Contains Nonbinding Recommendations

Draft Guidance on Niacin

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Niacin

Form/Route: Extended Release Tablets/Oral

Recommended studies: 3 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 1000 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional comments: Applicants may consider using a reference-scaled average bioequivalence approach for niacin. If using this approach, please provide evidence of high variability in the bioequivalence parameters AUC and/or Cmax (i.e., within-subject variability $\geq$ 30%). For general information on this approach, please refer to Haidar et al., Bioequivalence Approaches for Highly Variable Drugs and Drug Products, Pharm. Res. 25:237-241(2008).

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2. Type of study: Fed
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 1000 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional comments: See above

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3. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 750 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional comments: See above.

Analytes to measure (in appropriate biological fluid): Niacin and its metabolite nicotinuric acid in plasma.

Bioequivalence based on (90% CI): Niacin.

If niacin cannot be reliably measured, a confidence interval approach for bioequivalence determination should be used for nicotinuric acid.

Waiver request of in-vivo testing: 500 mg based on (i) acceptable bioequivalence studies on the 1000 mg strength, (ii) proportionally similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times:

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.

For modified release products, dissolution profiles generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer, water) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for twelve tablets. Specifications will be determined upon review of the data submitted in the application.