

Draft Guidance on Rivaroxaban

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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, 2-treatment, 2-sequence, 4-period, fully replicated crossover in vivo
Strength: 20 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments: All subjects should be tested on prothrombin time (PT), activated partial thromboplastin time (aPTT), and creatinine clearance (CrCl). The PT and aPTT results should be within normal range, and the CrCl value should be more than 50 mL/min for all subjects before dosing in order to prevent or avoid the possibility of bleeding.

Rivaroxaban demonstrated a steep exposure-response relationship for both efficacy and safety; therefore applicants should not use the reference-scaled average bioequivalence (BE) approach to widen the BE limits for rivaroxaban BE evaluation. Applicants should use the average BE approach with BE limits of 80-125%. The within-subject variability of test (T) and reference (R) 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.

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2. Type of study: Fed
Design: Single-dose, 2-treatment, 2-sequence, 4-period, fully replicated crossover in vivo
Strength: 20 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments: Same as comments above
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Analytes to measure (in appropriate biological fluid): Rivaroxaban in plasma

Bioequivalence based on (90% CI): Rivaroxaban

Waiver request of in vivo testing: 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: A Dissolution Methods Database is available to the public at the FDA Web site at <http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm>. The dissolution information for this product is available at this Web site. 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.

Additional Nasogastric and Gastronomy Tube In Vitro Studies:

In addition, according to the labeling, the product may also be crushed and suspended in 50 mL of water and administered via a nasogastric (NG) tube or gastric feeding tube. Therefore, applicants should conduct in vitro studies with NG tube and gastrostomy (G) tube as follows:

1. Determine comparative sedimentation depth (volume of sediment) of the suspension using 12 units each of the test and the reference products, for the 20 mg strength, in 50 ml of water at “0” (after gentle shaking for 30 seconds) and 15 min.
 - a) Crush the tablet and suspend in 50 mL of water. Prepare the catheter tip syringe, remove the syringe plunger, and transfer the suspension into the syringe. Insert the syringe plunger and gently rotate the syringe.
 - b) Place the syringe perpendicular to the bench with the tip up and record sedimentation depth (volume of sediment) at 0 min.
 - c) Using a new set of 12 units, repeat the process described in step (a) to prepare the suspension, then incubate for 15 min and record the sedimentation depth (volume of sediment).

Use the markings on the syringe to note the sedimentation depth (volume of sediment). Provide a qualitative description, e.g., particle aggregation and particles adhering to the syringe walls. Take photos of the contents of the syringe at various intervals throughout the testing process.

2. Determine the comparative particle size of the suspension using 12 units of 20 mg strength of the test and the reference products after delivery to the container through a combination of syringe and the 16 French nasogastric tube at 0 and 15 minutes as follows:
 - a) Prepare the feeding tube according to the manufacturer’s directions. Repeat the process described in 1(a) to prepare the suspension.
 - b) Attach the syringe to the feeding tube; then, using the syringe plunger, push the suspension through the syringe and the feeding tube into a collection container.

c) Perform particle size analysis of the collected fluid.

d) Repeat the testing described above with a fresh set of 12 units; except, after preparing the suspension in step a, wait 15 minutes before injecting the contents into the feeding tube.

Provide all particle size data at D10, D50, and D90 levels. Visually examine the tubing and the syringe for any aggregation, adherence, clogging, etc., report all the observations, and submit supporting photographs. Determine particle size using the method of laser diffraction or any method that is sufficiently reproducible and sensitive.

3. Conduct the comparative recovery studies of suspension of rivaroxaban from 1) a combination of oral syringe and 16 French nasogastric tube, and 2) a combination of funnel and G tube (the smallest gauge that may be used for this product, e.g., 16 FR) using at least 12 units of the test and the reference products of 20 mg strength in 50 ml water. Determine the percentage of rivaroxaban recovered at the NG tube and the G tube exit relative to the initial dose for both the test and the reference products at 0 min and 15 min. The T/R recovery ratio and the 90% confidence interval of the T/R recovery ratio should be calculated.
4. Submit standard operating procedures for sedimentation, particle size, and recovery testing. Include details about the tube and syringe used (e.g., material, brand, size, etc.), holding positions of the tube, shaking method, analytical site, testing dates, etc., for each of the studies. Submit individual data, mean values, standard deviations, and coefficient of variation (%CV) of each study in an Excel file. Photographs should be submitted to support your observations and results. Also provide the pre-study and within-study assay validation report. Conduct all the above testing on unexpired test and reference batches.

Additional comments: Take precautions to not inhale powder when crushing the tablet.