Contains Nonbinding Recommendations

Draft Guidance on Ranolazine

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Ranolazine

Form/Route: Tablet, Extended Release/Oral

Recommended study: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in-vivo
   Strength: 1000 mg
   Subjects: Healthy males and nonpregnant females, general population
   Additional comments: See additional comments below.

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2. Type of study: Fed
   Design: Single-dose, two-way crossover in-vivo
   Strength: 1000 mg
   Subjects: Healthy males and nonpregnant females, general population
   Additional comments: See additional comments below.

Additional comments applicable to both bioequivalence studies:

1) Subjects should not use any prescription drugs or over-the-counter medications implicated in Torsade de Pointes (TdP) or cardiac arrhythmia for at least 7 days prior to dosing with ranolazine.

2) In order to assure reasonable subject safety in a study utilizing the 1000 mg dose of ranolazine, each subject's EKG profile should be monitored during the study and any subject experiencing EKG changes in the first period should be dropped from the study prior to dosing in the second period.

3) Additional subject monitoring:

   a. Baseline EKG at screening and prior to administration of drug. Exclude subjects having a QT > 440 ms (female) or QT > 420 ms (male).
   b. Peak serum concentration may not correspond to the peak effect on QT/QTc interval. Subject monitoring should, therefore, include EKGs at time points around the Cmax.
   c. The protocol should specify the method for calculation of the QTc (Fridericia, Bazett, other).

d. Criteria for subject withdrawal should be clearly stated using the following guidelines:
    i. Absolute QTc interval prolongation:
        1. QTc interval > 450
        2. QTc interval > 480
        3. QTc interval > 500
    ii. Change from baseline in QTc interval:
        1. QTc interval increases from baseline >30
        2. QTc interval increases from baseline >60

Analytes to measure: Ranolazine

Bioequivalence based on (90% CI): Ranolazine

Waiver request of in-vivo testing: 500 mg based on (i) acceptable bioequivalence studies on the 1000 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 Method Database is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. 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.

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH: 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2 and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.