Contains Nonbinding Recommendations

Draft Guidance on Edoxaban Tosylate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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, 2-treatment, 2-sequence, 4-period, fully replicated crossover in vivo
   Strength: 60 mg
   Subjects: Healthy males and nonpregnant, nonnursing 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 reduce the possibility of bleeding.

   Edoxaban demonstrated a steep exposure-response relationship for safety[1]; therefore applicants should not use the reference-scaled average bioequivalence (BE) approach to widen the BE limits for edoxaban 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: 60 mg
   Subjects: Healthy males and nonpregnant females, general population
   Additional comments: Same as comments above

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

[1] http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206316Orig1Orig2s000ClinPharmR.pdf.

Bioequivalence based on (90% CI): Edoxaban

Waiver request of in-vivo testing: 15mg and 30mg based on (i) acceptable bioequivalence studies on the 60mg 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 all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).