Contains Nonbinding Recommendations

Draft Guidance on Rivastigmine Tartrate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Capsule; oral

Recommended Studies: Two options: BCS waiver or in vivo studies

I. Biopharmaceutics Classification System waiver option:

It may be possible to request a waiver of in vivo testing for all the strength of this product, provided that the appropriate documentation regarding high solubility, high permeability, and rapid dissolution as detailed in the Guidance for Industry: Waiver of In vivo Bioavailability and Bioequivalence for Immediate- Release Solid Oral Dosage Forms Based on the Biopharmaceutics Classification System is submitted in the application. You 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 Agency to make a judgment regarding the quality of the studies. A decision regarding the acceptability of the waiver request can only be made upon review of the data submitted in the application.

II. In vivo options:

1. Type of study: Fasting
   Design: Single-dose, two-way, crossover in vivo
   Strength: 1.5 mg
   Subjects: Healthy males and nonpregnant females, general population
   Additional Comments: N/A

2. Type of study: Fed
   Design: Single-dose, two-way, crossover in vivo
   Strength: 1.5 mg
   Subjects: Healthy males and nonpregnant females, general population
   Additional Comments: Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies.

3. Type of study: Fed
   Design: Single-dose, two-way, crossover in vivo
   Strength: 6 mg

Subject: For safety reasons, the study should be conducted in patients who are already receiving a stable twice-daily dose of 6 mg as described in the reference product label.

Additional Comments: Due to short half-life of rivastigmine and its metabolites (≤ 2 hour), the test and reference product may be dosed on two consecutive days. If the products are administered on two consecutive days, the test product and reference listed drug (RLD) treatments should be administered at the same time of the day, e.g., both in the morning, of Day 1 (Period I of the study) and Day 2 (Period II of the study). Since the patients are on a twice-daily dosing regimen, the patients should receive their usual dose of rivastigmine as per their dosing regimen between the two periods. The drug product used to administer the dose between the two periods does not have to be the same as that used in the first study period; it can be the same as that used by the patients for their current dosing regimen.

No change in dose or regimen should be made for the purpose of the bioequivalence study.

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

Bioequivalence based on (90% CI): Rivastigmine

Waiver request of in-vivo testing: 3 mg strength based on (i) acceptable bioequivalence studies on the 1.5 mg strength, (ii) acceptable in vitro dissolution testing on the 1.5 mg and 3 mg strengths, and (iii) proportional similarity in the formulations of the 1.5 mg and 3 mg strengths.

4.5 mg strength based on (i) acceptable bioequivalence study on the 6 mg strength, (ii) acceptable in vitro dissolution testing on the 4.5 mg and 6 mg strengths, and (iii) proportional similarity in the formulations of the 4.5 mg and 6 mg strengths.

Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in vivo testing.

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 the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.