Contains Nonbinding Recommendations

Draft Guidance on Benazepril Hydrochloride; Hydrochlorothiazide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Benazepril hydrochloride; Hydrochlorothiazide

Dosage Form; Route: Tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-period, two-sequence, two-treatment crossover in vivo
   Strength: 20 mg/25 mg
   Subjects: Healthy males and nonpregnant females, general population
   Additional comments: Females should not be pregnant or lactating, and, if applicable, should practice abstention or contraception during the study. See additional warning on fetal toxicity in the approved drug label.

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2. Type of study: Fed
   Design: Single-dose, two-period, two-sequence, two-treatment crossover in vivo
   Strength: 20 mg/25 mg
   Subjects: Healthy males and females, general population
   Additional comments: Same as comments above

Analytes to measure (in appropriate biological fluid): Benazepril, its active metabolite, benazeprilat, and hydrochlorothiazide in plasma

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

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 Cmax.

Waiver request of in vivo testing: 5 mg/6.25 mg, 10 mg/12.5 mg, and 20 mg/12.5 mg strengths based on (i) acceptable bioequivalence studies on the 20 mg/25 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods Web site, available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).