

Draft Guidance on Edoxaban Tosylate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-sequence, four-period, fully replicated crossover in vivo
Strength: EQ 60 mg Base
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: All subjects should be tested on prothrombin time (PT), activated partial thromboplastin time (aPTT), creatinine clearance (CrCL) and body weight (BW). The PT and aPTT results should be within normal range, the CrCL value should be more than 50 mL/min and BW should be more than 60 kg for all subjects before dosing in order to prevent or avoid the possibility of bleeding.

Edoxaban demonstrated a steep exposure-response relationship for safety; therefore, applicants should not use the reference-scaled average bioequivalence approach to widen the bioequivalence limits. Use the average bioequivalence approach with bioequivalence limits of 80.00- 125.00%. The within-subject variability of test and reference products should be compared, and the upper limit of the 90% CI 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 product specific guidance on warfarin sodium.

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2. Type of study: Fed
Design: Single-dose, two-treatment, two-sequence, four-period, fully replicated crossover in vivo
Strength: EQ 60 mg Base
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: Same comments above
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Analyte to measure (in appropriate biological fluid): Edoxaban in plasma

Bioequivalence based on (90% CI): Edoxaban

Waiver request of in vivo testing: EQ 15 mg Base and EQ 30 mg Base based on (i) acceptable bioequivalence studies on the EQ 60 mg Base strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across 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 each 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 approved labeling for the reference product states that the product may be administered through a gastric tube. Conduct the in vitro feeding tube studies including comparative recovery, granule size distribution, and sedimentation volume testing. Refer to the Lansoprazole Delayed-Release Orally Disintegrating Tablet Guidance for additional information regarding procedures of in vitro feeding tube studies.

Testing tube: gastric tube (12 French) with 3 different tubing materials

Testing strength: EQ 60 mg Base

Dispersion medium: Mix crushed powder with 75 mL water with different pH (5.5, 7.0, and 8.5) followed by 3 × 55 mL water rinses of mortar and pestle.

Incubation time: 0 and 15 minutes