal Bleeding or Inflammation	14	CLINICAL STUDIES
6	ADVERSE REACTIONS	14.1	Long-term, Randomized, Controlled, Safety and Efficacy Trial
6.1	Clinical Trials Experience	14.2	Fixed-Dose Trial
7	DRUG INTERACTIONS	16	HOW SUPPLIED/STORAGE AND HANDLING
8	USE IN SPECIFIC POPULATIONS	16.1	How Supplied
8.1	Pregnancy	16.2	Storage and Handling
8.2	Labor and Delivery	17	PATIENT COUNSELING INFORMATION
8.3	Nursing Mothers	17.1	Dosing Recommendations
8.4	Pediatric Use	17.2	Adverse Reactions
8.5	Geriatric Use		

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Ferric Citrate is a phosphate binder indicated for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing and Dose Adjustment

The recommended starting dose is 2 tablets orally 3 times per day with meals. Serum phosphorus levels should be monitored and the dose of Ferric Citrate titrated in decrements or increments of 1 to 2 tablets per day as needed to maintain serum phosphorus at target levels, up to a maximum dose of 12 tablets daily. Dose can be titrated at 1-week or longer intervals.

In a clinical trial conducted in the United States, patients required an average of 8 to 9 tablets a day to control serum phosphorus levels.

3 DOSAGE FORMS AND STRENGTHS

Tablet: Ferric Citrate 210 mg ferric iron, equivalent to 1 g ferric citrate, film-coated, peach-colored, and oval-shaped tablet embossed with “KX52”.

4 CONTRAINDICATIONS

Ferric Citrate is contraindicated in patients with iron overload syndromes (e.g., hemochromatosis) [*see Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Iron Overload

Iron absorption from Ferric Citrate may lead to excessive elevations in iron stores. Increases in serum ferritin and transferrin saturation (TSAT) levels were observed in clinical trials. In a 56-week safety and efficacy trial in which concomitant use of Ferric Citrate and IV iron was permitted, 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.

Assess iron parameters (e.g., serum ferritin and TSAT) prior to initiating Ferric Citrate and monitor iron parameters while on therapy [*see Contraindications (4), Overdosage (10) and Clinical Pharmacology (12.2)*]. Patients receiving IV iron may require a reduction in dose or discontinuation of IV iron therapy.

5.2 Accidental Overdose of Iron

Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6 years of age. Keep this product out of the reach of children. In case of accidental overdose, call a doctor or poison control center immediately.

5.3 Patients with Gastrointestinal Bleeding or Inflammation

Patients with inflammatory bowel disease or active, symptomatic gastrointestinal bleeding were excluded from clinical trials. Safety has not been established in these populations.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to adverse reaction rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse *reactions* to a drug are most readily ascertained by comparison with placebo, but there is little placebo-controlled experience with Ferric Citrate, so this section describes adverse *events* with Ferric Citrate, some of which may be disease-related, rather than treatment-related.

A total of 289 patients were treated with Ferric Citrate and 149 patients were treated with active control (sevelamer carbonate and/or calcium acetate) during the 52-week, randomized, open-label, active control phase of a trial in patients on dialysis. A total of 322 patients were treated with Ferric Citrate for up to 28 days in three short-term trials. Across these trials, 557 unique patients were treated with Ferric Citrate; dosage regimens in these trials ranged from 210 mg to 2,520 mg of ferric iron per day, equivalent to 1 to 12 tablets of Ferric Citrate. In these trials, adverse events reported for Ferric Citrate were similar to those reported for the active control group.

Adverse events reported in more than 5% of patients treated with Ferric Citrate in these trials included diarrhea (21%), nausea (11%), constipation (8%), vomiting (7%), and cough (6%).

During the 52-week, active-control period, 60 patients (21%) on Ferric Citrate discontinued study drug because of an adverse event, as compared to 21 patients (14%) in the active control arm. Patients who were previously intolerant to any of the active control treatments (calcium acetate and sevelamer carbonate) were not eligible to enroll in the study. Gastrointestinal adverse reactions were the most common reason for discontinuing Ferric Citrate (14%).

Ferric Citrate is associated with discolored feces (dark stools) related to the iron content, but this staining is not clinically relevant and does not affect laboratory tests for occult bleeding, which detect heme rather than non-heme iron in the stool.

7 DRUG INTERACTIONS

Table 1: Oral drugs that can be administered concomitantly with Ferric Citrate	
Amlodipine Aspirin Atorvastatin Calcitriol Clopidogrel Digoxin Doxercalciferol Enalapril Fluvastatin Levofloxacin Metoprolol Pravastatin Propranolol Sitagliptin Warfarin	
Oral drugs that have to be separated from Ferric Citrate and meals	
Dosing Recommendations	
Doxycycline	Take at least 1 hour before Ferric Citrate

Oral medications not listed in Table 1

There are no empirical data on avoiding drug interactions between Ferric Citrate and most concomitant oral drugs. For oral medications where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, consider separation of the timing of the administration of the two drugs. The duration of separation depends upon the absorption characteristics of the medication concomitantly administered, such as the time to reach peak systemic levels and whether the drug is an immediate release or an extended release product. Consider monitoring clinical responses or blood levels of concomitant medications that have a narrow therapeutic range.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women. It is not known whether Ferric Citrate can cause fetal harm when administered to a pregnant woman. Animal reproduction studies have not been conducted.

The effect of Ferric Citrate on the absorption of vitamins and other nutrients has not been studied in pregnant women. Requirements for vitamins and other nutrients are increased in pregnancy. An overdose of iron in pregnant women may carry a risk for spontaneous abortion, gestational diabetes and fetal malformation [see *Nonclinical Toxicology (13.1)*].

8.2 Labor and Delivery

The effects of Ferric Citrate on labor and delivery are unknown.

8.3 Nursing Mothers

Data from rat studies have shown the transfer of iron into milk by divalent metal transporter-1 (DMT-1) and ferroportin-1 (FPN-1). Hence, there is a possibility of infant exposure when Ferric Citrate is administered to a nursing woman.

8.4 Pediatric Use

The safety and efficacy of Ferric Citrate have not been established in pediatric patients.

8.5 Geriatric Use

Clinical studies of Ferric Citrate included 106 subjects aged 65 years and older (33 subjects aged 75 years and older). Overall, the clinical study experience has not identified any obvious differences in responses between the elderly and younger patients in the tolerability or efficacy of Ferric Citrate.

10 OVERDOSAGE

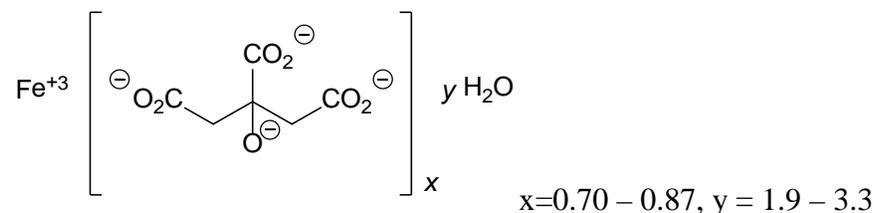
No data are available regarding overdose of Ferric Citrate in patients. In patients with chronic kidney disease on dialysis, the maximum dose studied was 2,520 mg ferric iron (12 tablets of Ferric Citrate) per day. Iron absorption from Ferric Citrate may lead to excessive elevations in iron stores, especially when concomitant IV iron is used [see *Warnings and Precautions (5.1)*].

In clinical trials, one case of elevated iron in the liver as confirmed by biopsy was reported in a patient administered IV iron and Ferric Citrate.

Because accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6 years of age, this product must be kept out of the reach of children. In case of accidental overdose, a doctor or poison control center should be contacted immediately [see *Warnings and Precautions (5.2)*].

11 DESCRIPTION

Ferric Citrate is known chemically as iron (+3), x (1, 2, 3-propanetricarboxylic acid, 2-hydroxy-), y (H_2O)



Ferric Citrate 210 mg ferric iron tablets, equivalent to 1g ferric citrate, are film-coated, peach-colored, and oval-shaped tablets embossed with “KX52”. The inactive ingredients are pregelatinized starch and calcium stearate. In addition, the film-coating contains the following inactive ingredients; hypromellose, titanium dioxide, triacetin, and 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ferric iron binds dietary phosphate in the GI tract and precipitates as ferric phosphate. This compound is insoluble and is excreted in the stool. By binding phosphate in the GI tract and decreasing absorption, ferric citrate lowers the phosphate concentration in the serum.

12.2 Pharmacodynamics

In addition to effects on serum phosphorus levels, Ferric Citrate has been shown to increase serum iron parameters, including ferritin, iron and TSAT. In dialysis patients treated with Ferric Citrate in a 52-week study in which IV iron could also be administered, mean (SD) ferritin levels rose from 593 (293) ng/mL to 895 (482) ng/mL, mean (SD) TSAT levels rose from 31% (11) to 39% (17) and mean (SD) iron levels rose from 73 (29) mcg/dL to 88 (42) mcg/dL. In contrast, in patients treated with active control, these parameters remained relatively constant [see *Contraindications* (4) and *Warnings and Precautions* (5.1)].

12.3 Pharmacokinetics

Absorption and Distribution

Formal pharmacokinetic studies have not been performed with Ferric Citrate. Examination of serum iron parameters has shown that there is systemic absorption of iron from Ferric Citrate [see *Contraindications* (4), *Warnings and Precautions* (5.1) and *Clinical Pharmacology* (12.2)].

Drug Interaction Studies

In vitro

Of the drugs screened for an interaction with ferric citrate in vitro, only doxycycline showed the potential for interaction with at least 70% decrease in its concentration. This interaction can be avoided by spacing the administration of doxycycline and ferric citrate [*see Drug Interactions (7)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Data from carcinogenesis studies have shown that ferric citrate is not carcinogenic in mice and rats when administered intramuscularly or subcutaneously. Ferric citrate was neither mutagenic in the bacterial reverse mutation assay (Ames test) nor clastogenic in the chromosomal aberration test in Chinese hamster fibroblasts.

14 CLINICAL STUDIES

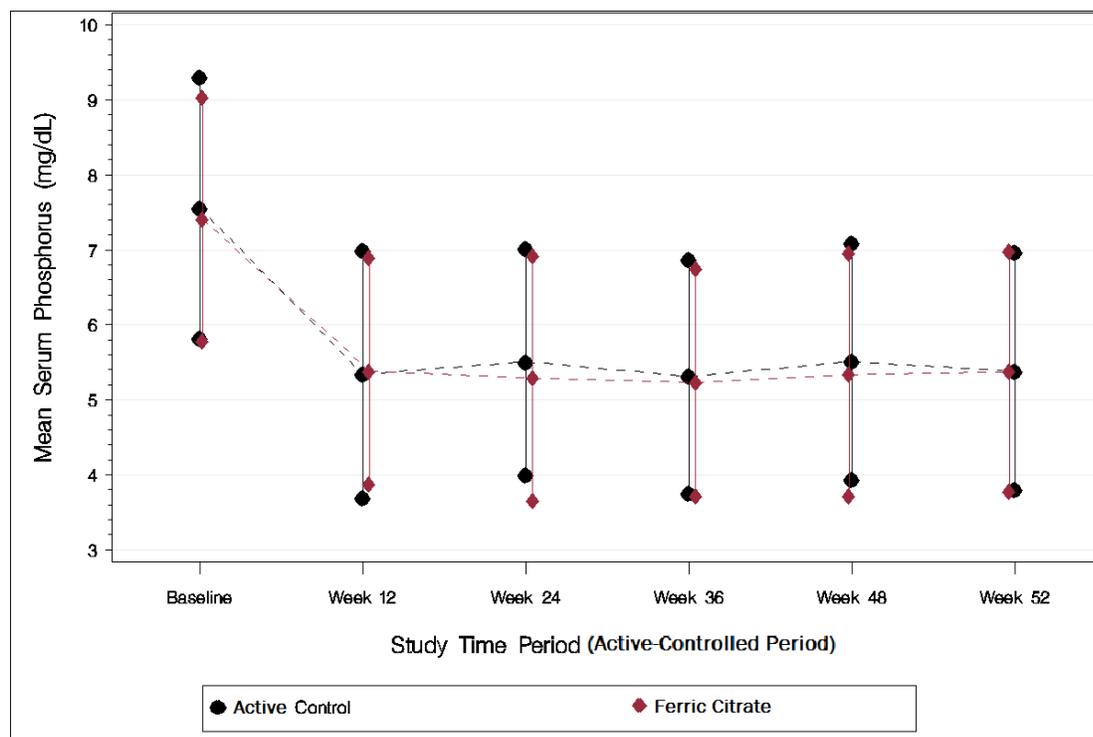
The ability of Ferric Citrate to lower serum phosphorus in patients with CKD on dialysis was demonstrated in randomized clinical trials: one 56-week, safety and efficacy trial, consisting of a 52-week active-controlled phase and a 4-week, placebo-controlled, randomized withdrawal period, and one 4-week open-label trial of different fixed doses of Ferric Citrate. Both trials excluded subjects who had an absolute requirement for aluminum containing drugs with meals.

14.1 Long-term, Randomized, Controlled, Safety and Efficacy Trial

After the 2-week washout period during which phosphate binders were held, patients with a mean serum phosphorus of 7.5 mg/dL during washout were randomized 2:1 to Ferric Citrate (N=292) or active control (calcium acetate and/or sevelamer carbonate; N=149). The majority (>96%) of subjects were on hemodialysis. The starting dose of Ferric Citrate was 6 tablets/day, divided with meals. The starting dose of active control was the patient's dose prior to the washout period. The dose of phosphate binder was increased or decreased as needed to maintain serum phosphorus levels between 3.5 and 5.5 mg/dL, to a maximum of 12 tablets/day.

As shown in the figure below, serum phosphorus levels declined following initiation of therapy. The phosphorus lowering effect was maintained over 52 weeks of treatment.

Figure 1: Serum Phosphorus Control over 52 Weeks



Following completion of the 52-week active-controlled phase, Ferric Citrate-treated patients were eligible to enter a 4-week placebo-controlled randomized withdrawal phase, in which patients were re-randomized in a 1:1 ratio to receive Ferric Citrate (N=96) or placebo (N=96). During the placebo-controlled period, the serum phosphorus concentration rose by 2.2 mg/dL on placebo relative to patients who remained on Ferric Citrate.

Table 2: Effect of Ferric Citrate on serum phosphorus during randomized withdrawal

Primary Endpoint (Week 56)	Ferric Citrate	Placebo	Treatment Difference (95% CI)	p-value
Serum phosphorus (mg/dL)				
Mean baseline (Week 52)	5.12	5.44		
Mean change from baseline (Week 56)	-0.24	1.79	-2.18 (-2.59, -1.77)	<0.0001 ^a

^a The LS mean treatment difference and p-value for the change in mean were created via an ANCOVA model with treatment as the fixed effect and Week-52 baseline (phosphorus) as the covariate. Between-treatment differences were calculated as the LS mean (KRX-0502) – LS mean (placebo or active control).

Note: Analyses using ANCOVA with last observation carried forward. ANCOVA=analysis of covariance; CI=confidence interval.

14.2 Fixed-Dose Trial

Following a 1- to 2-week washout from all phosphate-binding agents, 154 patients with hyperphosphatemia (mean serum phosphorus of 7.5 mg/dL) and CKD on dialysis were randomized in a 1:1:1 ratio to 1, 6, or 8 tablets/day of Ferric Citrate for 4 weeks. Ferric Citrate was administered with meals; subjects receiving 1 tablet/day were instructed to take it with their

largest meal of the day, and subjects on 6 or 8 tablets/day took divided doses in any distribution with meals. Dose-dependent decreases in serum phosphorus were observed by Day 7 and remained relatively stable for the duration of treatment. The demonstrated reductions from baseline to Week 4 in mean serum phosphorus were significantly greater with 6 and 8 tablets/day than with 1 tablet/day ($p < 0.0001$). Mean reduction in serum phosphorus at Week 4 was 0.1 mg/dL with 1 tablet/day, 1.9 mg/dL with 6 tablets/day, and 2.1 mg/dL with 8 tablets/day.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Tablets: Ferric Citrate 210 mg ferric iron tablets equivalent to 1 g of ferric citrate are supplied as 200 tablets in 400-cc high-density polyethylene bottles. The 210 mg ferric iron tablets are film-coated, peach-colored, and oval-shaped tablets embossed with “KX52.”

1 Bottle of 200-count 210 mg ferric iron tablets (NDC 59922)

16.2 Storage and Handling

Storage: Store at 20 to 25°C (68 to 77°F); excursions permitted to 15° to 30°C (59°F to 86°F) [See USP controlled room temperature]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

17.1 Dosing Recommendations

Inform patients to take Ferric Citrate as directed with meals and adhere to their prescribed diets. Instruct patients on concomitant medications that should be dosed apart from Ferric Citrate.

17.2 Adverse Reactions

Advise patients that Ferric Citrate may cause discolored (dark) stools, but this staining of the stool is considered normal with oral medications containing iron.

Ferric Citrate may cause diarrhea, nausea, constipation and vomiting. Advise patients to report severe or persistent gastrointestinal symptoms to their physician.

Manufactured for and Distributed by:

Keryx Biopharmaceuticals, Inc.
750 Lexington Avenue, 20th Floor
New York, NY 10022

US Patents Nos 5,753,706; 6,903,235; 7,767,851; 8,093,423; 8,299,298; 8,338,642; 8,609,896; 8,754,257 and pending, comparable and/or related patents.

Issued 09/2014

Top Panel

See package insert for dosage information.
200 TABLETS

Ferric Citrate
tablets
210 mg*

Side Panel A

Front Panel

Side Panel B

Ferric Citrate
tablets

*Each Ferric Citrate tablet contains 210 mg of ferric iron equivalent to 1 g of ferric citrate.

Contains FD&C Yellow No. 6.
See package insert for dosing and full prescribing information.

Store between 20 to 25°C (68 to 77°F), excursions permitted to 15 to 30°C (59 to 86°F) [See USP controlled room temperature].
Protect from moisture.

Manufactured for and distributed by:
KERYX BIOPHARMACEUTICALS, INC.
750 Lexington Avenue, 20th Floor
New York, NY 10022 USA

NDC 59922-631-01 **RX ONLY**

Ferric Citrate
tablets

210 mg*

See package insert for dosage information. 200 TABLETS

WARNING: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately.

Barcode



Back Panel

LOT
EXP

Bottom Panel

*Each Ferric Citrate tablet contains 210 mg of ferric iron equivalent to 1 g of ferric citrate.

Contains FD&C Yellow No. 6. See package insert for dosing and full prescribing information.

Store between 20 to 25°C (68 to 77°F), excursions permitted to 15 to 30°C (59 to 86°F) [See USP controlled room temperature].
Protect from moisture.

Manufactured for and distributed by:
KERYX BIOPHARMACEUTICALS, INC.
750 Lexington Avenue, 20th Floor
New York, NY 10022 USA

NDC 59922-631-01 **RX ONLY**

Ferric Citrate
tablets

210 mg*

See package insert for dosage information. 200 TABLETS

WARNING: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately.



Barcode

LOT

EXP

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
09/05/2014