

Draft Guidance on Amlodipine Besylate; Benazepril Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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; Benazepril Hydrochloride

Form/Route: Capsules/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: EQ. 10 mg base/40 mg
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, please provide evidence of high variability in the bioequivalence parameters of AUC and/or C_{max} (i.e., within-subject variability > 30%). For general information on this approach, please refer to the Bioequivalence Recommendations for Specific Products on Progesterone Capsules.
In addition, applicants may also consider additional sample collections at early time points to better characterize the absorption phase of benazepril.

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2. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: EQ. 10 mg base/40 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: Please see comment above.

Analytes to measure: Amlodipine, Benazepril, and active metabolite, Benazeprilat, in plasma.

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

Please 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} .

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 based on (i) acceptable bioequivalence studies 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. Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in vivo testing.

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.accessdata.fda.gov/scripts/cder/dissolution/>. 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.