Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Patiromer Sorbitex Calcium

May 2026

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In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient:	Patiromer sorbitex calcium
Dosage Form:	Powder
Route:	Oral
Strengths:	EQ 1 gm Base/packet | EQ 8.4 gm Base/packet | EQ 16.8 gm Base/packet | EQ 25.2 gm Base/packet
Reference Listed Drug:	NDA 205739
Recommended Studies:	Comparative characterization studies to support active ingredient sameness, in vitro bioequivalence studies, and supportive compatibility studies

Recommendations to support active ingredient sameness:
Sameness of patiromer sorbitex calcium can be established based on the reaction scheme and comparative physicochemical characterizations. Comparative characterization should be performed on a minimum of three batches of the test active ingredient and active ingredient from three batches of the reference listed drug (RLD) to assess active ingredient sameness and robustness of the manufacturing process. The active ingredient sameness can be demonstrated by evaluating equivalence of the following:

1. Fundamental reaction scheme
The cross-linked patiromer is synthesized through polymerization of methyl 2-fluoroacrylate, divinylbenzene, and 1,7-octadiene, followed by hydrolysis under basic conditions.[1] Generic applicants should follow similar synthetic transformation to manufacture generic patiromer. If an alternative synthetic transformation is proposed, the applicant should contact FDA to obtain concurrence, as the patiromer obtained by such an approach may need additional characterizations besides the ones outlined in this draft guidance to support active ingredient sameness.

2. Chemical composition and physicochemical properties
Generic applicants should use data from manufacturing process and active ingredient characterization results to define the chemical composition of patiromer, including the degree of polymer cross-linking. In addition, the structure and composition of the test active ingredient should be equivalent to the structure and composition of the active ingredient from the RLD. Generic applicants should perform comparative physicochemical characterizations of the test active ingredient and the active ingredient from the RLD, which should include, but are not limited to the following:
    a. ^{13}C solid-state nuclear magnetic resonance (SSNMR) spectroscopy[2]
    b. Patiromer, calcium, sorbitol and fluorine content
    c. Fourier transform infrared spectroscopy (FTIR)
    d. Thermogravimetric analysis (TGA)
    e. Differential scanning calorimetry (DSC)
    f. Swelling index
    g. Particle size with particle size distribution
    h. Morphology
    i. Total potassium binding capacity

3. Class of study: Bioequivalence
Type of study: In vitro equilibrium binding study
Design: With and without acid pre-treatment, at pH 4.5 and 6.8
Strength: EQ 16.8 gm base/packet[3]
Subjects: Not applicable

[1] Li L, Harrison SD, Cope MJ, Park C, Lee L, Salaymeh F, Madsen D, Benton WW, Berman L, Buysse J. Mechanism of action and pharmacology of patiromer, a nonabsorbed cross-linked polymer that lowers serum potassium concentration in patients with hyperkalemia. *J Cardiovasc Pharmacol Ther*. 21, pp 456-465 (2016).
[2] Comparative ^{13}C SSNMR study data should be analyzed to demonstrate that the test active ingredient is equivalent to the reference active ingredient in chemical composition and degree of cross-linking. For a similar ^{13}C SSNMR study on the drug product, see Jarrells TW, Zhang D, Li S, Munson EJ. Quantification of monomer units in insoluble polymeric active pharmaceutical ingredients using solid-state NMR spectroscopy I: Patiromer. *AAPS PharmSciTech* 21, pp 116-129 (2020).
[3] Testing of a strength(s) other than the designated reference standard (RS) strength, or a portion of the strength (i.e., part of a packet), and waiving of other strengths may be acceptable. Justification may include, but is not limited to, why testing of the other strength(s), or portion of, is representative of the designated RS strength.

Study design recommendations:

- The equilibrium binding study is considered the pivotal bioequivalence study.
- This study should be conducted by incubating the test product and reference standard (RS) with at least eight different concentrations of potassium, at pH 4.5, and 6.8 buffer, with and without acid pretreatment.
- The potassium concentrations for each study condition should be appropriately selected to represent the adsorption isotherm including that the maximum binding capacity (i.e., attainment of adsorption plateau) is clearly established.
- All incubations should be conducted at 37°C.
- Each binding study should be repeated at least 12 times. Each replicate should be from a separate patiromer sorbitex calcium sample (packet).
- Data should be provided demonstrating that the selected potassium incubation time ensures adsorption equilibrium conditions are met.
- For general considerations on similar equilibrium binding study design, refer to the product-specific guidances *Lanthanum Carbonate Oral Chewable Tablet* (NDA 021468) and *Sevelamer Hydrochloride Oral Tablet* (NDA 021179).[a] Also see Swearingen, et al., "Determination of the Binding Parameter Constants for Renagel® Using the Langmuir Approximation at Various pH Values by Ion Chromatography," *J. Pharm. Biomedical Anal.* 29 (2002), pp. 195-201.

4. Class of study: Bioequivalence
Type of study: In vitro kinetic binding study
Design: Without acid pretreatment
Strength: EQ 16.8 gm Base/packet[3]
Subjects: Not applicable
Study design recommendations:

- The kinetic binding study should be used to support the pivotal equilibrium binding study.
- Both the test product and RS should be incubated with at least three potassium concentrations: the lowest and highest concentrations used in the corresponding equilibrium binding study, and the mid concentration of approximately 50% of the highest concentration used.
- The study should be conducted at pH 4.5, and 6.8 buffer, without acid pretreatment.
- Potassium binding should be monitored as a function of time.
- At least eight different time points should be selected up to 24 hours that adequately illustrate the binding rate profile, including time in which binding equilibrium is achieved, under each condition.
- All incubations should be conducted at 37°C under constant gentle shaking, and each binding study should be repeated at least 12 times.

Analyte to measure: Unbound potassium in filtrate (to calculate potassium bound to patiromer)

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

For the in vitro kinetic binding study, the test/RS bound potassium ratios at various times should be compared but not subjected to the 90% CI criteria.

Bioequivalence based on (90% CI): The Langmuir binding constant k_2 from the equilibrium binding study.

5. Class of study: Comparative Characterization
   Type of study: In vitro potassium binding study with water, beverage, soft food and milk
   Design: Without acid pretreatment, at pH 6.8
   Strength: EQ 16.8 gm Base/packet[3]
   Subjects: Not applicable
   Study design recommendations:
   - The compatibility binding study is considered a supportive study to the bioequivalence studies described above. The study samples should be pretreated with water, one beverage (e.g., orange juice), one soft food (e.g., apple sauce) and milk.[4]
   - After pretreatment, the samples should be centrifuged, washed with water and dried.
   - The pretreated samples should then be subjected to potassium equilibrium binding study in a pH 6.8 buffer with the highest potassium concentration used in the corresponding equilibrium binding study.
   - Each potassium binding study should be repeated at least three times for both the test and RS products in each testing media.

Bioequivalence of additional strengths: Waiver request of EQ 1 gm Base/packet, EQ 8.4 gm Base/packet, and EQ 25.2 gm Base/packet strengths based on (i) acceptable in vitro equilibrium binding and kinetic binding studies on the EQ 16.8 gm Base/packet strength and (ii) proportionally similar formulations of the EQ 1 gm Base/packet, EQ 8.4 gm Base/packet, and EQ 25.2 gm Base/packet to the EQ 16.8 gm Base/packet strength.[3]

Dissolution test method and sampling times: Not applicable.

Document History: Recommended May 2026

[a] We update guidances periodically. For the most recent version of a product-specific guidance, refer to the FDA guidance webpage at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.

[4] In terms of drug/beverage ratio, the dosing instruction in the labeling may serve as a reference which is to mix a packet of 8.4 gm of patiromer in 1/3 cup (approximately 80 mL) of beverage.