

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

AURYXIA (ferric citrate) tablets, for oral use

Initial U.S. Approval: 2014

RECENT MAJOR CHANGES

Indications and Usage, Iron Deficiency Anemia in Chronic Kidney Disease (1) **11/2017**
Dosage and Administration, Dosage for Iron Deficiency Anemia in Chronic Kidney Disease (2.2) **11/2017**

INDICATIONS AND USAGE

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

Auryxia is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease not on dialysis (1)

DOSAGE AND ADMINISTRATION

- Hyperphosphatemia in Chronic Kidney Disease on Dialysis:
 - Starting dose is 2 tablets orally 3 times per day with meals (2.1)
 - 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. (2.1)
- Iron Deficiency Anemia in Chronic Kidney Disease Not on Dialysis:
 - Starting dose is 1 tablet orally 3 times per day with meals (2.2)
 - Adjust dose as needed to achieve and maintain hemoglobin goal, up to a maximum of 12 tablets daily (2.2)

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 intravenous 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)

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 5\%$) are discolored feces, diarrhea, constipation, nausea, vomiting, cough, abdominal pain, and hyperkalemia (6.1)

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

DRUG INTERACTIONS

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2017

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Hyperphosphatemia in Chronic Kidney Disease on Dialysis

Auryxia is indicated for the control of serum phosphorus levels in adult patients with chronic kidney disease on dialysis.

1.2 Iron Deficiency Anemia in Chronic Kidney Disease Not on Dialysis

Auryxia is indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease not on dialysis.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Hyperphosphatemia in Chronic Kidney Disease on Dialysis

The recommended starting dose is 2 tablets orally 3 times per day with meals. Monitor serum phosphorus levels and titrate the Auryxia dose 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, patients required an average of 8 to 9 tablets a day to control serum phosphorus levels.

2.2 Dosage for Iron Deficiency Anemia in Chronic Kidney Disease Not on Dialysis

The recommended starting dose is 1 tablet orally 3 times per day with meals. Titrate the dose of Auryxia as needed to achieve and maintain hemoglobin at target levels, up to a maximum dose of 12 tablets daily.

In a clinical trial in patients with chronic kidney disease not on dialysis (CKD-NDD), patients required an average of 5 tablets per day to increase hemoglobin levels.

3 DOSAGE FORMS AND STRENGTHS

Tablets: Auryxia 210 mg ferric iron, equivalent to 1 g ferric citrate, film-coated, peach-colored, and oval-shaped tablet debossed with “KX52”.

4 CONTRAINDICATIONS

Auryxia 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 Auryxia 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

evaluating the control of serum phosphate levels in patients with chronic kidney disease on dialysis in which concomitant use of intravenous iron was permitted, 55 (19%) of patients treated with Auryxia 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 Auryxia and monitor iron parameters while on therapy [see *Contraindications (4)*, *Overdosage (10)* and *Clinical Pharmacology (12.2)*]. Patients receiving intravenous iron may require a reduction in dose or discontinuation of intravenous iron therapy.

5.2 Risk of Overdosage in Children Due to Accidental Ingestion

Accidental ingestion and resulting overdose of iron-containing products is a leading cause of fatal poisoning in children under 6 years of age [see *Overdosage (10)*]. Advise patients of the risks to children and to keep Auryxia out of the reach of children.

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.

Hyperphosphatemia in Chronic Kidney Disease on Dialysis

A total of 289 patients were treated with Auryxia 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 Auryxia for up to 28 days in three short-term trials. Across these trials, 557 unique patients were treated with Auryxia; 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 Auryxia.

Adverse reactions reported in more than 5% of patients treated with Auryxia in these trials included diarrhea (21%), discolored feces (19%), nausea (11%), constipation (8%), vomiting (7%), and cough (6%).

During the 52-week, active-control period, 61 patients (21%) on Auryxia discontinued study drug because of an adverse reaction, 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 Auryxia (14%).

Iron Deficiency Anemia in Chronic Kidney Disease Not on Dialysis

Across two trials, 190 patients with CKD-NDD were treated with Auryxia. This included a study of 117 patients treated with Auryxia and 116 patients treated with placebo in a 16-week, randomized, double-blind period and a study of 75 patients treated with Auryxia and 73 treated with placebo in a 12-week randomized double-blind period. 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 Auryxia.

Adverse reactions reported in at least 5% of patients treated with Auryxia in these trials are listed in [Table 1](#).

Table 1: Adverse Reactions Reported in Two Clinical Trials in at least 5% of patients receiving Auryxia

Body System Adverse Reaction	Auryxia % (N=190)	Placebo % (N=188)
Any Adverse Reaction	75	62
Metabolism and Nutrition Disorders		
Hyperkalemia	5	3
Gastrointestinal Disorders		
Discolored Feces	22	0
Diarrhea	21	12
Constipation	18	10
Nausea	10	4
Abdominal Pain	5	2

During the 16-week, placebo-control trial, 12 patients (10%) on Auryxia discontinued study drug because of an adverse reaction, as compared to 10 patients (9%) in the placebo control arm. Diarrhea was the most common adverse reaction leading to discontinuation of Auryxia (2.6%).

7 DRUG INTERACTIONS

Table 2: Oral drugs that can be administered concomitantly with Auryxia	
Amlodipine	Metoprolol
Aspirin	Pravastatin
Atorvastatin	Propranolol
Calcitriol	Sitagliptin
Clopidogrel	Warfarin
Digoxin	
Diltiazem	
Doxercalciferol	
Enalapril	
Fluvastatin	
Glimepiride	
Levofloxacin	
Losartan	
Oral drugs that have to be separated from Auryxia and meals	
Dosing Recommendations	
Doxycycline	Take at least 1 hour before Auryxia
Ciprofloxacin	Take at least 2 hours before or after Auryxia

Oral medications not listed in Table 2

There are no empirical data on avoiding drug interactions between Auryxia 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

Risk Summary

There are no available data on Auryxia use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Animal reproduction studies have not been conducted using Auryxia. Skeletal and encephalic malformation was observed in neonatal mice when ferric gluconate was administered intraperitoneally to gravid dams on gestation days 7-9. However, oral administration of other ferric or ferrous compounds to gravid CD1-mice and Wistar-rats caused no fetal malformation.

An overdose of iron in pregnant women may carry a risk for spontaneous abortion, gestational diabetes and fetal malformation.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

The effect of Auryxia 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.

8.2 Lactation

Risk Summary

There are no human data regarding the effect of Auryxia in human milk, the effects on the breastfed child, or the effects on milk production. 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 Auryxia is administered to a nursing woman. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for Auryxia and any potential adverse effects on the breastfed child from Auryxia or from the underlying maternal condition.

8.4 Pediatric Use

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

8.5 Geriatric Use

Clinical studies of Auryxia included 292 subjects aged 65 years and older (104 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 Auryxia.

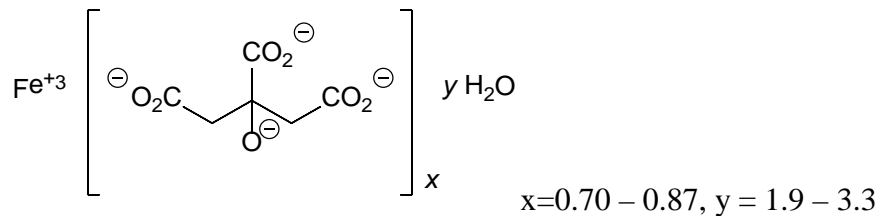
10 OVERDOSAGE

No data are available regarding overdose of Auryxia in patients. In patients with chronic kidney disease, the maximum dose studied was 2,520 mg ferric iron (12 tablets of Auryxia) per day. Iron absorption from Auryxia may lead to excessive elevations in iron stores, especially when concomitant intravenous 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 on dialysis administered intravenous iron and Auryxia.

11 DESCRIPTION

Auryxia (ferric citrate), a phosphate binder and iron replacement product, is known chemically as iron (+3), x (1, 2, 3-propanetricarboxylic acid, 2-hydroxy-), y (H₂O)



Auryxia 210 mg ferric iron tablets for oral administration, equivalent to 1g ferric citrate, are film-coated, peach-colored, and oval-shaped tablets debossed 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

Hyperphosphatemia in Chronic Kidney Disease on Dialysis

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.

Iron Deficiency Anemia in Chronic Kidney Disease Not On Dialysis

Ferric iron is reduced from the ferric to the ferrous form by ferric reductase in the GI tract. After transport through the enterocytes into the blood, oxidized ferric iron circulates bound to the plasma protein transferrin, and can be incorporated into hemoglobin.

12.2 Pharmacodynamics

Hyperphosphatemia in Chronic Kidney Disease on Dialysis

Auryxia reduces serum phosphorus levels and has also been shown to increase serum iron parameters, including ferritin, iron and TSAT. In dialysis patients treated with Auryxia for hyperphosphatemia in a 52-week study in which intravenous 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)*].

Iron Deficiency Anemia in Chronic Kidney Disease Not On Dialysis

Auryxia may increase hemoglobin levels and has also been shown to reduce serum phosphorus levels. In chronic kidney disease patients not on dialysis treated with Auryxia for iron deficiency anemia in a 16-week placebo-controlled study, mean (SD) phosphorus levels decreased from 4.23 (0.91) mg/dL at baseline to 3.72 (0.60) mg/dL. In comparison, in patients treated with placebo control, mean (SD) phosphorus levels decreased from 4.12 (0.68) mg/dL at baseline to 3.87 (0.68) mg/dL.

12.3 Pharmacokinetics

Absorption and Distribution

Formal pharmacokinetic studies have not been performed with Auryxia. Examination of serum iron parameters has shown that there is systemic absorption of iron from Auryxia [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)*].

In vivo

Six drug interaction studies (N=26-60/study) were conducted to establish the effects of Auryxia (administered as 3 x 2 g/day with meals) on the disposition of concomitantly orally administered clopidogrel, ciprofloxacin, digoxin, diltiazem, glimepiride and losartan in healthy subjects. With the exception of ciprofloxacin, Auryxia did not alter the systemic exposure of the tested drugs, as measured by the area under the curve (AUC) and Cmax of the tested drugs when either co-administered with Auryxia or given 2 hours later. Auryxia decreased the relative bioavailability of concomitantly administered ciprofloxacin by approximately 45%. However, there was no interaction when Auryxia and ciprofloxacin were taken 2 hours apart. Consequently, ciprofloxacin should be taken at least 2 hours before or after Auryxia is dosed [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.

The potential for ferric citrate to impair reproductive performance or to cause fetal malformation has not been evaluated.

14 CLINICAL STUDIES

14.1 Hyperphosphatemia in Chronic Kidney Disease on Dialysis

The ability of Auryxia 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

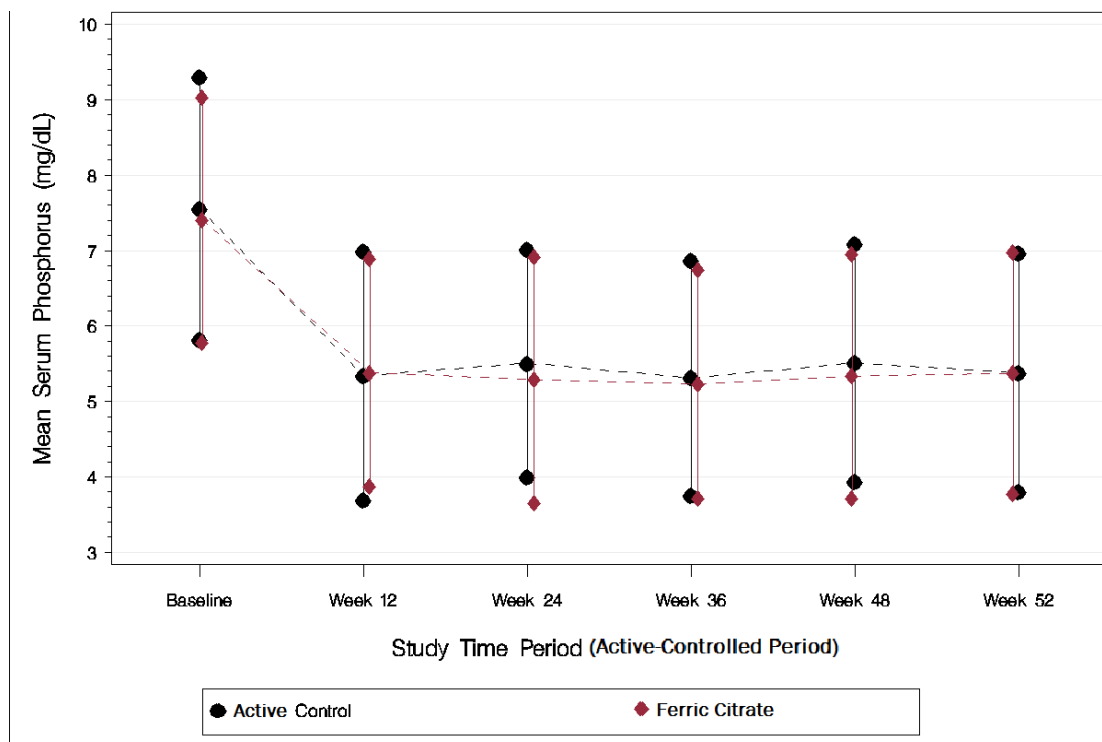
phase and a 4-week, placebo-controlled, randomized withdrawal period, and one 4-week open-label trial of different fixed doses of Auryxia. Both trials excluded subjects who had an absolute requirement for aluminum containing drugs with meals.

Study KRX-0502-304 (NCT 01191255)

Study KRX-0502-304 was a 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 Auryxia (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 Auryxia 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, Auryxia-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 Auryxia (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 Auryxia.

Table 3: Effect of Auryxia on serum phosphorus during randomized withdrawal

Primary Endpoint (Week 56)	Auryxia	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 (Auryxia) – LS mean (placebo or active control).

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

Study KRX-0502-305 (NCT 01074125)

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 Auryxia for 4 weeks. Auryxia 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.

14.2 Iron Deficiency Anemia in Chronic Kidney Disease Not On Dialysis

Study KRX-0502-306 (NCT 02268994)

The efficacy of Auryxia for the treatment of iron deficiency anemia in adult patients with CKD not on dialysis was demonstrated in a 24-week study consisting of a 16-week, randomized, double-blind, placebo-controlled, efficacy period followed by an 8-week open-label safety extension period in which all patients remaining in the study, including the placebo group, received Auryxia. Patients with eGFR < 60 mL/min/1.73m², who were intolerant of or have had an inadequate therapeutic response to oral iron supplements, with Hgb ≥ 9.0 g/dL and ≤ 11.5 g/dL, serum ferritin ≤ 200 ng/mL and TSAT $\leq 25\%$ were enrolled. Patients were randomized to treatment with either Auryxia (n=117) or placebo (n= 117). Dosing with Auryxia or placebo was initiated at 3 tablets/day with meals. Dose titration could occur at Weeks 4, 8 and 12 during Randomized Period, and at Weeks 18 and 20 during Safety Extension Period based on Hgb response. Use of oral or intravenous iron, erythropoiesis stimulating agents (ESAs) was not permitted at any time during the study.

The mean age of the patients was 65 years (range 26 to 93); 63% were female, 69% Caucasian, 30% were African American and $< 2\%$ were other races.

The main efficacy outcome measure was the proportion of subjects achieving an increase in Hgb of ≥ 1.0 g/dL at any time point between baseline and the end of the 16-week Randomized Period.

Table 4: Efficacy of Auryxia in Iron Deficiency Anemia in Chronic Kidney Disease (Not on Dialysis)

	Auryxia (N=117)	Placebo (N=115)	p-value
Proportion of patients achieving an increase in hemoglobin of \geq 1.0 g/dL at any time point during the 16 week randomized period	52%	19%	<0.001

During the 16-week randomized period 49% of subjects in the Auryxia arm and 15% of subjects in the placebo arm ($p < 0.001$) had a mean change in hemoglobin from baseline ≥ 0.75 g/dL over any 4-week time period provided that an increase of at least 1.0 g/dL had occurred during that 4-week period. Increases in mean hemoglobin (0.75 ± 0.09 g/dL), serum ferritin (163 ± 9 ng/mL) and transferrin saturation ($18 \pm 1\%$) were observed from baseline during the 16-week randomized period in the Auryxia arm.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Tablets: Auryxia 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 debossed with “KX52”.

1 Bottle of 200-count 210 mg ferric iron tablets (NDC 59922-631-01)

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

Dosing Recommendations

Instruct patients to take Auryxia as directed with meals and adhere to their prescribed diets. Instruct patients on concomitant medications that should be dosed apart from Auryxia [see *Dosage and Administration (2)*]. Advise patients not to chew or crush Auryxia because tablets may cause discoloration of mouth and teeth.

Adverse Reactions

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

Auryxia may cause diarrhea, nausea, constipation, vomiting, hyperkalemia, abdominal pain, and cough. Advise patients to report severe or persistent gastrointestinal symptoms to their physician [see *Adverse Reactions (6.1)*].

Accidental Ingestion

Advise patients to keep this product out of the reach of children and to seek immediate medical attention in case of accidental ingestion by a child.

Manufactured for and Distributed by:

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