

Draft Guidance on Hydrochlorothiazide; Losartan Potassium

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in-vivo
Strength: 25 mg/100 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 $\geq 30\%$). Please refer to the Progesterone Capsule Draft Guidance for additional information regarding highly variable drugs.

2. Type of study: Fed
Design: Single-dose, two-way crossover in-vivo
Strength: 25 mg/100 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: Please see additional comments above.

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

*For the carboxylic metabolite, the following data should be submitted: (1) individual and mean concentrations, (2) individual and mean pharmacokinetic parameters, and (3) geometric means and ratios of means for AUC and C_{max}.

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:

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.