

Draft Guidance on Carbamazepine

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Carbamazepine

Dosage Form; Route: Extended-release tablets; oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-sequence, four-period, fully replicated crossover in vivo
Strength: 400mg
Subjects: Normal healthy males and nonpregnant females, general population
Additional comments: Only females who are either surgically sterile or practicing an adequate method of contraception should be included in the bioequivalence (BE) study. The applicant should use the reference-scaled average BE approach for carbamazepine.

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2. Type of study: Fed
Design: Single-dose, two-treatment, two-sequence, four-period, fully replicated crossover in vivo
Strength: 400mg
Subjects: Normal healthy males and nonpregnant females, general population
Additional comments: Same as above
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Analytes to measure: Carbamazepine in plasma

Bioequivalence based on (90% CI): Carbamazepine

Waiver request of in vivo testing: In vivo BE studies for the 100 mg and 200 mg strengths may not be needed based on (i) acceptable BE studies for the 400 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths. Refer to the mirtazapine tablet draft guidance for additional information regarding waivers of in vivo testing.

Dissolution test method and sampling times: Note that a Dissolution Methods Database is available to the public on the FDA website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm>. Dissolution information for this product is available on this website. Conduct comparative dissolution testing on 12 dosage

units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

In addition to the method above, for modified-release products, dissolution profiles on 12 dosage units each of the test and reference products generated using U.S. Pharmacopoeia (USP) Apparatus I at 100 rpm and/or 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. Agitation speeds may be increased, if necessary. It is acceptable to add a small amount of surfactant, if necessary. Include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

Explanation: FDA has concluded that carbamazepine is a narrow therapeutic index (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 doses or concentrations lead to therapeutic failure or severe toxicity
- Carbamazepine is subject to therapeutic monitoring based on pharmacokinetics measures
- Carbamazepine has low-to-moderate within-subject variability

The study should be a fully replicated crossover design in order to:

- Scale BE limits to the variability of the reference product
- Compare test and reference products' within-subject variability

For information about the Method for Statistical Analysis Using the Reference-Scaled Average Bioequivalence Approach for NTI drugs, refer to the draft guidance on warfarin sodium.