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Draft Guidance on Acarbose

May 2022

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This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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In August 2017, FDA issued a finalized product-specific guidance for industry on generic acarbose. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient: Acarbose

Dosage Form; Route: Tablet; oral

Recommended Studies: Two options: (1) in vitro comparative dissolution studies or (2) one in vivo pilot bioequivalence study and one in vivo pivotal bioequivalence study with pharmacodynamic endpoints

I. Option 1: In vitro comparative dissolution studies

If the test product formulations are qualitatively (Q1) and quantitatively (Q2) the same as the reference product with respect to inactive ingredients, the bioequivalence of all tablet strengths may be established based solely on in vitro comparative dissolution studies.

In addition to the FDA dissolution testing method recommended below, the following multi-media comparative dissolution method should be conducted on 12 tablets for each of test and reference products:

Strengths:	25 mg, 50 mg, and 100 mg
Apparatus:	U.S. Pharmacopeia (USP) Apparatus 2 (paddle)
Media:	0.1N HCl, pH 4.5 buffer and pH 6.8 buffer
Volume:	900 mL
Rotation speed:	50 rpm
Temperature:	37 ± 0.5 °C
Sampling times:	10, 15, 20, 30, 45 and 60 minutes

II. Option 2: One in vivo pilot and one in vivo pivotal bioequivalence study with pharmacodynamic endpoints

If the test product formulations are not Q1 and Q2 the same as the reference product with respect to inactive ingredients, the bioequivalence should be established by conducting a study with pharmacodynamic endpoints. The most appropriate endpoint for acarbose is the change in plasma glucose concentrations. A pilot study should first be conducted to determine the appropriate dose and the appropriate number of study subjects needed to provide adequate statistical power to show bioequivalence in the pivotal bioequivalence study as described below:

1. Pilot bioequivalence study

The pilot study should use the reference product given with 75 g of sucrose and identify the lowest possible dose that will yield a pharmacodynamic response above baseline. This is to assure that at the selected dose the glucose-lowering response is in the sensitive and discriminating region of dose-response curve to detect the formulation difference, not near the plateau of the dose-response curve. The first dose tested should be the reference product one unit of 25 mg strength tablet. If treatment with this dose does not elicit a measurable response relative to baseline with a sucrose challenge, it may be necessary to repeat the study with multiple units of the 25 mg strength, beginning with two units of 25 mg strength tablet. 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.

Additional comments:

- 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.
- Measure plasma glucose as a pharmacodynamic endpoint for acarbose. The bioanalytical method used to assay for plasma glucose should be properly validated.
- Obtain a baseline for plasma glucose in the following manner:

- a. 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.
 - b. Following the administration of sucrose, blood samples should be collected for measurement of plasma glucose concentration for up to 4 hours. Administration of acarbose should be initiated on the following day.
 - c. On the drug treatment day, acarbose should be given concomitantly with 75 g of sucrose. Blood samples should be collected for measurement of plasma glucose concentration for up to 4 hours after acarbose/ sucrose administration.
- The literature suggests that the maximum reduction of plasma glucose concentration following acarbose administration upon sucrose challenge occurs within the first hour. Therefore, intensive blood sampling during the first hour post-dose is recommended to adequately capture the maximum reduction in plasma glucose concentrations.
 - Bioequivalence evaluation will be based on the reduction of plasma glucose concentrations following treatment with acarbose and sucrose together relative to the baseline plasma glucose concentrations observed (on the prior day) following the sucrose baseline challenge. Thus, the appropriate parameters used for bioequivalence statistics are baseline-corrected maximum reduction in plasma glucose concentration (C_{max}) and baseline-corrected area under the plasma glucose reduction versus time curve through 2 hours, AUEC(0-2). 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. The AUEC represents the difference in areas computed from the glucose concentrations following the baseline sucrose challenge and following the acarbose and sucrose administration. Of note, AUEC should be calculated using linear trapezoidal rule.

2. Pivotal bioequivalence study

The pivotal bioequivalence 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.

Additional comments: See comments above.

Analyte to measure: Glucose in plasma

Submit the plasma glucose concentration data for each individual subject during the time window that covers the entire glucose fluctuation after the drug treatment, i.e., 0-4 hours after the administration of acarbose as supportive information. It is not necessary to measure plasma concentrations of acarbose.

Bioequivalence based on (90% CI): Baseline-corrected glucose

To establish bioequivalence between the test and the reference products in the pharmacodynamic endpoint study, refer to the following:

1. For baseline-corrected C_{max}, the 90% confidence intervals for the arithmetic mean test/reference ratio should be within the limits of 0.8 to 1.25.
2. For baseline-corrected AUEC(0-2), the point estimate of the arithmetic mean test/reference ratio should be within the limits of 0.8 to 1.25.

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

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units for each of all strengths of the test and reference products. Specifications will be determined upon evaluation of the ANDA.

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