Contains Nonbinding Recommendations

Draft Guidance on Carbamazepine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Carbamazepine

Dosage Form; Route: Tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, 2-treatment, 2-sequence, 4-period, fully replicated crossover in vivo
   Strength: 200mg
   Subjects: Normal healthy males and nonpregnant females, general population
   Additional comments: Only females who are either surgically sterile or practicing a recognized, safe method of contraception should be included in a study. The applicant should use the reference-scaled average bioequivalence (BE) approach for carbamazepine.

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2. Type of study: Fed
   Design: Single-dose, 2-treatment, 2-sequence, 4-period, fully replicated crossover in vivo
   Strength: 200mg
   Subjects: Normal healthy males and nonpregnant females, general population
   Additional comments: Same as comments above

Analytes to measure: Carbamazepine in plasma

Bioequivalence based on (90% CI): Carbamazepine

Waiver request of in vivo testing: If an applicant desires to develop the entire product line (100 mg, 200 mg, 300 mg, and 400 mg), separate in vivo BE studies should be conducted with both 200 mg and 400 mg strengths, and reference the RLDs for this guidance. Questions related to selection of an RLD for a development program may be submitted to OGD as controlled correspondence.

In vivo BE study requirements for the 100 mg strength may be waived based on (i) acceptable BE studies on the 200 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

In vivo BE study requirements for the 300 mg strength may be waived based on (i) acceptable BE studies on 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 guidance for additional information regarding waivers of in vivo testing.

Dissolution test method and sampling times: A Dissolution Methods Database is available to the public at the FDA Web site at http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm. The dissolution information for this product is available at this Web site. 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.

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 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 guidance on warfarin sodium.