

Draft Guidance on Trazodone Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Trazodone Hydrochloride

Form/Route: Extended Release Tablet/Oral

Recommended studies: 1 Study

1. Type of study: Fasting
Design: Single-dose, two-way crossover in-vivo
Strength: 150 mg
Subjects: Healthy males and nonpregnant females, general population
Additional Comments: Due to safety concerns, the study should be conducted using the 150 mg strength. The following special considerations are recommended for the enrollment criteria of healthy volunteers in the bioequivalence study:
 - Exclude any potential subject taking antihypertensive medications
 - Prohibit azole antifungals, barbiturates, carbamazepine, central nervous system depressants, digoxin, HIV protease inhibitors, phenothiazines, phenytoin, SSRI antidepressants, and warfarin
 - Prohibit alcohol in the study
 - A fed study is not requested. Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed study exemption criteria.

Analytes to measure: Trazodone in plasma

Bioequivalence based on (90% CI): Trazodone

Waiver request of in-vivo testing: 300 mg strength based on (i) an acceptable bioequivalence study on the 150 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity in the formulations across all strengths. Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in-vivo testing.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.

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2 and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

Due to concerns of dose dumping from this drug product when taken with alcohol, please conduct additional dissolution testing on all strengths using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus II (paddle) @ 100 rpm, with and without the alcohol (see below):

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV on both strengths.