Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Amlodipine Besylate; Atorvastatin Calcium

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: Amlodipine besylate; Atorvastatin calcium

Dosage Form: Tablet

Route: Oral

Strengths: EQ 2.5 mg Base; EQ 10 mg Base,
EQ 2.5 mg Base; EQ 20 mg Base,
EQ 2.5 mg Base; EQ 40 mg Base,
EQ 5 mg Base; EQ 10 mg Base, EQ 5 mg Base; EQ 20 mg Base,
EQ 5 mg Base; EQ 40 mg Base, EQ 5 mg Base; EQ 80 mg Base,
EQ 10 mg Base; EQ 10mg Base, EQ 10 mg Base; EQ 20mg Base,
EQ 10 mg Base; EQ 40 mg Base, EQ 10 mg Base; EQ 80 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: EQ 10 mg Base; EQ 80 mg Base
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of amlodipine. Alternatively, a parallel study design may be considered. Applicants may consider using a reference-scaled average bioequivalence approach. If using this approach, provide evidence of high variability in the pharmacokinetic parameters (i.e., within-subject variability ≥30%) for the reference listed drug. 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: 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.

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 C_{max}.

Waiver request of in vivo testing: EQ 2.5 mg Base; EQ 10 mg Base, EQ 2.5 mg Base; EQ 20 mg Base, EQ 2.5 mg Base; EQ 40 mg Base, EQ 5 mg Base; EQ 10 mg Base, EQ 5 mg Base; EQ 20 mg Base, EQ 5 mg Base; EQ 40 mg Base, EQ 5 mg Base; EQ 80 mg Base, EQ 10 mg Base; EQ 10 mg Base, EQ 10 mg Base; EQ 20 mg Base and EQ 10 mg Base; EQ 40 mg Base, strengths based on (i) acceptable bioequivalence study on the EQ 10 mg Base; EQ 80 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 reference listed drug (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.*