

Draft Guidance on Dexmethylphenidate Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Dosage Form; Route: Extended-release capsule, oral

Recommended Studies: Three studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 40 mg
Subjects: Healthy males and non-pregnant females, general population
Additional comments: The fasting bioequivalence (BE) study may be conducted in a single-dose, two-treatment, two-sequence, four-period, replicated design. The 90% confidence intervals (CIs) of the geometric mean test/reference (T/R) ratios for the metrics (C_{max} , AUC_{0-3} , AUC_{3-7} , AUC_{7-12} , $AUC_{0-\infty}$) should fall within the limits of 80-125%.

2. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: 40 mg
Subjects: Healthy males and non-pregnant females, general population
Additional comments: The fed BE study may be conducted in a single-dose, two-treatment, two-sequence, four-period, replicated design. The 90% CIs of the geometric mean T/R ratios for the metrics (C_{max} , AUC_{0-4} , AUC_{4-8} , AUC_{8-12} , $AUC_{0-\infty}$) should fall within the limits of 80-125%. Refer to the amantadine hydrochloride tablet draft guidance for additional information regarding fed studies.

3. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 40 mg
Subjects: Healthy males and non-pregnant females, general population
Additional comments: Fasting study, with contents sprinkled over a spoonful of applesauce in accordance with the approved labeling of the reference listed drug (RLD). The fasting BE study may be conducted in a single-dose, two-treatment, two-sequence, four-period, replicated design. The 90% CIs of the geometric mean T/R ratios for the metrics (C_{max} , AUC_{0-3} , AUC_{3-7} , AUC_{7-12} , $AUC_{0-\infty}$) should fall within the

limits of 80-125%.

Analytes to measure (in appropriate biological fluid): Dexmethylphenidate in plasma

Bioequivalence based on (90% CI): Dexmethylphenidate

Refer to additional comments above for more guidance regarding BE.

Waiver request of in vivo testing: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, and 35 mg strengths based on (i) acceptable BE studies on the 40 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths. Refer to the mirtazapine tablet draft guidance for additional information regarding waivers of in vivo testing.¹

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).

In addition to the method above, for modified-release products, dissolution profiles on 12 dosage units each of test and reference products generated using U.S. Pharmacopoeia (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. 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 the drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the FDA currently requests that additional in vitro dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing conditions: 900 mL, 0.1N HCl, USP apparatus I (basket) at 100 rpm, with and without alcohol

Test 1: 12 units tested according to the proposed method (with 0.1N 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

¹ CFR § 320.24(b)(6)

USP and data collection every 15 minutes for a total of 2 hours

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