

Draft Guidance on Amitriptyline Hydrochloride; Chlordiazepoxide

October 2024

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Active Ingredients:	Amitriptyline hydrochloride; Chlordiazepoxide
Dosage Form:	Tablet
Route:	Oral
Strengths:	EQ 12.5 mg Base; 5 mg, EQ 25 mg Base; 10 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 25 mg Base; 10 mg
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: None

Analytes to measure: Amitriptyline and its active metabolite, nortriptyline, and chlordiazepoxide 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 area under the curve and maximum concentration.

Bioequivalence based on (90% CI): Amitriptyline and chlordiazepoxide

Waiver request of in vivo testing: EQ 12.5 mg Base; 5 mg strength based on (i) acceptable bioequivalence study on the EQ 25 mg Base; 10 mg strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportionally similarity 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 both strengths of the test product and reference listed drug (RLD).¹ Specifications will be determined upon review of the abbreviated new drug application.

Document History: Recommended February 2018; Revised October 2024

Unique Agency Identifier: PSG_016949

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*.