Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Ferric Citrate

August 2024

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Active Ingredient:	Ferric citrate
Dosage Form:	Tablet
Route:	Oral
Strength:	EQ 210 mg iron
Recommended Studies:	Demonstrate active pharmaceutical ingredient (API) sameness, and two options to demonstrate bioequivalence: (1) one in vitro bioequivalence study (comparative dissolution) or (2) two in vitro phosphate binding studies, and one comparative clinical endpoint bioequivalence study

Recommendations for demonstrating API sameness:

Sameness of ferric citrate can be established based on comparative physico-chemical characterizations, including, but not limited to: (i) oxidation state of the iron in API; (ii) the ratio of ferric iron to citrate; (iii) elemental analysis data; and (iv) spectroscopic data such as high-resolution mass spectroscopy, Mössbauer spectroscopy, and x-ray powder diffraction. Perform side-by-side comparative testing using the API from the test and the reference listed drug (RLD). To assess API sameness, a minimum of three batches of the test API and three batches of the extracted RLD API should be characterized. Based on the characterization data, the applicant should define and prove the chemical structure and molecular formula of the test API in comparison with the RLD API.

Recommendations for demonstrating bioequivalence:

I. Option 1: One in vitro bioequivalence study (comparative dissolution)

If the test product formulation is qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the RLD in terms of inactive ingredients, bioequivalence may be established by conducting an in vitro bioequivalence study (comparative dissolution).

Bioequivalence based on: Acceptable in vitro comparative dissolution testing, which should be provided for 12 tablets each of the test and RLD products. The tests should be performed in at least three dissolution media (e.g., 0.1 N HCl, pH 4.5 buffer, and pH 6.8 buffer).

An f2 test, using mean dissolution profiles, should be conducted to assure comparable dissolution between the test and RLD across the physiological pH range. The f2 value comparing the test and RLD in each medium should be 50 or greater. Note that the f2 test is not necessary when both the test and RLD dissolve 85% or more in 15 minutes or less. The methodology used for in vitro comparative dissolution testing should be able to discriminate the effects of formulation and manufacturing process variability on the production of the test drug product.[3]

II. Option 2: Two in vitro bioequivalence studies (phosphate binding) and one comparative clinical endpoint bioequivalence study

1. Type of study: In vitro equilibrium binding study
   Design: At pH 3.0 and pH 7.5
   Strength: EQ 210 mg iron
   Additional comments:
   a. The equilibrium binding study should be conducted on whole tablets. This study should be conducted by incubating the test and RLD with at least eight different concentrations of phosphate at both pH 3.0 and pH 7.5. The maximum phosphate binding region (attainment of plateau) should be demonstrated prior to selecting these eight phosphate concentrations. The concentrations of phosphate should be spaced along the spectrum until the maximum binding is established. All incubations should be conducted at 37°C. Wait at least one hour until equilibrium pH has been reached. The pH should be monitored and adjusted as necessary every 15 minutes. Each binding study should be replicated at least 12 times. In addition, data should be provided to demonstrate that the selected incubation period with the phosphate-containing medium yields maximum phosphate binding.

[1] Q1 (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD.
[2] Q2 (quantitative sameness) means that the concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the RLD.
[3] Note that an in vitro dissolution method used as part of the quality control specifications may and/or can be different than the dissolution method developed to support bioequivalence determination and will be assessed at the time of review of the abbreviated new drug application.

b. Refer to the most recent version of the FDA product-specific guidance for *Lanthanum Carbonate Chewable Tablets* (NDA 021468)[a] for additional details on a similar equilibrium binding study design.

2. Type of study: In vitro kinetic binding study
Design: At pH 3.0 and pH 7.5
Strength: EQ 210 mg iron
Additional comments:

a. The kinetic binding study should complement the equilibrium binding study. For this study, whole tablets should be incubated with the three following phosphate concentrations: the lowest and highest concentrations used in the corresponding equilibrium binding study, and a mid-concentration that is approximately 50% of the highest concentration used. The study is to be conducted at both pH 3.0 and pH 7.5. The binding of ferric citrate to phosphate should be monitored as a function of time. Select at least eight time points up to 24 hours to adequately evaluate binding under each condition. Ensure all incubations are maintained at 37°C with constant gentle shaking. Each binding study should be repeated at least 12 times.

3. Type of study: Comparative clinical endpoint bioequivalence study
Design: Randomized, double blind, parallel, placebo-controlled, in vivo study
Strength: EQ 210 mg iron
Subjects: Male and non-pregnant and non-lactating females with iron deficiency anemia with chronic kidney disease not on dialysis (CKD-NDD)
Additional comments:

a. Conduct a bioequivalence study with clinical endpoints in the treatment of iron deficiency anemia in adult patients with CKD-NDD. Patients should be randomized to receive a test product, RLD or placebo tablet orally three times per day with meals for 4 weeks (28 days), treatment period for the study.

b. Inclusion criteria (applicants may add additional criteria):
- Males and non-pregnant, non-lactating females at least 18 years of age with Stage 3 to 5 CKD-NDD with estimated glomerular filtration rate (eGFR) <60 mL/min
- Hemoglobin (Hb) ≥ 9.0 g/dL and <12 g/dL at screening
- Serum ferritin ≤ 300 ng/mL and transferrin saturation (TSAT) ≤ 30% at screening

c. Exclusion criteria (applicants may add additional criteria):
    - Serum phosphorus concentrations at screening < 3.5 mg/dL
    - Symptomatic gastrointestinal bleeding or inflammatory bowel disease within 12 weeks prior to screening
    - Acute renal insufficiency or requirement for dialysis within 12 weeks prior to randomization
    - Use of intravenous (IV) iron, Erythropoiesis Stimulating Agents (ESA), or blood transfusion within 4 weeks prior to screening visit
        - Use of oral or IV antibiotics within 2 weeks
        - Anemia other than iron deficiency or CKD
        - Known allergic reactions to oral or IV iron treatment or any of the excipients
        - Liver enzymes (aspartate aminotransferase or alanine aminotransferase) >3 times upper limit of normal at screening
        - Active drug or alcohol dependence or abuse within the 12 months prior to screening
        - Previous intolerance to oral ferric citrate
        - History of iron overload syndromes, such as hemochromatosis
        - Malignancy
        - Planned surgery or hospitalization (anticipated to last >72 hours) during the study

d. A screening period (up to 14 days prior to randomization) is recommended to assess study eligibility and baseline measures.

e. Separate concomitant administration of this product and other drugs by at least 2 hours to minimize any potential drug interactions.

f. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as IV or oral iron, ESA, blood transfusion, phosphate binder other than study drug.

g. The primary endpoint of the study is proportion of subjects with an increase in Hgb of ≥1.0 g/dL from baseline at Week 4. To establish bioequivalence, the 90% confidence interval of the test/RLD ratio of the proportion of subjects with an increase in Hgb of ≥1.0 g/dL from baseline to week 4 should be contained within [-0.20, +0.20], using the per protocol (PP) population.

h. Blood tests: at baseline and weekly
    - A complete blood count: Hgb, hematocrit (Hct), red blood cell (RBC), white blood cell (WBC) and platelet counts
    - Complete chemistry profile including liver function tests and serum albumin
    - Iron parameters: ferritin, serum iron, total iron-binding capacity

(TIBC), TSAT, unsaturated iron-binding capacity (UIBC)
- Phosphorus concentrations

i. Discontinuation from the study should be considered for the following conditions:
   - Other illness, medical event or hospitalization necessitating study drug discontinuation
   - Investigator's discretion for the best interest of the patient
   - Serum phosphorus < 2.0 mg/dL
   - Rapid increase in iron storage parameters (i.e., TSAT ≥ 70% or ferritin ≥ 700 ng/mL)
   - Hgb < 9 g/dL for two consecutive visits at least 7 days apart. For those subjects discontinued due to lack of treatment effect should be identified and included for the bioequivalence evaluation.

j. After completing the study, all subjects should continue to receive treatment using the RLD as instructed in the labeling or alternative therapy with clinical evaluation by investigators or their healthcare providers.

k. Refer to the most recent version of the FDA product-specific guidance for *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[a] for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.

l. Study data should be submitted in a standardized format. Refer to the study data standards resources, https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources.

Analyte to measure: Unbound phosphate in filtrate, to calculate phosphate bound to ferric citrate

For the in vitro equilibrium binding study, the Langmuir binding constants k_1 and k_2 should be determined. The test/reference ratio should be calculated for k_1. The 90% confidence interval should be calculated for k_2, with the acceptance criteria of 80% - 120%.

For the in vitro kinetic binding study, the test/reference bound phosphate ratios at the various times should be compared but not subjected to the 90% confidence interval criteria.

Bioequivalence based on (90% CI): The Langmuir binding constant k_2 from the equilibrium binding study, and the clinical endpoint of the in vivo bioequivalence study

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

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[a] For the most recent version of a product-specific guidance, check the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.