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Draft Guidance on Azilsartan Kamedoxomil; Chlorthalidone

October 2025

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredients: Azilsartan kamedoxomil; Chlorthalidone

Dosage Form: Tablet

Route: Oral

Strengths: EQ 40 mg medoxomil; 12.5 mg, EQ 40 mg medoxomil; 25 mg

Recommended Study: Two in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 40 mg medoxomil; 25 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of chlorthalidone. Alternatively, a parallel study design may be considered.

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 40 mg medoxomil; 25 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: See comments above.

Analytes to measure: Azilsartan and chlorthalidone in plasma

Bioequivalence based on (90% CI): Azilsartan and chlorthalidone

Waiver request of in vivo testing: EQ 40 mg medoxomil;12.5 mg strength based on (i) acceptable bioequivalence studies on the EQ 40 mg medoxomil; 25 mg strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between both 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 both strengths of the test product and reference listed drug (RLD). Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Alternative approach to in vivo bioequivalence studies:
Azilsartan medoxomil is a biopharmaceutics classification system class IV prodrug converted to its active form during gastrointestinal absorption. The RLD contains pH control agents for stability enhancement. Based on the pharmacokinetic variabilities in bioequivalence study results from different formulations, both fasting and fed bioequivalence studies are recommended.

However, FDA is supportive of the development of alternative bioequivalence approaches. In order to clarify FDA's expectations for prospective applicants early in product development and to assist applicants to submit an ANDA, FDA encourages applicants to discuss their development program for an alternative approach to bioequivalence with FDA via the pre-ANDA meeting pathway.

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