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Draft Guidance on Rivastigmine Tartrate

October 2024

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Active Ingredient:	Rivastigmine tartrate
Dosage Form:	Capsule
Route:	Oral
Strengths:	EQ 1.5 mg Base, EQ 3 mg Base, EQ 4.5 mg Base, EQ 6 mg Base
Recommended Studies:	Two options: (1) Biopharmaceutics Classification System (BCS)-based biowaiver or (2) two in vivo bioequivalence studies with pharmacokinetic endpoints

I. Option 1: BCS Class I-based biowaiver

A waiver request of in vivo testing for all the strengths of this product may be considered provided that the appropriate documentation regarding high solubility, high permeability and rapid dissolution as detailed in the most recent version of the FDA guidance for industry on *M9 Biopharmaceutics Classification System-Based Biowaivers*[a] is submitted in the application. Applicants may use the information contained in the approved labeling of the reference listed drug (RLD). 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 assessment of the data submitted in the application.

II. Option 2: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 1.5 mg Base
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: None

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 6 mg Base
   Subjects: Patients who are already receiving a stable twice-daily dose of EQ 6 mg Base as described in the RLD 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 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.

Analyte to measure: Rivastigmine in plasma

Bioequivalence based on (90% CI): Rivastigmine

Waiver request of in vivo testing: EQ 3 mg Base strength based on (i) acceptable bioequivalence study on the EQ 1.5 mg Base strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations across both strengths

EQ 4.5 mg Base strength based on (i) acceptable bioequivalence study on the EQ 6 mg Base strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations across 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 for each of all strengths of the test product and RLD.[1] Specifications will be determined upon review of the abbreviated new drug application.

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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.

[1] If the RLD is not available, refer to the most recent version of the FDA guidance for industry on *Referencing Approved Drug Products in ANDA Submissions.*