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Draft Guidance on Lithium Carbonate

May 2023

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Active Ingredient: Lithium carbonate

Dosage Form; Route: Tablet; Oral

Recommended Studies: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, four-way, fully replicate crossover in vivo
   Strength: 300 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: This drug product is classified as a narrow therapeutic index drug. See the Explanation section for further information.

2. Type of study: Fed
   Design: Single-dose, four-way, fully replicate crossover in vivo
   Strength: 300 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: See comments above.

Analyte to measure: Lithium in plasma

Bioequivalence based on (90% CI): Lithium

Waiver request of in vivo testing: Not applicable

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

Explanation: FDA has concluded that lithium is a narrow therapeutic index drug based on the following evidence:

- The range between the effective lithium concentrations and the concentrations associated with serious toxicity is narrow.
- Sub-optimal lithium concentrations lead to severe therapeutic failure or toxicity.
- Lithium is subject to therapeutic drug monitoring based on pharmacokinetics measures.
- Lithium exhibits low-to-moderate within-subject variability.

The in vivo bioequivalence studies should be of a fully replicate crossover design to:

- Scale bioequivalence limits to the variability of the reference product.
- Compare test and reference product within-subject variability.

For details about the method for statistical analysis using the reference-scaled average bioequivalence approach for narrow therapeutic index drugs, refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.[a]

Revision History: Recommended February 2010; Revised May 2023

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[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.