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Draft – Not for Implementation

Draft Guidance on Ranolazine

November 2022

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Ranolazine

Dosage Form; Route: Granules, extended release; oral

Recommended Studies: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 1000 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Exclude subjects with risk factors for prolonged QT interval and Torsades de Pointes. Sprinkle granules on one tablespoonful of applesauce and consume immediately in accordance with the approved labeling of the reference listed drug.

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 1000 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: See comments above.

Analyte to measure: Ranolazine in plasma

Bioequivalence based on (90% CI): Ranolazine

Additional strength: Bioequivalence of the 500 mg strength to the corresponding reference product strength may be demonstrated based on principles laid out in the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application*.[a]

Dissolution test method and sampling times: For modified release drug products, applicants should develop specific discriminating dissolution methods. Alternatively, applicants may use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA's database, http://www.accessdata.fda.gov/scripts/cder/dissolution/, provided that applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed, submit the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for each strength of the test and reference products. Specifications will be determined upon review of the Abbreviated New Drug Application (ANDA).

In addition to the method above, submit dissolution profiles on 12 dosage units for each strength of the test and reference products generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (e.g., pH 1.2, 4.5 and 6.8 buffer). Agitation speeds may be increased if appropriate. It is acceptable to add a small amount of surfactant if necessary. 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.

Alcohol dose dumping studies: Due to concerns of dose dumping of drug from this product when taken with alcohol, conduct additional dissolution testing on all strengths using various concentrations of ethanol in the dissolution medium as follows:

Testing Conditions: 900 mL, 0.1N HCl, USP Apparatus 2 (paddle) at 50 rpm, with or without alcohol

> Test 1: 12 units tested according to the proposed method (with 0.1 N HCl) with data collected every 15 minutes for a total of 2 hours
>
> Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours
>
> Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours
>
> Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Conduct testing on both test and reference products accordingly, and provide data on individual unit, means, range and %CV.

Product-specific testing conditions for in vitro feeding tube studies: The approved labeling for the reference product states that the product may be administered by a nasogastric (NG) tube or gastric (G) tube. Conduct the in vitro feeding tube studies including comparative recovery

testing with two repeated administrations, sedimentation volume and redispersibility testing, in-use stability in designated dispersion media (i.e., water), particle size distribution study, and dissolution testing. For general procedures of in vitro feeding tube studies, refer to the most recent version of the FDA guidance for industry on *Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations*.[a]

Testing tubes: NG tube (12 French) and G tube (12 French)

Testing strength: 1000 mg

Dispersion medium: Water with different pH values (e.g., pH 5.5, 7.0 and 8.5)

Incubation times: 0 and 15 minutes

Unique Agency Identifier: PSG_216018

[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.