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Draft Guidance on Sevelamer Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 the 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

Dosage Form; Route: Tablet; oral

Overview:

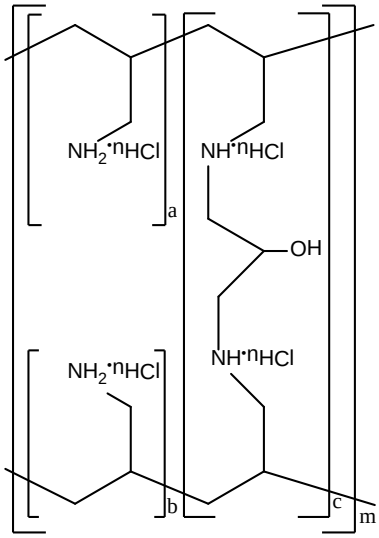
This draft guidance provides recommendations for the development of a generic drug product, sevelamer hydrochloride tablets, using sevelamer hydrochloride as the active pharmaceutical ingredient (API). First, FDA provides recommendations for supporting a demonstration of API sameness. Second, FDA provides recommendations for demonstrating bioequivalence (BE) of this product.

Recommendations for Demonstrating API Sameness:

The API, sevelamer hydrochloride, is a polymeric drug substance. According to the labeling of the reference listed drug (RLD) (Renagel®) tablets, sevelamer hydrochloride is poly (allylamine hydrochloride) crosslinked with epichlorohydrin in which 40 percent of the amines are protonated. FDA encourages sponsors to follow the same synthetic route to manufacture the API. Sponsors should contact the Office of Generic Drugs (OGD) to obtain concurrence if they wish to propose an alternative synthetic route, which may require characterizations in addition to the ones outlined in the current draft guidance to demonstrate API sameness. Sameness of sevelamer hydrochloride can be established based on its synthetic route and comparative physico-chemical characterizations. The information on manufacturing process and in-process controls should be provided to the Agency. The sponsor is advised to perform side-by-side comparative testing using the test API and the API extracted from the RLD product. The method of API extraction should be submitted to the Agency. At least three batches of the test API and at least three batches of the extracted reference API should be characterized to assess API sameness and robustness in the manufacturing process. Based on the data generated from the characterization, the sponsor should define and prove the chemical structure and molecular formula of the test API in comparison to the Reference API. A schematic representation of sevelamer hydrochloride is shown in Figure 1[1]. The individual parameters (i.e., a, b, c, and n) associated with various molecular sub-groups in the schematic should be measured and reported by the sponsor.

Figure 1. Chemical Structure of Sevelamer Hydrochloride[1]

[1] The labeling information of Renagel® tablets.



a, b = number of primary amine groups a + b = 9
c = number of crosslinking groups c = 1
n = fraction of protonated amines n = 0.4
m = large number to indicate extended polymer network

The methods and results of the following characterizations of the test and reference APIs should be reported to the Agency. The claim of API sameness should be supported by comparative characterization results of the test and reference APIs.

1. Degree of crosslinking (i.e., ratio of crosslinked amine groups to total amine groups): The Agency recommends that sponsors use ^{13}C solid-state nuclear magnetic resonance (^{13}C SSNMR) spectroscopy to quantify the degree of crosslinking in the APIs by quantitative peak-area analysis.[2]
2. Degree of protonation (chloride content): Titration is recommended to quantify the chloride content as a measure of the degree of protonation.
3. Total titratable amine: Titration is recommended to quantify the total-titratable-amine content.
4. Particle size: Particle size distributions of the APIs should be reported.
5. Elemental analysis: The results should include C, H, N, and Cl elements.
6. Swelling index: The range of swelling index of the APIs should be reported.
7. The Agency encourages the sponsor to perform additional characterization including, but not limited to, Fourier transformation infrared spectroscopy (FTIR), Raman spectroscopy, X-ray diffraction (XRD), and differential scanning calorimetry (DSC) to further characterize the chemical structure and physico-chemical properties of the APIs.

[2] Berendt, et al., "Spontaneous Carbonate Formation in an Amorphous, Amine-Rich, Polymeric Drug Substance: Sevelamer HCl Product Quality," *J. Pharm. Sci.* 101 (2012), pp. 2681-2685.

Recommendations for demonstrating bioequivalence:

Recommended Studies: Two in vitro studies

1. Type of study: In vitro equilibrium binding study
   Design: With and without acid pre-treatment at pH 4 and pH 7
   Strength: 800 mg
   Subjects: Not applicable (N/A)
   Additional comments: The equilibrium binding study is considered the pivotal BE study. This study should be conducted by incubating the test and reference products with at least eight different concentrations of phosphate, with and without acid pretreatment, at pH 4 and pH 7. Whole tablets should be used in the study. Each phosphate incubation medium should contain 80 mM NaCl and 100 mM N,N-Bis (hydroxyethyl)-2-aminoethanesulfonic acid. Phosphate concentrations should be spaced along the spectrum until the maximum binding is clearly established. All incubations should be conducted at 37°C. Each binding study should be repeated at least 12 times. In addition, data should be provided demonstrating that the length of time selected for incubation with the phosphate-containing medium yields maximum binding.

For additional details on a similar equilibrium binding study design, see the cholestyramine powder/oral guidance. 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.

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2. Type of study: In vitro kinetic binding study
   Design: With and without acid pre-treatment at pH 4 and pH 7
   Strength: 800 mg
   Subjects: N/A
   Additional comments: The kinetic binding study should be used to support the pivotal equilibrium binding study. This study should be conducted by incubating the test and reference products for at least eight different lengths of time, with two different phosphate concentrations, with and without acid pre-treatment, at pH 4 and pH 7. Whole tablets should be used in the study. The phosphate concentrations used in each kinetic binding study should be the lowest and highest used in the corresponding equilibrium binding study.

   Each incubation medium should contain 80 mM NaCl and 100 mM N,N-Bis (hydroxyethyl)-2-aminoethanesulfonic acid. Times should be selected along the spectrum until the maximum binding is clearly established. All incubations should be conducted at 37°C. Each binding study should be repeated at least 12 times.

For additional details on a similar equilibrium binding study design, see the cholestyramine powder/oral guidance. 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.

Analytes to measure: Unbound phosphate in filtrate (to calculate phosphate bound to resin)

For the in vitro equilibrium binding study, 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 (CI) should be calculated for k_2 with the acceptance criteria of 80% to 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% CI criterion.

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 (i) acceptable equilibrium and kinetic in vitro BE studies on the 800 mg strength, (ii) proportional similarity in the formulations of the 400 mg and 800 mg strengths, and (iii) acceptable disintegration testing in 0.1 N HCl.

Dissolution test method and sampling times: N/A

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).