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Draft Guidance on Hydrochlorothiazide; Losartan Potassium

October 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

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Active Ingredients: Hydrochlorothiazide; Losartan potassium

Dosage Form: Tablet

Route: Oral

Strengths: 12.5 mg; 50 mg, 12.5 mg; 100 mg, 25 mg; 100 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: 25 mg; 100 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: 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 (RLD). 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]

Analytes to measure: 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 C_{max}.

Recommended May 2007; Revised Aug 2007; Finalized May 2008; Revised Sep 2012, Dec 2012; Finalized Aug 2017; Revised Oct 2024

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 strengths based on (i) acceptable bioequivalence study 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 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*.