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Draft Guidance on Tramadol Hydrochloride

November 2024

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Active Ingredient:	Tramadol hydrochloride
Dosage Form:	Tablet
Route:	Oral
Strengths:	25 mg, 50 mg, 75 mg, 100 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: 100 mg
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: Monitor vital signs (e.g., pulse oximetry and continuous respiratory monitoring) during the study and implement standards and practice for detection and management of respiratory depression. Subjects should be evaluated prior to discharge for cognitive impairment such as drowsiness, dizziness, and confusion and instructed not to drive or operate machinery until their cognitive function returns to baseline level. Tramadol hydrochloride tablet is under a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU), which restricts its use. All pertinent elements of the REMS/ETASU must be incorporated into the protocol and informed consent.

Analyte to measure: Tramadol in plasma

Bioequivalence based on (90% CI): Tramadol

Waiver request of in vivo testing: 25 mg, 50 mg, and 75 mg strengths based on (i) an acceptable bioequivalence study on the 100 mg strength, (ii) acceptable in vitro dissolution testing of all the 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*.