Contains Nonbinding Recommendations

Draft Guidance on Rivaroxaban

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-sequence, four-period, fully replicate crossover in vivo
   Strength: 20 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: Due to the risk of bleeding, conduct a testing on prothrombin time (PT), activated partial thromboplastin time (aPTT), and creatinine clearance (CrCl). Exclude subjects with PT and aPTT results above the normal range, and the CrCl value less than 50 mL/min.

   Rivaroxaban demonstrates a steep exposure-response relationship for both efficacy and safety; therefore, use the average bioequivalence approach with bioequivalence limits of 80.00-125.00% without reference scaling. 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 ≤ 2.5. For details about the Method for Statistical Analysis comparing within-subject variability of test and reference products, refer to the guidance on warfarin sodium tablet.

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-sequence, four-period, fully replicate crossover in vivo
   Strength: 20 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: See comments above

Analyte to measure: Rivaroxaban in plasma

Bioequivalence based on (90% CI): Rivaroxaban

Waiver request of in vivo testing: 2.5 mg, 10 mg and 15 mg strengths based on (i) acceptable BE studies on the 20 mg strength, (ii) proportional similarity across all strengths, and (iii) acceptable in vitro dissolution testing of 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 for each of all strength of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

Product-specific testing conditions for in vitro feeding tube studies: The reference product can be administered via a nasogastric (NG) or gastric (G) tube. Therefore, conduct the in vitro feeding tube studies including comparative recovery testing and sedimentation volume testing. Take precautions to not inhale powder when crushing the tablets in the preparation of feeding tube administration. Refer to the Lansoprazole Delayed-Release Orally Disintegrating Tablet Guidance for additional information regarding procedures of in vitro feeding tube studies.

Testing tube: NG tube (8 French), G tube (12 French)

Testing strength: 20 mg

Dispersion medium: 50 mL water

Incubation times: 0 and 4 h