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Draft Guidance on Clorazepate Dipotassium

October 2024

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Active Ingredient: Clorazepate dipotassium

Dosage Form: Tablet

Route: Oral

Strengths: 3.75 mg, 7.5 mg, 15 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: 15 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 nordiazepam. Alternatively, a parallel study design may be considered.

Analytes to measure: Clorazepate and its metabolite, nordiazepam (N-desmethyldiazepam)

Bioequivalence based on (90% CI): Clorazepate

If clorazepate plasma concentrations can be reliably measured and its pharmacokinetic parameters accurately determined, applicants 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.

If clorazepate cannot be reliably measured, applicants 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 strengths based on (i) acceptable bioequivalence study on the 15 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*.