Contains Nonbinding Recommendations

Draft Guidance on Esomeprazole Magnesium

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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: 40 mg
   Subjects: Males and non-pregnant females, general population.

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2. Type of study: Fed
   Design: Single-dose, two-way crossover in vivo
   Strength: 40 mg
   Subjects: Males and non-pregnant 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 in the bioequivalence parameters of AUC and/or Cmax (i.e., within-subject variability $\geq$ 30%). Please refer to the Progesterone Capsule 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: 40 mg
   Subjects: Healthy males and non-pregnant females, general population
   Additional comments: Fasting study, with content sprinkled over a spoonful of applesauce in accordance with the approved labeling of the RLD.

Analytes to measure: Esomeprazole using an achiral assay

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) proportional similarity of the formulations between both strengths, and (iii) acceptable in vitro dissolution testing of 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).

Esomeprazole is an acid labile drug substance; therefore, please measure esomeprazole from the beadlets of the EC capsule and not from the dissolution medium (0.1N HCl) during the acid stage. Using 12 additional capsules of the test and reference products, proceed to the buffer stage. Dissolution specifications will be determined upon review of the data in the 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: 40mg

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 100 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.