Contains Nonbinding Recommendations

Draft Guidance on Apixaban

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, 2-way, crossover in vivo
   Strength: 5 mg
   Subjects: Healthy males and non-pregnant females

   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.

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2. Type of study: Fed
   Design: Single-dose, 2-way, crossover in vivo
   Strength: 5 mg
   Subjects: Healthy males and non-pregnant females
   Additional comments: Same as comments above

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

Bioequivalence based on (90% CI): Apixaban

Waiver request of in-vivo testing: 2.5mg based on (i) acceptable bioequivalence studies on the 5mg strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between both 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 both strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

In Vitro Comparative Nasogastric Tube Studies:

The approved labeling for the reference product states that the product may be crushed and suspended in 60 mL of water or 5% dextrose in water (D5W) and promptly delivered through a nasogastric (NG) tube. Conduct the following in vitro studies with 8 French NG tube to compare the performance of the test product to that of the reference product to support NG tube administration.

NG tube preparation procedure: Prepare the NG tube studies using 12 units of the test and the reference products at the 5 mg strength for 0 and 15 minutes by the following procedure:

a. Prepare the dispersion by crushing the tablet and suspending it in 60 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. Attach the syringe to the NG tube, using the syringe plunger push the suspension through the syringe and the NG tube into a collection container. Flush the syringe with additional amount of water until no granules remain in the syringe. Record the total amount of water used.

c. Repeat the testing described above with a fresh set of 12 units. However, after preparing the suspension in step 'a', wait for 15 min prior to injecting the contents into the NG tube.

Repeat this test using 60 mL of D5W in place of water.

1. Comparative recovery test: conduct the comparative recovery studies of suspension of apixaban to determine what percentage of the initial dose passes through a combination of oral syringe and NG tube. Follow the feeding tube preparation procedure outline above. Determine the percentage of apixaban recovered at the NG tube exit relative to the initial dose for both the test and the reference products, using a validated analytical method. The T/R recovery ratio and the 90% confidence interval of the T/R recovery ratio should be calculated. If high variability is observed, the applicant may increase the number of units used for this test. Visually examine the tube and the syringe for any aggregation, adherence, clogging, etc.

2. Risk assessment of administration conditions: NG tubes may be made with different materials (e.g., PVC, silicone, and polyurethane) and excipients in the suspension may interact with tubing material differently. Therefore, the applicant should consider material of various NG tubes that may be used for product administration and justify that the

conditions used in the equivalence testing conducted below are sufficient for risk evaluation. Justification of testing conditions may be made on the basis of recovery studies (testing procedure as above). Studies should be performed demonstrating the recovery of the suspension through NG tubes and tested to determine the worst case scenario conditions (including, but not necessarily limited to tubing material) which will be used for the equivalence testing above.

3. Standard operating procedure submission: Submit standard operating procedures for the above in vitro testing. Include details about the type of water, the pH of water, flushing volume used in the studies, the tube and syringe used (e.g. material, brand, size, etc.), holding positions of the tube, crushing procedure, shaking method, analytical site and testing dates, etc. for each of the studies. Please submit individual data, mean values, standard deviations, and coefficient of variation (%CV) of each study in an excel file. Visually examine the tubing and the syringe for any aggregation, adherence, clogging, etc., and report all observations and supply supporting photographs. For recovery studies, video may be provided to document the testing process and associated observations. Provide the pre-study and within-study assay validation report. Conduct all the above testing on unexpired test and reference batches. Provide explanation if additional pressure is needed during the testing to ensure complete recovery.