Contains Nonbinding Recommendations

Draft Guidance on Dabigatran Etexilate Mesylate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Capsule; 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: 150mg
   Subjects: Normal healthy males and females, general population.

   Additional comments: Dabigatran demonstrated a steep exposure-response relationship for both efficacy and safety.[1] Therefore, applicants should not use the reference-scaled average bioequivalence approach to widen the BE limits for dabigatran bioequivalence evaluation. Applicants should use the average bioequivalence approach with BE limits of 80-125%. 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 $\leqslant$ 2.5. For details about the Method for Statistical Analysis comparing within-subject variability of test and reference products, refer to *Guidance on Warfarin Sodium*.

   All subjects should have prothrombin time (PT), activated partial thromboplastin time (aPTT) and creatinine clearance (CrCl) measured. The PT and aPTT should be within the normal range and the CrCl value should be more than 50 mL/min for each subject before dosing in order to prevent or avoid the possibility of bleeding.

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2. Type of study: Fed
   Design: Single-dose, 2-treatment, 2-sequence, 4-period, fully replicated crossover in vivo
   Strength: 150mg
   Subjects: Normal healthy males and females, general population.
   Additional comments: See comments above

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[1] http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000SumR.pdf

Analytes to measure (in appropriate biological fluid): free (non-conjugated) dabigatran and total dabigatran (non-conjugated plus conjugated dabigatran after complete alkaline cleavage of dabigatran glucuronides) in plasma
Bioequivalence based on (90% CI): free (non-conjugated) dabigatran and total dabigatran (non-conjugated plus conjugated dabigatran)

Waiver request of in-vivo testing: 75 mg and 110 mg based on (i) acceptable bioequivalence studies on the 150 mg 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:
Please note that a Dissolution Methods Database is available to the public at the FDA website at http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm. Please find the dissolution information for this product at this website. Please 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.