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Draft – Not for Implementation

Draft Guidance on Donepezil Hydrochloride; Memantine Hydrochloride

August 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredients:	Donepezil hydrochloride; Memantine hydrochloride
Dosage Form:	Capsule, extended release
Route:	Oral
Strengths:	10 mg; 7 mg, 10 mg; 14 mg, 10 mg; 21 mg, 10 mg; 28 mg
Recommended Studies:	Three in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strengths: 10 mg; 28 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: An antiemetic drug may be administrated as needed during the in vivo bioequivalence study. Ensure that there is no drug-drug interaction between the antiemetic drug and donepezil or memantine, and that the antiemetic drug does not interfere with the bioanalytical method used to analyze donepezil or memantine plasma concentrations. Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of memantine. Alternatively, a parallel study design may be considered.

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strengths: 10 mg; 28 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: See comments above.

3. Type of study: Fasting, sprinkle in applesauce
Design: Single-dose, two-treatment, two-period crossover or parallel design in vivo
Strength: 10 mg; 28 mg
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: Mix the entire contents of the capsule on one teaspoon of applesauce and administer the full amount to the subject. See comments above.

Analytes to measure: Donepezil and memantine in plasma

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

Additional strengths: Bioequivalence of the 10 mg; 7 mg, 10 mg; 14 mg, and 10 mg; 21 mg strengths to the corresponding reference listed drug (RLD) strengths may be demonstrated based principles laid out in the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.[a]

Dissolution test method and sampling times: For modified release drug products, applicants should develop specific discriminating dissolution methods. Alternatively, applicants may use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA's database, http://www.accessdata.fda.gov/scripts/cder/dissolution/, provided that applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed, submit the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for each strength of the test and RLD products. Specifications will be determined upon review of the abbreviated new drug application.

In addition to the method above, submit dissolution profiles on 12 dosage units for each strength of the test and reference standard generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (e.g., pH 1.2, 4.5, and 6.8 buffer). Agitation speeds may 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.

Alcohol dose dumping studies: Not applicable

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.