Contains Nonbinding Recommendations

Draft Guidance on Amitriptyline Hydrochloride and Chlordiazepoxide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient: Amitriptyline hydrochloride; Chlordiazepoxide

Dosage Form; Route: Tablet; oral

Recommended studies: Two studies

1.	Type of study:	Fasting
	Design:	Single-dose, two-way crossover *in-vivo*
	Strength:	Eq. 25 mg (base); 10 mg
	Subjects:	Healthy males and non-lactating, non-pregnant females
	Additional Comments:	None

2.	Type of study:	Fed
	Design:	Single-dose, two-way crossover *in-vivo*
	Strength:	Eq. 25 mg (base); 10 mg
	Subjects:	Healthy males and non-lactating, non-pregnant females.
	Additional comments:	None

Analytes to measure (in appropriate biological fluid): Amitriptyline, active metabolite Nortriptyline and Chlordiazepoxide in plasma

Please 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 Cmax.

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

Waiver request of in-vivo testing: Eq. 12.5 mg (Base); 5 mg strength tablets based on (i) acceptable bioequivalence studies on the Eq. 25 mg (Base); 10 mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. 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 abbreviated new drug application (ANDA).