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Draft Guidance on Carbamazepine

August 2022

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This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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This is a new draft product-specific guidance for industry on generic carbamazepine.

Active Ingredient: Carbamazepine

Dosage Form; Route: Tablet, chewable; oral

Recommended Studies: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-sequence, four-period, fully replicate crossover in vivo
   Strength: 200 mg
   Subjects: Healthy males and female subjects not of reproductive potential
   Additional comments: The tablet should be chewed, then swallowed with water. This drug product is classified as a narrow therapeutic index (NTI) drug. See the Explanation section for further information.

2. Type of study: Fed
Design: Single-dose, two-treatment, two-sequence, four-period, fully replicate crossover in vivo
Strength: 200 mg
Subjects: Healthy males and female subjects of not of reproductive potential
Additional comments: See comments above.

Analyte to measure: Carbamazepine in plasma

Bioequivalence based on (90% CI): Carbamazepine

Waiver request of in vivo testing: 100 mg strength based on (i) acceptable bioequivalence studies on the 200 mg strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between 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 both strengths of the test and reference products. Specifications will be determined upon evaluation of the ANDA.

If any strength of the tablet product has a functional score, additional dissolution profile testing should be conducted for each segment of the split tablet after manual and mechanical splitting as per the most recent version of the FDA guidance for industry on *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*.[a]

Explanation: FDA has concluded that carbamazepine is an NTI drug based on the following evidence:

- The range between the effective carbamazepine concentrations and the concentrations associated with serious toxicity is narrow
- Sub-optimal carbamazepine concentrations lead to severe therapeutic failure or toxicity
- Carbamazepine is subject to therapeutic drug monitoring based on pharmacokinetics measures
- Carbamazepine has low-to-moderate within-subject variability
- Dose adjustments are in small increments in clinical practice

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 NTI 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]

Unique Agency Identifier: PSG_018281

[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.