Contains Nonbinding Recommendations

Draft Guidance on Betrixaban

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Capsule; 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: 80 mg
   Subjects: Healthy males and non-pregnant females

   Additional comments:

   Betrixaban is likely to have a steep exposure-response relationship for both efficacy and safety. Therefore, applicants should not use the reference-scaled average bioequivalence approach to widen the BE limits for betrixaban bioequivalence evaluation. Applicants should use the average bioequivalence approach with BE limits of 80-125%. The within-subject variability of test and reference products should be compared and the upper limit of the 90% confidence interval for the test-to-reference ratio of the within-subject variability should be $\leq$ 2.5. For details about the Method for Statistical Analysis comparing within-subject variability of test and reference products, refer to Guidance on Warfarin Sodium.

   All subjects should be tested on Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), Creatinine Clearance (CrCL), and liver function. The PT, aPTT and liver function results should be within normal range and the CrCL value should be more than 50 mL/min for all subjects before dosing to prevent or avoid the possibility of bleeding.

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2. Type of study: Fed
   Design: Single-dose, 2-treatment, 2-sequence, 4-period, fully replicated crossover in vivo
   Strength: 80 mg
   Subjects: Healthy males and non-pregnant females

Analytes to measure (in appropriate biological fluid): Betrixaban in plasma

Bioequivalence based on (90% CI): Betrixaban

Waiver request of in vivo testing: 40 mg based on (i) acceptable bioequivalence studies on the 80 mg strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between both 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 both strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.