

Draft Guidance on Memantine Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Dosage Form; Route: Extended release capsule; oral

Recommended Studies: Three studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover or parallel design in vivo
Strength: 28 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments: Due to the long half-life of this drug, applicants may consider conducting a parallel study. Refer to the *Guidance for Industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (December 2013) for more information on long half-life drugs.

2. Type of study: Fed
Design: Single-dose, two-way crossover or parallel design in vivo
Strength: 28 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments: Same as additional comments above

3. Type of study: Fasting; sprinkle over applesauce
Design: Single-dose, two-way crossover or parallel design in vivo
Strength: 28 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments: Administer the dose after sprinkling the entire contents of the capsule on a teaspoonful of applesauce in accordance with the approved labeling of the reference listed drug (RLD). In addition, see additional comments above.

Analytes to measure: Memantine in plasma

Bioequivalence based on (90% CI): Memantine

Waiver request of in vivo testing: 7 mg, 14 mg, and 21 mg based on (i) acceptable bioequivalence studies on the 28 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 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 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 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 Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing conditions: 900 mL, pH 1.2 buffer (simulated gastric fluid, without enzyme), USP apparatus 1 (basket) @ 100 rpm, with or without alcohol

Test 1: 12 units tested according to the proposed method (with pH 1.2 buffer, simulated gastric fluid without enzyme), 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.