Contains Nonbinding Recommendations

Draft Guidance on Lanthanum Carbonate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Lanthanum carbonate

Dosage Form; Route: Chewable tablets; oral

Recommended Studies: Two options: In Vitro or In Vivo studies

1. In Vitro Option

The following in vitro dissolution, phosphate equilibrium binding and phosphate kinetic binding studies are recommended to establish bioequivalence of the test and RLD tablets at the 1000 mg strength.

A. Dissolution Studies:

Dissolution should be conducted on 12 whole and 12 crushed tablets each of test and reference products. Crushed tablets should be prepared by gently crushing each tablet to a fine powder. These data are to be submitted in addition to the method specified in the Dissolution Methods Database (see below), which is to be used for stability and quality control testing.

Apparatus:	USP Apparatus 2 (paddle)
Rotatiions Speed:	50 rpm
Media:	0.1 N HCl, pH 3.0 buffer and pH 5.0 buffer[1]
Volume:	900 mL
Temperature:	37 C
Samole times:	At least 8 time points up to 24 hours or until 85% or more of the drug dissolves

An f_2 test should be performed using mean profiles to compare test (T) and reference (R) product drug release under a range of pH conditions. Note that it is not necessary to determine f_2 when both T and R dissolve 85% or more in 30 minutes or less.

B. Phosphate Binding Studies:

[1] The types of pH 3.0 and 5.0 buffers are not specified. It is the firm's responsibility to select the appropriate types of buffer. For example, a phosphate buffer should not be selected because it interferes with the binding studies. If the anions of the buffer system react with lanthanum cation and form an insoluble salt, the buffer system should not be selected.

In addition to the dissolution data requested above and the dissolution data needed for stability and quality control, please conduct in vitro equilibrium and kinetic phosphate binding studies to compare the extent and rate of phosphate binding between the test and reference tablets. Any interference in phosphate binding from the inactive ingredients in the test or reference products should be documented. Studies should be conducted using 12 replicates for each condition. Each study should be conducted based on one 1000 mg lanthanum carbonate chewable tablet using the entire tablet. Please submit individual data and summary statistics based on the following studies.

a) Equilibrium Binding Study:
The equilibrium binding study may be conducted on a whole tablet or on a crushed tablet. The recommended steps for equilibrium study are the following:

1. Incubate the whole or crushed tablet in the 0.1 N HCl (pH 1.2) medium until it completely dissolves.
2. Adjust the pH to the target pH (1.2, 3.0, or 5.0) if necessary.
3. Wait for at least one hour.
4. Add phosphate solutions to various final concentrations and the pH should be monitored and further adjusted during the addition of phosphate. The final reaction system should be 250 mL.
5. The solution should be incubated at 37°C until the maximum lanthanum- phosphate binding is achieved.

Inclusion of the acid pretreatment step is to expedite the tablet dissolution and facilitate the equilibrium binding study. Binding conditions should contain at least eight different phosphate concentrations in 250 mL. The maximum phosphate binding region (attainment of plateau) should be clearly demonstrated prior to selecting these eight phosphate concentrations for the study. The eight concentrations should approximately range from the plateau downward to about one-tenth of that concentration and should characterize the rapidly rising portion of the binding curve. Each concentration should also be conducted at pH 3.0 and 5.0. For each set of conditions, the solution should be incubated at 37°C until the maximum lanthanum-phosphate binding is achieved.

The Langmuir binding constants k1 and k2 for each pH should be determined in the equilibrium binding study. The test/reference ratio should be calculated for k1. The 90% confidence interval should be calculated for k2.

b) Kinetic Binding Study: For the kinetic study, the three following phosphate concentrations should be used to incubate crushed lanthanum carbonate tablets: the lowest and highest concentrations used in the corresponding equilibrium binding study, and the mid concentration of approximately 50% of the highest concentration used. Furthermore, the study should be conducted in 250 mL at pH 1.2, 3.0 and 5.0. Lanthanum-phosphate binding should be monitored as a function of time. At least 8 time points should be chosen up to 24 hours that adequately address binding under each condition. All incubations should be conducted at 37°C under constant gentle shaking.

An f2 test should be performed using mean profiles to compare lanthanum-phosphate binding kinetics of test (T) and reference (R) tablets under a range of phosphate concentrations and pH conditions.
Additional information about assay conditions is published by Yang et al. In vitro bioequivalence approach for a locally acting gastrointestinal drug: lanthanum carbonate. Mol. Pharm. 2013 Feb 4;10(2):544-50. doi: 10.1021/mp300517p. Epub 2013 Jan 4.

Waiver requests of in vitro studies in Option 1: 500 mg and 750 mg based on (i) acceptable in vitro bioequivalence studies on the 1000 mg strength, (ii) proportional similarity in the formulations across all strengths, and (iii) acceptable in vitro dissolution of all strengths.

2. In Vivo Option
In the case where BE will be demonstrated through the in vivo option, BE should be established by conducting a study using pharmacodynamic endpoints in healthy subjects. The most appropriate endpoint is change in urinary phosphate excretion.

A pilot study should first be conducted using the RLD to determine the most sensitive dose for the pivotal BE study.

Waiver request of in vivo testing for Option 2: Strength(s) not used in the pharmacodynamic bioequivalence study based on (i) acceptable pharmacodynamic bioequivalence study on the tablet strength used as identified in the pilot study, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution comparison of all strengths.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods Web site, 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).