Contains Nonbinding Recommendations

Draft Guidance on Carbamazepine

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Suspension; 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: 100mg/5 mL
   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: 100mg/5mL
   Subjects: Normal healthy males and nonpregnant females, general population
   Additional comments: Same as above

Analytes to measure: Carbamazepine in plasma

Bioequivalence based on (90% CI): Carbamazepine

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. 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 abbreviated new drug application (ANDA).

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 the test and reference products' within-subject variability

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Method for Statistical Analysis Using the Reference-Scaled Average Bioequivalence Approach for NTI drugs, refer to the draft guidance on warfarin sodium.