

Draft Guidance on Acarbose

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Active ingredient: Acarbose

Form/Route: Tablets/Oral

Recommended studies: **2 Options: In Vitro or In Vivo Studies**

1. In Vitro Option

If your test product formulations are qualitatively (Q1, i.e., contains all of the same inactive ingredients) and quantitatively (Q2) the same as the reference listed drug (RLD) with respect to inactive ingredients, then bioequivalence (BE) of all tablet strengths may be established based solely on comparative dissolution. This means that (1) the amount of any excipient in the test product should not be more than $\pm 5\%$ different than the corresponding excipient in the RLD; and (2) the total weight of the test product tablet should not be more than $\pm 5\%$ different than the total weight of the RLD tablet.

For Q1 and Q2 formulations, the following comparative dissolution testing of 12 tablets each of test and reference products is recommended:

- a. This FDA dissolution testing method is to be used for stability and quality control testing. The dissolution specification will be determined upon review of the ANDA.

| | |
|----------------|----------------------------|
| Apparatus | USP Apparatus 2 (paddle) |
| Media | Water |
| Volume | 900 mL |
| Rotation speed | 75 rpm |
| Sampling times | 10, 15, 20, 30, 45 minutes |

- b. In addition, the following multi-media dissolution method should be conducted on 12 tablets each of test and reference products.

| | |
|----------------|--|
| Apparatus | USP Apparatus 2 (paddle) |
| Media | 0.1N HCl, pH 4.5 buffer, and pH 6.8 buffer |
| Volume | 900 mL |
| Rotation speed | 50 rpm |
| Sampling times | 10, 15, 20, 30, 45 and 60 minutes |

An f2 test should be performed using mean profiles to assure comparable test (T) and reference (R) product drug release under a range of pH conditions. The f2 test comparing T vs. R in each media should be 50 or greater. Note that the f2 test is not necessary when both T and R dissolve 85% or more in 15 minutes or less using all three media.

2. In Vivo Option

If your test product formulations are NOT qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug (RLD) with respect to inactive ingredients, bioequivalence should be established by conducting a study with pharmacodynamic endpoints. The most appropriate endpoint for acarbose is the change in serum glucose concentrations. A pilot study should first be conducted to determine the appropriate dose for the pivotal BE study, as described below:

a. Pilot Study

A pilot study is necessary for two reasons, to determine (1) the appropriate dose for the pivotal BE study; and (2) the appropriate number of study subjects needed to provide adequate statistical power to show bioequivalence in the pivotal study. The pilot study should use the RLD given with 75 g of sucrose, and should identify the lowest possible dose that will yield a pharmacodynamic response above baseline. This is done to assure that the glucose-lowering response is not near the plateau of the dose-response curve. Thus, the first dose tested should be the RLD 1*25mg tablet. If treatment with this dose does not elicit a measurable response relative to baseline, it may be necessary to repeat the study with multiples of the 25mg strength, beginning with 2*25mg. The treatments to establish the appropriate dose can be studied in the same group of subjects, with a one-week washout between each treatment, until the optimal dose for the pivotal study is identified.

b. Bioequivalence Study

The pivotal BE study should use the 25-mg strength of test and reference products administered at the dose identified in the pilot study. The recommended study design is a randomized balanced two-way crossover study, with a one-week washout between treatments.

A separate fed bioequivalence study is not necessary.

3. General Information for Pilot and BE Studies

- a. The diet and physical activity of the study subjects should be strictly controlled prior to and during the study. In addition, because sensitivity to potential differences between products may be reduced in obese subjects, the protocol should specify an acceptable subject weight range.
- b. Please measure serum glucose as a pharmacodynamic endpoint for acarbose. The bioanalytical method used to assay for serum glucose should be properly validated. Please consult the CDER Guidance for Industry: Bioanalytical Method Validation, posted May 2001, for recommendations about the appropriate approach.
- c. We recommend that you obtain a baseline for serum glucose in the following manner:
 - Subjects should receive a challenge dose of 75 g of sucrose on the day prior to drug treatment. The sugar may be given as a solution, 75 g in 150 mL water. The sucrose challenge should follow an overnight fast.
 - Following the administration of sucrose, blood should be sampled for serum glucose for up to 4 hours. Drug treatment will take place on the following day.
 - On the drug treatment day, drug should be given together with 75 g of sucrose. Blood should be sampled for serum glucose for up to 4 hours after acarbose/sucrose administration.

- d. The literature suggests that the maximum reduction of serum glucose following acarbose administration upon sucrose challenge occurs within the first hour. Therefore, we recommend intensive sampling during the first hour post-dosing to adequately capture the maximum reduction in serum glucose levels.
- e. Bioequivalence evaluation will be based on the reduction of serum glucose levels following treatment with acarbose and sucrose together relative to the baseline serum glucose levels observed (on the prior day) following the sucrose baseline challenge. Thus, the appropriate parameters used for bioequivalence statistics are baseline-adjusted (1) maximum reduction in serum glucose concentration (C_{max}); and (2) area under the serum glucose reduction versus time curve through 4 hours, AUEC(0-4). The C_{max} represents the maximum difference between the baseline glucose profile determined on the day prior to drug treatment and the glucose profile determined on the day of drug treatment. AUEC(0-4) represents the difference in areas computed from the glucose levels following the baseline challenge and following the acarbose and sucrose administration.
- e. To establish bioequivalence between your product and the RLD in the pharmacodynamic endpoint study, the 90% confidence intervals for the test/reference ratios for AUEC(0-4) and C_{max} should fall within the bioequivalence limits of 0.8 to 1.25.
- f. It is not necessary to measure plasma concentrations of acarbose.
- g. We recommend that you submit protocols for evaluation prior to initiating the pilot and pivotal bioequivalence studies.

Waiver request of in-vivo testing: 50 mg and 100 mg based on (i) acceptable in vivo bioequivalence study on the 25 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations.

Dissolution test method and sampling times:

Regardless of the option chosen, please provide dissolution data on 12 dosage units each of test and reference products for all strengths using the three different media described in the In Vitro Option section above.

In addition, please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Please 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 application.