Contains Nonbinding Recommendations

Draft Guidance on Lovastatin; Niacin

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Extended Release Tablets/Oral

Recommended studies: 5 studies

1. Type of study: Fasting
   Design: Single-dose, two-way, crossover *in-vivo*
   Strength: 20 mg/ 1000 mg
   Subjects: Normal healthy males and females, general population
   Additional Comments: Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study.

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2. Type of study: Fasting
   Design: Single-dose, two-way, crossover *in-vivo*
   Strength: 20 mg/ 750 mg
   Subjects: Normal healthy males and females, general population
   Additional comments: Please see comments above.

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3. Type of study: Fasting
   Design: Single-dose, two-way, crossover *in-vivo*
   Strength: 20 mg/ 500 mg
   Subjects: Normal healthy males and females, general population
   Additional comments: Please see comments above.

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4. Type of study: Fasting
   Design: Single-dose, two-way, crossover *in-vivo*
   Strength: 40 mg/ 1000 mg
   Subjects: Normal healthy males and females, general population
   Additional comments: Please see comments above.

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5. Type of study: Fed
   Design: Single-dose, two-way, crossover *in-vivo*
   Strength: 40 mg/ 1000 mg
   Subjects: Normal healthy males and females, general population
   Additional comments: Please see comments above.

Special Considerations: Applicants may consider using a reference-scaled average bioequivalence approach for lovastatin and niacin. If using this approach, the applicant should provide evidence of high variability (i.e., within-subject variability ≥ 30%) in bioequivalence parameters. Applicants who would like to use this approach are encouraged to submit a protocol for review by the Division of Bioequivalence in the Office of Generic Drugs.

Analytes to measure: Niacin, Lovastatin and their respective metabolites, nicotinuric acid and lovastatin acid in plasma.

Bioequivalence based on (90% CI): Niacin and Lovastatin

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

Please submit the metabolite data for lovastatin acid as supportive evidence of comparable therapeutic outcome.

For the metabolites when submitted as supportive evidence, 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.

Waiver request of in-vivo testing: Not Applicable

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.fda.gov/cder/ogd/index.htm. 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.