Contains Nonbinding Recommendations

Draft Guidance on Everolimus

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, 4-way, fully replicated crossover design in vivo
   Strength: 0.75 mg
   Subjects: Healthy males and females (nonpregnant), general population
   Additional comments: 1. Applicants may consider using the reference-scaled average bioequivalence approach for everolimus. 2. This recommendation is for everolimus tablets for transplant use only. The 2.5 mg, 5 mg, 7.5 mg, and 10 mg everolimus tablets for oncology use are not covered in the current recommendation.

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2. Type of study: Fed
   Design: Single-dose, 4-way, fully replicated crossover design in vivo
   Strength: 0.75 mg
   Subjects: Healthy males and females (nonpregnant), general population
   Additional comments: Please see additional comments above.

Analytes to measure (in appropriate biological fluid): Everolimus in whole blood

Bioequivalence based on (90% CI): Everolimus

Waiver request of in vivo testing: 0.25 mg and 0.5 mg based on (i) acceptable bioequivalence studies on the 0.75 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulation across all strengths

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 everolimus is a narrow therapeutic index (NTI) drug based on the following evidence:

- The range between therapeutic and toxic concentrations of everolimus is narrow
- Sub-therapeutic concentrations lead to serious therapeutic failure
- Everolimus is subject to therapeutic drug monitoring based on pharmacokinetic measures
- Everolimus has low-to-moderate within-subject variability; and
- Doses are adjusted in small increments (less than 20%) in clinical practice

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

- Scale bioequivalence limits to the variability of the reference product; and
- Compare test and reference product within-subject variability

For details about "Method for Statistical Analysis Using the Reference-Scaled Average Bioequivalence Approach for narrow therapeutic index drugs," please refer to the guidance on warfarin sodium.