Contains Nonbinding Recommendations

Draft Guidance on Esomeprazole Strontium

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Delayed release capsule; oral

Recommended Studies: Three studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in vivo
   Strength: EQ 40 mg base
   Subjects: Males and nonpregnant females, general population.

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2. Type of study: Fed
   Design: Single-dose, two-way crossover in vivo
   Strength: EQ 40 mg base
   Subjects: Males and nonpregnant females, general population.
   Additional Comments: Applicants may consider using a reference-scaled average bioequivalence approach for esomeprazole. If using this approach, please provide evidence of high variability, from the studies, in the bioequivalence parameters of AUC and/or Cmax (i.e., within-subject variability $\geq$ 30%). Please refer to the Progesterone Capsule Draft Guidance for additional information regarding highly variable drugs.

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3. Type of study: Sprinkle
   Design: Single-dose, two-way crossover in vivo
   Strength: EQ 40 mg base
   Subjects: Males and nonpregnant females, general population.
   Additional Comments: Fasting study, with contents sprinkled over a tablespoonful of applesauce in accordance with the approved labeling of the RLD.

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

Bioequivalence based on (90% CI): Esomeprazole

Waiver request of in vivo testing: 20 mg based on (i) acceptable bioequivalence studies on the 40 mg 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/. For dissolution method development, please refer to USP, "Delayed-Release (Enteric-Coated) Articles-General Drug Release Standard." Esomeprazole is an acid labile drug substance; therefore, please measure esomeprazole from the pellets of the Enteric-Coated capsules and not from the dissolution medium (0.1 N HCl) during the acid stage. 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).

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. Conduct the in vitro feeding tube studies including comparative recovery testing, particle size distribution, comparative acid resistance stability testing, and sedimentation volume testing. Refer to the Lansoprazole Delayed-Release Orally Disintegrating Tablet Draft Guidance for additional information regarding procedures of in vitro feeding tube studies.

Testing tube: NG tube (8 French)

Testing strength: EQ 40 mg base

Dispersion medium: 50 mL water with different pH values (e.g., pH 5.5, 7.0 and 8.5)

Testing conditions for acid resistance stability testing: 300 mL of 0.1 N HCl maintained at 37 ± 0.5°C; USP Apparatus II at 75 rpm. Measure esomeprazole and analyze the amount of esomeprazole released from the pellets (not from the dissolution medium of 0.1N HCl) at 120 minutes.