Contains Nonbinding Recommendations

Draft Guidance on Niacin and Simvastatin

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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; Simvastatin

Form/Route: Extended Release Tablet/Oral

Recommended studies: 4 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 1000 mg/40 mg
   Subjects: Healthy males and nonpregnant females, general population.

2. Type of study: Fed
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 1000 mg/40 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional Comments: Please see comment above.

3. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 1000 mg/20 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional Comments: Please see comment above.
4. Type of study: Fasting
   Design: Single-dose, two-way crossover in-vivo
   Strength: 750 mg/20 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional Comments: Please see comment above.

Analytes to measure (in appropriate biological fluid): Niacin and its metabolite,
nicotinuric acid, simvastatin and its metabolite beta-hydroxyacid.

Please submit the metabolite data as supportive evidence of comparable therapeutic
outcome. For the metabolite, the following data should be submitted: individual and
mean concentrations, individual and mean pharmacokinetic parameters, and geometric
means and ratios of means for AUC and Cmax.

Bioequivalence based on (90% CI): Niacin and Simvastatin.

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/20 mg and 500 mg/40 mg based on (i)
acceptable bioequivalence studies on the 1000 mg/40 mg strength, (ii) acceptable in-vitro
dissolution testing of all strengths, and (iii) proportional similarity of the formulations
across all strengths.

Please refer to the Mirtazapine Tablet Draft Guidance for additional information
regarding proportional similarity.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guid
ances/UCM238058.pdf

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.

In addition to the method above, for modified release products, dissolution profiles on 12
dosage units each of test and reference products 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) 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. Please
include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least
80% of the drug is released, to provide assurance against premature release of drug (dose

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dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.