Contains Nonbinding Recommendations

Draft Guidance on Sevelamer Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Sevelamer Hydrochloride

Form/Route: Tablets/Oral

Recommended studies: 2 *in-vitro* studies

1. Type of study: *In-vitro* equilibrium binding
   Design: In-vitro
   Strength: 800 mg
   Subjects: Not Applicable
   Additional comments: The equilibrium binding study is considered the pivotal bioequivalence study. This study should be conducted by incubating sevelamer hydrochloride products with at least eight different phosphate concentrations. Concentrations should be spaced along the spectrum from the linear binding range until the maximum binding is clearly established. The Langmuir binding constants k_1 and k_2 should be determined in the equilibrium binding study. 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% to 125%.

---

2. Type of Study: *In-vitro* kinetic binding
   Design: In-vitro
   Strength: 800 mg
   Subjects: Not Applicable
   Additional Comments: The kinetic binding study should be used to support the pivotal equilibrium binding study. In the kinetic study, a constant phosphate concentration should be incubated with sevelamer hydrochloride for varying times. At least eight different times should be used. The test/reference ratios at the various times should be compared but not subjected to the 90% confidence interval criteria.

   Binding parameters should be determined under reaction conditions encountered in the gastrointestinal tract. Thus, each set of binding studies should be conducted at pH values of 1, 4, and 7. All incubations should be conducted at 37°C. An adequate number of replicates should be used for each set of conditions.

   Incubation media should contain 80 nM NaCl and 100 mM *N,N*-Bis (hydroxyethyl)-2-aminoethanesulfonic acid (BES). Additional information about assay conditions is published in Swearinger et al., Determination of the binding parameter constants of Renagel® capsules and tablets using the Langmuir approximation at various pH values by ion chromatography. *J. Pharm. Biomedical Anal.* **29** (2002), pp. 195-201.

You may submit a proposed protocol for review prior to initiating the studies

---

Analytes to measure (in appropriate biological fluid): Not Applicable

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

Waiver requests of *in-vitro* equilibrium and kinetic binding studies: 400 mg, based on (1) acceptable *in-vitro* bioequivalence studies on the 800 mg strength, (2) proportional similarity in the formulations of the 400 mg and 800 mg strengths, and (3) acceptable specifications for disintegration in 0.1 N HCl and phosphate binding in a standardized *in-vitro* assay.

Dissolution test method and sampling times:

In-vitro phosphate binding should be conducted using a composite of 10 capsules with 16, 20 and 24 mM phosphate solutions. Specifications for *in-vitro* phosphate binding will be set at the time of ANDA review.

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the information about regulatory disintegration testing for this product at this website. Please conduct comparative disintegration testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.