

Contains Nonbinding Recommendations
Draft Guidance on Everolimus

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Everolimus

Form/Route: Tablets/Oral

Recommended studies: 1 study

Type of study: Steady state

Design: Steady state, two-treatment, two-period crossover or parallel *in vivo* study

Strength: 10 mg tablet dosed once daily administered consistently with food or consistently without food

Subjects: Patients who are already receiving the drug at a dose of 10 mg once a day as their individual therapy and continuing on the same dose for both periods of the crossover or parallel study.

Additional Comments: 1) This recommendation is for Everolimus tablets for oncology use only. The 0.25-mg, 0.5-mg, and 0.75-mg Everolimus tablet for transplant use is not covered in the current recommendation, 2) We recommend the 10-mg tablets be swallowed in whole with a glass of water (approximately 240 mL), 3) Due to the long mean half-life (30 hrs), blood sampling for bioequivalence analysis should allow sufficient time on each product (test or reference) to assure attainment of steady state. Attainment of steady state should be demonstrated based on several consecutive trough levels, 4) Blood sampling for bioequivalence should consist of appropriate sampling times over a 24 hr period following attainment of steady state, 5) Women of childbearing potential should be advised to use an effective method of contraception while using everolimus and for up to 8 weeks after ending treatment, 6) Females should not be breastfeeding, 7) The study should be designed around each patient's existing 10 mg dose everolimus regimen, 8) No changes in dose or regimen should be made for the purpose of the bioequivalence study.

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

Bioequivalence based on (90% CI): Everolimus

Waiver request of *in-vivo* testing: 2.5 mg, 5 mg, and 7.5 mg based on (i) acceptable bioequivalence studies on the 10 mg strength, (ii) proportional similarity of all strengths, and (iii) acceptable *in vitro* dissolution testing across all strengths.

Dissolution test method and sampling times: Please note that a **Dissolution Method Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Please find the dissolution information for this product at this website. Please 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.