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Draft Guidance on Levetiracetam

October 2024

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Active Ingredient:	Levetiracetam
Dosage Form:	Tablet, for suspension
Route:	Oral
Strengths:	250 mg, 500 mg, 750 mg, 1 gm
Recommended Studies:	Two options: (1) Biopharmaceutics Classification System (BCS)-based biowaiver or (2) one in vivo bioequivalence study with pharmacokinetic endpoints

See "Important Administration Instruction" in the currently approved drug labeling. Proposed generic drugs are expected to meet both methods of administration as described in the drug labeling.

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: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 1 gm
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: FDA recommends the primary method of administration (allow to disintegrate in the mouth with a sip of water before swallowing) as described in the approved drug labeling for the recommended bioequivalence studies.

Analyte to measure: Levetiracetam in plasma

Bioequivalence based on (90% CI): Levetiracetam

Waiver request of in vivo testing: 250 mg, 500 mg, and 750 mg strengths based on (i) acceptable bioequivalence study on the 1 gm strength, (ii) acceptable in vitro multimedia dissolution testing (pH 1.2, 4.5, 6.8) of all strengths, and (iii) proportional similarity of the formulations across all 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] For bio-waiver of the lower strengths, dissolution profiles on 12 dosage units each of test and RLD generated using USP Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application.

In addition to the method above, disintegration testing should be used for quality control instead of dissolution testing for Levetiracetam Tablets for Oral Suspension. The disintegration specification 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.*