

Draft Guidance on Clorazepate Dipotassium

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Clorazepate Dipotassium

Form/Route: Tablet/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in-vivo
Strength: 15 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: Nordiazepam (N-desmethyldiazepam) has a long terminal elimination half-life, thus consider using a parallel study design. Ensure adequate washout periods between treatments in all crossover studies. An AUC truncated to 72 hours may be used in place of AUC_{0-t} or AUC_∞ for long half-life drug products. Collect sufficient blood samples in the bioequivalence studies to adequately characterize the peak concentration (C_{max}) and time to reach peak concentration (T_{max}). Please refer to the Amiodarone Hydrochloride Tablet Guidance for additional information regarding long half-life drugs.

Tranxene[®] (clorazepate dipotassium) Tablets has an innovator developed Risk Evaluation and Mitigation Strategy (REMS) to inform patients for the increased risk for suicidal thoughts and behavior. All pertinent elements of the REMS must be incorporated into the protocol and informed consent.

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2. Type of study: Fed
Design: Single-dose, two-way crossover in-vivo
Strength: 15 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies.

Analytes to measure (in appropriate biological fluid): Clorazepate and its metabolite, nordiazepam (N-desmethyldiazepam), in both studies. If clorazepate plasma concentrations can be reliably measured and its pharmacokinetic parameters accurately determined, you should analyze the clorazepate data using the confidence interval approach. The nordiazepam (N-desmethyldiazepam) data can be used to provide supportive evidence of comparable therapeutic outcome.

Bioequivalence based on (90% CI): Clorazepate

If clorazepate cannot be reliably measured, you should analyze the Nordiazepam (N-desmethyldiazepam) data obtained from these studies using the confidence interval approach.

Waiver request of in-vivo testing: 3.75 mg and 7.5 mg based on (i) acceptable bioequivalence studies on the 15 mg strength, (ii) acceptable in-vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

Please refer to Mirtazapine Tablet Draft Guidance for additional information regarding waiver of in-vivo testing.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Please 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 application.