Contains Nonbinding Recommendations

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Draft Guidance on Simvastatin; Sitagliptin Phosphate

October 2024

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In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredients: Simvastatin; Sitagliptin phosphate

Dosage Form: Tablet

Route: Oral

Strengths: 10 mg; EQ 50 mg Base, 10 mg; EQ 100 mg Base,
20 mg; EQ 50 mg Base, 20 mg; EQ 100 mg Base,
40 mg; EQ 50 mg Base, 40 mg; EQ 100 mg Base

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 40 mg; EQ 100 mg Base
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Females of reproductive potential should use effective contraception during the study. Monitor blood glucose concentrations and signs and symptoms of hypoglycemia during the study. Implement appropriate hypoglycemia management protocol. Applicants may consider using a reference-scaled average bioequivalence approach for this drug product (simvastatin component). If using this approach, provide evidence of high variability in the pharmacokinetic parameters (i.e., within-subject variability ≥30%) for the reference listed drug (RLD). For detailed information on this approach, refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.[a]

Analytes to measure: 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 C_{max}.

Bioequivalence based on (90% CI): Simvastatin and sitagliptin

Waiver request of in vivo testing: 10 mg; EQ 50 mg Base, 10 mg; EQ 100 mg Base, 20 mg; EQ 50 mg Base, 20 mg; EQ 100 mg Base, and 40 mg; EQ 50 mg Base strengths based on (i) acceptable bioequivalence study on the 40 mg; EQ 100 mg Base strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution. Conduct comparative dissolution testing on 12 dosage units for each of all strengths of the test product and RLD.[1] Specifications will be determined upon review of the abbreviated new drug application.

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[1] If the RLD is not available, refer to the most recent version of the FDA guidance for industry on *Referencing Approved Drug Products in ANDA Submissions.*