Contains Nonbinding Recommendations

Draft Guidance on Cyclosporine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Cyclosporine

Dosage Form; Route: Capsule (modified); 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: 100 mg
   Subjects: Normal healthy males and females (nonpregnant), general population
   Additional comments: None.

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2. Type of study: Fed
   Design: Single-dose, 2-treatment, 2-sequence, 4-period, fully replicated crossover in vivo
   Strength: 100 mg
   Subjects: Normal healthy males and females (nonpregnant), general population
   Additional comments: None

Analytes to measure: Cyclosporine in plasma or whole blood

Bioequivalence based on (90% CI): Cyclosporine

Waiver request of in vivo testing:

In vivo bioequivalence (BE) studies for the 25 mg strength may not be necessary based on (i) acceptable BE studies on the 100 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 Refer to the mirtazapine tablet draft guidance for additional information regarding waivers of in vivo testing.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.

Explanation: FDA has concluded that cyclosporine is a narrow therapeutic index (NTI) drug based on the following evidence:

- The range between the effective cyclosporine concentrations and the concentrations associated with serious toxicity is narrow.
- Sub-optimal doses or concentrations lead to therapeutic failure or severe toxicity.
- Cyclosporine is subject to therapeutic monitoring based on pharmacokinetics measures.
- Cyclosporine 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 guidance on warfarin sodium.