Contains Nonbinding Recommendations

Draft Guidance on Simvastatin and Sitagliptin Phosphate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in-vivo
   Strength: 40 mg; Eq. 100 mg (base)
   Subjects: Healthy males and non-lactating, non-pregnant females

   Additional Comment: 1. Female subjects must be on an acceptable form of birth control during the study. 2. Applicants may consider using a reference-scaled average bioequivalence approach for this drug product (simvastatin component). If using this approach, the applicant should provide evidence of high variability in the bioequivalence parameters of AUC and/or Cmax (i.e., within-subject variability >30%) from the bioequivalence studies. For general information on this approach, refer to the product-specific guidance on Progesterone Oral Capsules.

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2. Type of study: Fed
   Design: Single-dose, two-way crossover in-vivo
   Strength: 40 mg; Eq. 100 mg (base)
   Subjects: Healthy males and non-lactating, non-pregnant females

   Additional comment: See comments above.

Analytes to measure (in appropriate biological fluid): Sitagliptin, Simvastatin and its metabolite, beta-hydroxyacid of simvastatin in plasma.

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): Simvastatin and Sitagliptin

Waiver request of in-vivo testing: 10 mg/Eq. 100 mg (Base); 20 mg/Eq. 100 mg (Base), 10 mg/Eq. 50 mg (Base), 20 mg/Eq. 50 mg (Base) and 40 mg/Eq. 50 mg (Base) strength tablets based on (i) acceptable bioequivalence studies on the 40 mg/Eq. 100 mg (Base) strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website 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 all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).