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Draft – Not for Implementation

Draft Guidance on Amlodipine Besylate; Hydrochlorothiazide; Olmesartan Medoxomil

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:	Amlodipine besylate; Hydrochlorothiazide; Olmesartan medoxomil
Dosage Form:	Tablet
Route:	Oral
Strengths:	EQ 5 mg Base; 12.5 mg; 20mg, EQ 5 mg Base; 12.5 mg; 40mg, EQ 5 mg Base; 25 mg; 40 mg, EQ 10 mg Base; 12.5 mg; 40 mg EQ 10 mg Base; 25 mg; 40 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: EQ 10 mg Base; 25 mg; 40 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Females of reproductive potential should use effective contraception during the study. Due to safety concerns, subjects should remain in a comfortable recumbent position for up to 8 hours after dosing and remain under medical surveillance for up to 12 hours after dosing. Subjects should sit up with legs in a dependent position for one minute prior to standing up before they are allowed to ambulate. While standing immobile, they should be closely observed for blood pressure changes and/or orthostatic symptoms, including nausea, dizziness, or faintness for at least three minutes. Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of amlodipine. Alternatively, a parallel study design may be considered.

Analytes to measure: Amlodipine, hydrochlorothiazide, and olmesartan in plasma

Bioequivalence based on (90% CI): Amlodipine, hydrochlorothiazide, and olmesartan

Waiver request of in vivo testing: EQ 5 mg Base; 12.5 mg; 20 mg, EQ 5 mg Base; 12.5 mg; 40 mg, EQ 5 mg Base; 25 mg; 40 mg, EQ 10 mg Base; 12.5 mg, 40 mg strengths based on (i) acceptable bioequivalence study on the EQ 10 mg Base; 25 mg; 40 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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[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*.