Contains Nonbinding Recommendations

Draft Guidance on Amlodipine Besylate; Atorvastatin Calcium

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way, crossover *in-vivo*
   Strength: Eq 10 mg base; Eq 80 mg base
   Subjects: Healthy males and nonpregnant females, general population.
   Additional Comments: Applicants may consider using a reference-scaled average bioequivalence approach for this drug product. If using this approach, the applicant should provide evidence of high variability in the bioequivalence parameters AUC and/or Cmax (i.e., within-subject variability $\geq$ 30%). For general information on this approach, please refer to Haidar et al., Bioequivalence Approaches for Highly Variable Drugs and Drug Products, Pharm. Res. 25:237-241(2008).

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2. Type of study: Fed
   Design: Single-dose, two-way, crossover *in-vivo*
   Strength: Eq 10 mg base; Eq 80 mg base
   Subjects: Healthy males and nonpregnant females, general population.
   Additional comments: Please see comment above.

Analytes to measure: Amlodipine and atorvastatin in plasma

Bioequivalence based on (90% CI): Amlodipine and atorvastatin.

The active ortho- and para-hydroxylated metabolites of atorvastatin in plasma should be measured.

Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolites, 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: 2.5 mg/10 mg, 2.5 mg/20 mg, 2.5 mg/40 mg, 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 5 mg/80 mg, 10 mg/10 mg, 10 mg/20 mg and 10 mg/40 mg based on (i) acceptable bioequivalence studies on the Eq 10 mg base; Eq 80 mg base strength, (ii) acceptable dissolution testing across all strengths, and (iii) proportional similarity in the formulations across all strengths.

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.