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Draft – Not for Implementation

Draft Guidance on Rivaroxaban

February 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Rivaroxaban

Dosage Form: For suspension

Route: Oral

Strength: 1 mg/mL

Recommended Studies: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-sequence, four-period, fully replicate crossover in vivo
   Strength: 1 mg/mL at the dose of 20 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Exclude subjects with abnormal coagulation tests (e.g., prolonged prothrombin time or activated partial thromboplastin time). Exclude subjects who have recently undergone or plan to undergo any surgery or dental procedure prior to or during the study.

   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 most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application*.[a]

2. Type of study: Fed
Design: Single-dose, two-treatment, two-sequence, four-period, fully replicate crossover in vivo
Strength: 1 mg/mL at the dose of 20 mg
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: See comments above.

Analyte to measure: Rivaroxaban in plasma

Bioequivalence based on (90% CI): Rivaroxaban

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units for each of the test and reference products. Note that a dosage unit for a suspension is the labeled strength (1 mL). Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Product-specific testing conditions for in vitro feeding tube studies: The approved labeling for the reference product states that the product may be administered by a nasogastric (NG) or percutaneous endoscopic gastrotomy (G) tube. Conduct the in vitro feeding tube studies, including comparative recovery testing, sedimentation volume and redispersibility testing, and in-use stability in designated dispersion media (i.e., water). For general procedures of in vitro feeding tube studies, refer to the most recent version of the FDA guidance for industry on *Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations*.[a]

Testing tubes: NG tube (6 French) and G tube (12 French)

1. Three types of tube configurations including different materials and/or different designs, with at least one G tube tested with an inflated balloon design
2. Repeated administration

Sedimentation volume and redispersibility testing

Particle size distribution study

Testing strength: 1 mg/mL at the dose of 20 mg

Additional information:

Device:
The reference listed drug (RLD) is presented in a bottle co-packaged with a bottle adapter and two oral syringes. The oral syringes are the device constituent parts.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD devices when designing the test devices including:

- Volume markings
- Dose markings

User interface assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

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Unique Agency Identifier: PSG_215859

[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.