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Draft Guidance on Amlodipine Besylate; Benazepril Hydrochloride

October 2024

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Active Ingredients: Amlodipine besylate; Benazepril hydrochloride

Dosage Form: Capsule

Route: Oral

Strengths: EQ 2.5 mg Base; 10 mg, EQ 5 mg Base; 10 mg, EQ 5 mg Base; 20 mg, EQ 5 mg Base; 40 mg, EQ 10 mg Base; 20 mg, EQ 10 mg Base; 40 mg

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; 40 mg
   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] In addition, applicants may also consider additional sample collections at early time points to better characterize the absorption phase of benazepril.

Analytes to measure: Amlodipine, benazepril, and active metabolite, benazeprilat, in plasma

Bioequivalence based on (90% CI): Amlodipine and benazepril

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 area under the curve and maximum concentration.

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