

Draft Guidance on Donepezil Hydrochloride; Memantine Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Donepezil hydrochloride; Memantine hydrochloride

Dosage Form; Route: Extended-release capsule; oral

Recommended Studies: Three in vivo studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover or parallel design in vivo
Strength: 10 mg; 28 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments:
 - A. The most frequent adverse events leading to drug discontinuation are nausea and vomiting. Co-administer an anti-emetic drug as needed during the in vivo bioequivalence (BE) study. Ensure that there is no drug-drug interaction between the anti-emetic drug and donepezil or memantine, and that the anti-emetic drug does not interfere with the bioanalytical method used to analyze donepezil or memantine plasma concentrations. In addition, include appropriate safety precautions in the study protocols, adequate monitoring of vital signs, adverse events, stopping criteria and appropriate evaluation and management of adverse events. Assure that the investigator(s) will be vigilant in recognizing and managing any unacceptable clinical or laboratory findings.
 - B. Due to the long half-life of both active ingredients, 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: 10 mg; 28 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments: Same as comments above

3. Type of study: Fasting; sprinkle over applesauce
Design: Single-dose, two-way crossover or parallel design in vivo
Strength: 10 mg; 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 (in appropriate biological fluid): Donepezil and memantine in plasma

Bioequivalence based on (90% CI): Donepezil and memantine

Waiver request of in vivo testing: 10 mg/14 mg strengths based on (i) acceptable BE studies on the 10 mg/28 mg strengths, (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 Web site, 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, applicants should submit dissolution profiles on 12 dosage units each of test and reference products generated using U.S Pharmacopeia (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). 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: Volume: 900 mL, pH 1.2 buffer, Apparatus I (Basket)@100 rpm, with and without the alcohol

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

Test 2: Twelve 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: Twelve 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: Twelve 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.