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Draft Guidance on Carbamazepine

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Extended-release capsules; oral

Recommended Studies: Three studies

1. Type of study: Fasting
   Design: Single-dose, 2-treatment, 2-sequence, 4-period, fully replicated crossover in vivo
   Strength: 300mg
   Subjects: Normal healthy males and females, general population
   Additional comments: Female subjects should not be enrolled in bioequivalence (BE) studies of carbamazepine if they are pregnant. Only females who are either surgically sterile or practicing a recognized safe method of contraception should be included in a study. You should clearly define in the study protocol what is considered a safe method of contraception. The applicant should use the reference-scaled average BE approach for carbamazepine.

   BE studies conducted for this product may be referenced to support evidence of in vivo BE for generic products referencing Equetro. Submit separate applications for each reference listed drug (RLD).

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2. Type of study: Fed
   Design: Single-dose, 2-treatment, 2-sequence, 4-period, fully replicated crossover in vivo
   Strength: 300mg
   Subjects: Normal healthy males and females, general population
   Additional comments: Same as above

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3. Type of study: Fasting (capsule sprinkled on a spoonful of applesauce)
   Design: Single-dose, 2-treatment, 2-sequence, 4-period, fully replicated crossover in vivo
   Strength: 300 mg
   Subjects: Normal healthy males and 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:

In vivo BE studies for the 100 mg and 200 mg strengths may not be necessary based on (i) acceptable BE studies on the 300 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: 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).

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; and
- Compare test and reference products' within-subject variability.

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the "Method for Statistical Analysis Using the Reference-Scaled Average Bioequivalence Approach" for NTI drugs, see the draft guidance on warfarin sodium.