Contains Nonbinding Recommendations

Draft Guidance on Colesevelam Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Colesevelam hydrochloride

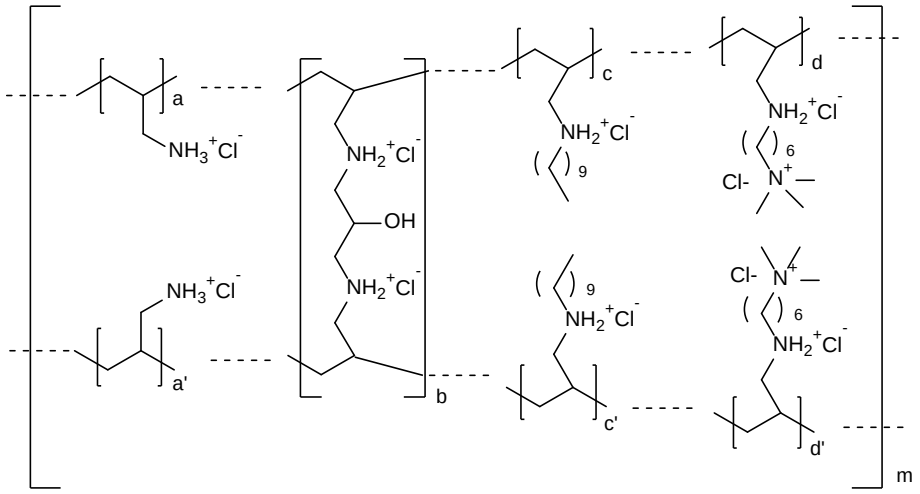
Dosage Form; Route: Tablet; oral

Overview:

This draft guidance provides recommendations for the development of a generic drug product, colesevelam hydrochloride tablets, using colesevelam hydrochloride as the active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

Recommendations for Demonstrating API Sameness

Figure 1. Schematic Structure of Colesevelam Hydrochloride[1]



where:
a + a' = 2
b = 1
c + c' = 7
d + d' = 6
m = amount of extended polymeric network

[1] See www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-141_welchol.cfm. Note: there were some errors in the drawing and labeling of the structure in the original documents, which are corrected in the current documents. Also, colesevelam hydrochloride is a highly cross-linked polymer. Therefore, a "double chain" schematic drawing more accurately represents the structure of the active ingredient. In addition, the use of the relative number of each type of group in a basic polymeric unit in the representation is consistent with its molecular formula.

Molecular Formula for a Basic Polymeric Unit:
$(C_3H_8NCl)_2(C_9H_{20}N_2OCl_2)_1(C_{13}H_{28}NCl)_7(C_{12}H_{28}N_2Cl_2)_6$

The structure of colesevelam hydrochloride is shown in Figure 1, with substituents on the backbone and their relative numbers.[2] The molecular formula of the basic unit of colesevelam hydrochloride is also shown. Sameness of colesevelam hydrochloride can be established based on the reaction scheme and comparative physicochemical characterizations. Generic drug sponsors are advised to perform side-by-side comparative testing using the proposed API (Test) and the API extracted from the RLD products (Reference).[3] The method of API extraction should be documented and submitted to the Agency in the abbreviated new drug application (ANDA). The Agency recommends that applicants characterize at least three batches of the Test API and three batches of API extracted from RLD to assess API sameness and robustness in the manufacturing process. The sameness of colesevelam hydrochloride active ingredient can be demonstrated by showing equivalence between the Test and the RLD products per the following three criteria:

1. Fundamental reaction scheme
2. Chemical structure and molecular formula
3. Physicochemical properties

A. Equivalence of fundamental reaction scheme

According to the RLD labeling, colesevelam hydrochloride is a poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide.[4] FDA recommends that generic sponsors follow the synthetic transformation indicated in the product labeling to manufacture generic colesevelam hydrochloride. If an alternative synthetic transformation is proposed, the sponsors should contact the Office of Generic Drugs (OGD) to obtain concurrence, as the API obtained in such approach may need additional characterizations besides the ones outlined in this draft guidance to demonstrate API sameness.

B. Equivalence of chemical structure and molecular formula

The sponsor should define the chemical structure and molecular formula of the proposed colesevelam hydrochloride (i.e., define the descriptive (a+a'), b, (c+c'), and (d+d') values) using data obtained from the manufacturing process and characterization. The structure and molecular formula of the Test API should be consistent with the structure and molecular formula defined in this draft guidance.

[2] See footnote 1.
[3] Based on documents available at www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-141_welchol.cfm, currently colesevelam hydrochloride is the same active ingredient in Welchol Tablets and Welchol for Oral Suspension. Depending on the extraction method, the sponsor is advised to consider whether the same process should also be applied to the Test API before side-by-side characterizations.
[4] See the labeling information for Welchol.

Since the physicochemical characterizations of the colesevelam hydrochloride API alone may not be sufficient to support its molecular formula, generic drug sponsors are advised to characterize the cross-linked poly(allylamine hydrochloride) intermediate as per the approaches described in the draft guidance for sevelamer hydrochloride,[5] and to perform studies to quantify the disappearance of the alkylating agents used in the process over time. Findings from these studies can be used to define the structure and molecular formula of the Test API, and should be reported to the Agency. The following studies are recommended:

1. Degree of cross-linking: To quantify the degree of cross-linking in the intermediate by quantitative peak-area analysis using Solid State ^{13}C Nuclear Magnetic Resonance (^{13}C SSNMR) spectroscopy[6]
2. Other characterizations for the intermediate, including glass transition temperature (T_g): To confirm the quantification of the degree of cross-linking in the intermediate[7]
3. Alkylation studies: To quantify the degree of alkylation in the active ingredient, by providing information on the disappearance of alkyl halide starting materials (1-bromodecane and (6-bromohexyl)-trimethylammonium bromide) over time during the alkylating process

C. Equivalence of physicochemical properties

Generic sponsors should also perform side-by-side comparative physicochemical characterizations of the Test API and the API extracted from the RLD. Methods used and results from the characterizations should be reported to the Agency. The sameness claim should be supported by the following:

1. ^{13}C SSNMR spectra
2. Data for C, H, N, Cl, and Br content by elemental analysis
3. Chloride content by titration to quantify the degree of protonation
4. Total titratable amines by titration
5. Bromide content by titration
6. Particle size with particle size distribution
7. Swelling Index
8. Spectroscopic characterizations by Fourier Transformation infrared spectroscopy (FT-IR) and Raman spectroscopy
9. Glass transition temperature by Differential Scanning Calorimetry (DSC)
10. Thermogravimetric analysis (TGA)

Recommendations for Demonstrating Bioequivalence of Drug Product

[5] Draft guidance on sevelamer hydrochloride, FDA, Recommended Sep 2008; Revised Jul 2009; May; Aug 2010; Aug 2011; Oct 2014.
[6] 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.
[7] Hudson et al., "Enhancement and Restriction of Chain Motion in Polymer Networks". Int. J. of Pharm. 430 (2012), pp. 34 – 41.

1. Type of study: In vitro equilibrium binding
   Design: With and without acid pre-treatment at pH 6.8
   Strength: 625 mg
   Subjects: Not applicable (N/A)
   Additional comments: The equilibrium binding study is considered the pivotal bioequivalence study. Whole tablets should be used in the study. This study should be conducted by incubating the generic (Test) and Reference products with at least eight different concentrations of total bile salts, with and without acid pretreatment. Each bile salt-containing incubation medium should contain glycocholic acid (GCA), glycochenodeoxycholic acid (GCDA), and taurodeoxycholic acid (TDCA). Total bile salt 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 total bile salt-containing medium yields maximum binding.

2. Type of study: In vitro kinetic binding
   Design: Without acid pre-treatment
   Strength: 625 mg
   Subjects: N/A
   Additional comments: The kinetic binding study should be used to support the pivotal equilibrium binding study. Whole tablets should be used in the study. This study should be conducted by incubating the Test and Reference products for at least eight different lengths of time, with two different constant total bile salt concentrations, without acid pre-treatment. The total bile acid concentrations used should be 0.3 mM and 3.0 mM, similar to concentrations used in the in vitro kinetic binding studies of cholestyramine drug product. 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 the study design, please see the cholestyramine powder/oral guidance.

Analytes to measure (in appropriate biological fluid): Unbound bile salts in filtrate (to calculate bile salts bound to resin)

For the in vitro equilibrium binding study, the Langmuir binding constants k_1 and k_2 should be determined based on total bile salt binding (GC+GCDC+TDC). 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 120%.

For the in vitro kinetic binding study, the Test/Reference bound bile acid salt 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.

Waiver request of in vitro testing: N/A

Dissolution test method and sampling times: N/A

Disintegration Test: A Dissolution Methods Database is available to the public at the FDA Web site at http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm. The information about regulatory disintegration testing for this product is available at this Web site. 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.