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Draft Guidance on Donepezil Hydrochloride

November 2021

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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In April 2010, FDA issued a draft product-specific guidance for industry on generic donepezil hydrochloride. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient:	Donepezil hydrochloride
Dosage Form; Route:	Tablet, orally disintegrating; oral
Recommended Studies:	Two options: Biopharmaceutics Classification System (BCS) based waiver or two in vivo studies

I. BCS Class 1-based biowaiver option:

A waiver request of in vivo testing for this product may be considered provided that the appropriate documentation regarding high solubility, high permeability and rapid dissolution as detailed in the ICH guidance for industry on *M9 Biopharmaceutics Classification System-Based Biowaivers* is submitted in the application. Applicants may use information contained in the approved labeling of the reference product. Peer-reviewed articles may not contain the necessary details of the testing for the FDA to make a judgment regarding the quality of the studies. A

decision regarding the acceptability of the waiver request will be made upon assessing the data submitted in the application.

II. In vivo bioequivalence study option:

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 10 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: The orally disintegrating tablet should be placed on the tongue, allowed to disintegrate, and swallowed with water. The most frequent adverse events leading to drug discontinuation are nausea and vomiting. Consider co-administering an anti-emetic drug in the in vivo bioequivalence study. Ensure that there is no drug-drug interaction between the anti-emetic drug and donepezil, and that the anti-emetic drug does not interfere with the bioanalytical method used to analyze donepezil plasma concentrations. Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of donepezil. Alternatively, a parallel study design may be considered.

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 10 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: See comments above

Analyte to measure: Donepezil in plasma

Bioequivalence based on (90% CI): Donepezil

Waiver request of in vivo testing: 5 mg based on (i) acceptable bioequivalence studies on the 10 mg strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between both strengths.

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of both strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

Revision History: Recommended May 2007; Finalized May 2008; Revised April 2010, November 2021

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