Contains Nonbinding Recommendations

Draft Guidance on Miglitol

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet; oral

Recommended Studies: Two options: in vitro or in vivo studies

1. In Vitro Option

If the test product (T) formulations are qualitatively (Q1) and quantitatively (Q2) the same as that of the corresponding strengths of the reference drug product (R) with respect to inactive ingredients, the bioequivalence (BE) of all strengths may be established based solely on comparative in vitro dissolution testing. Therefore, (1) the amount of any excipient in T (all strengths) should not be more than ± 5% different than the corresponding excipient in the corresponding strength of R; and (2) the total weight of the T tablet (all strengths) should not be more than ± 5% different than the total weight of the corresponding strength of the R tablet.

For Q1&Q2-the-same formulations, the comparative dissolution testing of 12 tablets each of T and R is recommended for all strengths:

- For BE purposes, the following multi-media dissolution method should be conducted on 12 tablets each of T and R for all strengths.

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:	75 rpm
Sampling times:	10, 15, 20, 30, 45, and 60 minutes

A similarity factor (f2) test should be performed using mean profiles to assure comparable T and R drug release under a range of pH conditions. The f2 test comparing T vs. R in each medium 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.

Waiver request of in vivo testing: The BE of all strengths of T with Q1&Q2-the-same formulation as the corresponding strength of R may be established based solely on comparative in vitro dissolution testing.

2. In Vivo Option

If the T formulations are NOT Q1&Q2-the-same as that of the corresponding strength of R with respect to inactive ingredients, the BE of all strengths should be established by conducting two studies in healthy males and females: one with pharmacodynamic endpoints and one with pharmacokinetic endpoints. The most appropriate pharmacodynamic endpoint for miglitol is the change in serum glucose concentrations. A pilot study should first be conducted to determine the appropriate dose for the BE study with PD endpoints, as described below:

Pilot Study

A pilot study should be conducted 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 BE in the pivotal study. The pilot study should use R (Glyset®), 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 Glyset® 1x25mg 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 25 mg strength, beginning with 2x25 mg. 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.

BE Study with PD endpoints

Type of the study: Fasting
Design: Randomized, balanced, two-way crossover study, with a one-week washout between treatments
Strength: 25 mg strength of T and R, administered at the dose identified in the pilot study
Subjects: Healthy males and nonpregnant females, general population

Additional comments for pilot and BE studies with PD endpoints:

i). 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.

ii). Measure serum glucose as a pharmacodynamic endpoint for miglitol. The bioanalytical method used to assay for serum glucose should be properly validated. Consult the CDER guidance for industry *Bioanalytical Method Validation*, posted in September 2013, for recommendations about the appropriate approach.

iii). 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 should take place on the following day.

- On the drug treatment day, the drug should be given together with 75 g of sucrose. Blood should be sampled for serum glucose for up to 4 hours after miglitol/sucrose administration.

iv). Maximum reduction of serum glucose following miglitol administration upon sucrose challenge is expected to occur within the first hour. Therefore, FDA recommends intensive sampling during the first hour post-dosing to adequately capture the maximum reduction in serum glucose levels.

v). BE evaluation should be based on the reduction of serum glucose levels following treatment with miglitol and sucrose together relative to the baseline serum glucose levels observed (on the prior day) following only sucrose challenge. Thus, the appropriate parameters used for BE statistics are baseline-adjusted (1) maximum reduction in serum glucose concentration (Cmax); and (2) area under the serum glucose reduction versus time curve through 4 hours, AUEC(0-4). The Cmax 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 miglitol and sucrose administration.

vi). To establish BE between T and R in the pharmacodynamic endpoint study, the 90% confidence intervals for the T/R ratios for AUEC(0-4) and Cmax should fall within the BE limits of 0.8 to 1.25.

BE study with PK endpoints

Type of the study: Fasting
Design: Randomized, balanced, two-way crossover study, with a one-week washout between treatments
Strength: 25 mg strength of T and R, administered at the dose identified in the pilot study
Subjects: Healthy males and nonpregnant females, general population

Plasma miglitol should be measured and subject to bioequivalence criteria determination with 90% confidence intervals for AUCt, AUCi, and Cmax.

Analytes to measure (in appropriate biological fluid): Miglitol in plasma

Bioequivalence based on (90% CI): Miglitol

Waiver request of in vivo testing: 50 mg and 100 mg strengths based on (i) acceptable in vivo BE studies 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: 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 T and R. Specifications will be determined upon review of the abbreviated new drug application (ANDA).