Guidance on Hydrochlorothiazide; Losartan Potassium

Active Ingredient: Hydrochlorothiazide; Losartan potassium

Dosage Form; Route: Tablets; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in-vivo
   Strength: 25 mg/100 mg
   Subjects: Healthy males and non-pregnant, non-lactating females, general population
   Additional comments:
   - Female subjects should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study.
   - Applicants may consider using a reference-scaled average bioequivalence approach. For the method of statistical analysis using the reference-scaled average bioequivalence approach, refer to the Progesterone Capsule Draft Guidance.

2. Type of study: Fed
   Design: Single-dose, two-way crossover in-vivo
   Strength: 25 mg/100 mg
   Subjects: Healthy males and non-pregnant, non-lactating females, general population
   Additional comments: See comments above.

Analytes to measure (in appropriate biological fluid): Hydrochlorothiazide, losartan, and its carboxylic metabolite in plasma

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.

Bioequivalence based on (90% CI): Hydrochlorothiazide and losartan

Waiver request of in-vivo testing: 12.5 mg/50 mg and 12.5 mg/100 mg based on (i) acceptable bioequivalence studies on the 25 mg/100 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 on the FDA-Recommended Dissolution Methods website, 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 all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).