Contains Nonbinding Recommendations

Draft Guidance on Sirolimus

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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: 2 mg
   Subjects: Healthy males and nonpregnant females, general population
   Additional comments: Due to the long half-life, the blood sampling time can be truncated at 72 hours (AUC_{0-72}). Applicants may consider using the reference-scaled average bioequivalence (BE) approach for sirolimus.

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

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

Bioequivalence based on (90% CI): Sirolimus

Waiver request of in vivo testing: 0.5 mg and 1 mg based on (i) acceptable BE studies on the 2 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations 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 Web site, 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 sirolimus is a narrow therapeutic index (NTI) drug, based on the following evidence:

- The range between sirolimus therapeutic and toxic sirolimus whole blood concentrations is narrow
- Some sirolimus toxicities are serious and/or irreversible
- Subtherapeutic sirolimus concentrations may lead to morbidity/mortality associated with graft rejection
- Sirolimus requires individual dose titration to achieve a satisfactory balance between maximizing efficacy and minimizing serious dose-related toxicity
- Therapeutic drug monitoring is routinely employed to facilitate sirolimus dose titration
- Sirolimus has small-to-medium 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, see the draft guidance on warfarin sodium.