

Draft Guidance on Donepezil Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Tablet/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in-vivo
Strength: 23 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. You may co-administer an anti-emetic drug as needed during the in vivo bioequivalence study. Please 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. In addition, please include appropriate safety precautions in your protocols. These include adequate monitoring of vital signs, adverse events, stopping criteria and appropriate evaluation and management of adverse events. Please assure that the investigator(s) will be vigilant in recognizing and managing any unacceptable clinical or laboratory findings.
 - B. Donepezil has a long terminal elimination half-life. Please ensure adequate washout periods between treatments in the crossover studies. You may also consider using a parallel study design due to donepezil's long half-life. For long half-life drug products, an AUC truncated to 72 hours may be used in place of AUC_{0-t} or $AUC_{0-\infty}$. Please collect sufficient blood samples in the bioequivalence studies to adequately characterize the peak concentration (C_{max}) and time to reach peak concentration (t_{max}).

2. Type of study: Fed
Design: Single-dose, two-way crossover in-vivo
Strength: 23 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: Please see the posted Amantadine guidance for additional information regarding fed studies.

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

Bioequivalence based on (90% CI): Donepezil

Waiver request of in-vivo testing: Not Applicable

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Please 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 application.