Contains Nonbinding Recommendations

Draft Guidance on Lovastatin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Extended release tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 60 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: Women of childbearing potential should be advised to use an effective contraceptive method to prevent pregnancy while participating in the study. Applicants may consider using a reference-scaled average bioequivalence approach. If using this approach, applicant should provide evidence of high variability in the pharmacokinetic parameters area under the plasma concentration time curve and/or peak concentration from the study (i.e., within-subject variability≥30%). For the method for statistical analysis using the reference-scaled average bioequivalence approach, refer to the detailed information described in the Product Specific Guidance for Progesterone Capsules.

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 60 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: See comments above

Analytes to measure (in appropriate biological fluid): Lovastatin and lovastatin acid in plasma

Bioequivalence based on (90% CI): Lovastatin

Additional strengths: Bioequivalence of 20 mg and 40 mg strengths to the corresponding reference product strengths may be demonstrated based on principles laid out in the FDA guidance on "Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA"

Dissolution test method and sampling times:

For modified release drug products, FDA recommends that applicants develop specific discriminating dissolution methods. Applicants may also use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA's database (available at http://www.accessdata.fda.gov/scripts/cder/dissolution/), provided that applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed for the modified release drug product, FDA recommends that the submission includes the dissolution method development and validation report with the complete information/data supporting the proposed method. 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 abbreviated new drug 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. 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 dumping) from the formulation.