

Draft Guidance on Esomeprazole Magnesium

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Powder for delayed-release suspension; oral

Recommended Studies: Two in vivo studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 40 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments: None

2. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: 40 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments: None

Special Consideration: Applicants may consider using a reference-scaled average bioequivalence (BE) approach for esomeprazole. If using this approach, provide evidence of high variability in the BE parameters of AUC and/or C_{max} (i.e., within-subject variability \geq 30%). Refer to the progesterone capsule guidance for additional information regarding highly variable drugs.

Analytes to measure (in appropriate biological fluid): Esomeprazole in plasma, using an achiral assay

Bioequivalence based on (90% CI): Esomeprazole

Waiver request of in vivo testing: EQ 2.5 mg, 5 mg, 10 mg, and 20 mg Base/packet strengths based on (i) acceptable BE studies on the 40 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity in the formulations across all 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 all 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 administered by a nasogastric (NG) tube or gastric tube. Conduct the following in vitro comparative testing using French size 6 (for 5 mg strength) and size 8 NG tubes (for 40 mg strength) to compare the performance of the test product to that of the reference product to support NG tube administration.

Since the pH for different types of water (e.g., distilled, sterile, and tap water) may vary between the range of 5.0 to 8.5, there is a concern that the process of dispersing an esomeprazole product in water with different pH using an oral syringe or an NG tube might adversely impact the integrity of the enteric coating. Therefore, water with different pH (pH 5.5, 6.5, and 7.5) is recommended in the in vitro NG tube studies.

1. Determine comparative sedimentation depth (volume of sediment) and particle size of granule dispersion using 12 units each of the test and reference products, for 2.5 mg and 5 mg strengths in 5 ml of water, and for 10 mg, 20 mg, and 40 mg strengths in 15 ml of water, with different pH (pH 5.5, 6.5, and 7.5), as follows:
 - a) Prepare the catheter tip syringe, remove the syringe plunger, open the packet, and empty the contents of one packet into the syringe. Insert the syringe plunger, draw up 5 ml or 15 ml of water for corresponding strengths, and shake the syringe vigorously for 15 seconds. Measure the pH of the water before and after mixing with dispersed granules.
 - b) Place the syringe perpendicular to the bench with the tip up and record sedimentation depth immediately (0 min). Remove the syringe plunger and determine the particle size of the granules in the syringe.
 - c) Using a new set of 12 units, repeat the process described in step (a) to prepare the granule dispersion, then incubate for 15 minutes, record the sedimentation depth, and determine the particle size of granules.

Repeat the above procedure with a fresh set of 12 units using water with each pH (pH 5.5, 6.5, and 7.5) and record the sedimentation depth and determine the particle size of granules. Provide all particle size data at the D10, D50, and D90 levels. You may use the markings on the syringe to note the sedimentation depth. Provide a qualitative description, e.g., particle aggregation and particles adhering to the syringe walls. Take photos of the contents of the syringe at various intervals throughout the testing process. Determine particle size using laser diffraction method or any method that is sufficiently reproducible and sensitive.

2. Determine the comparative particle size of the granule dispersion using 12 units each of the test and reference products, 5 mg and 40 mg strengths, after delivery to the container through a combination of syringe and the French size 6 (for 5 mg strength) or 8 (for 40 mg strength) NG tube at 0 and 15 minutes as follows:

- a) Prepare the feeding tube according to the manufacturer's directions. Repeat the process described in 1(a) to prepare the granule dispersion.
 - b) Attach the syringe to the feeding tube, then using the syringe plunger push the granule dispersion through the syringe and the feeding tube into a collection container.
 - c) Remove the syringe from the feeding tube, draw up additional water, shake the syringe gently, and flush the system by pushing the fluid through the feeding tube into the container. Measure the initial pH of water and pH of water after the dispersed granules are delivered through NG tube. Perform particle size analysis of the collected fluid.
 - d) Repeat the testing described above with a fresh set of 12 units. However, after suspending the packet content in step a, wait 15 minutes prior to injecting the contents into the feeding tube.
3. Conduct the comparative recovery studies of the dispersed granules from the French size 6 (for 5 mg strength) or 8 (for 40 mg strength) NG tubes. Use 12 units each of the test and the reference products of both strengths in 5 ml water for 5 mg strength and in 15 ml of water for 40 mg strength with different pH (pH 5.5, 6.5, and 7.5) and follow the process outlined in #2 (above). Determine the percentage of esomeprazole recovered at the tube exit relative to the initial dose for both the test (T) and the reference (R) products at 0 and 15 minutes 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, you may increase the numbers of units used for this test.
4. Conduct comparative acid resistance stability testing after recovery through a combination of oral syringe and French size 6 (for 5 mg strength) or 8 (for 40 mg strength) NG tube using 12 units each of the test and the reference products of both strengths in water with different pH (pH 5.5, 6.5, and 7.5) at 0 minutes and 15 minutes. Use the following method:
- a) Prepare the granule dispersion in 5 ml water for 5 mg strength and in 15 ml of water for 40 mg strength, and collect the contents of granule dispersion at the tube exit. Measure the initial pH of water and pH of the water after the dispersed granules are delivered through the NG tube.
 - b) Transfer the contents of granule dispersion into dissolution vessel containing 300 mL of 0.1 N HCl maintained at $37 \pm 0.5^\circ\text{C}$.
 - c) Flush the NG tube with additional water and transfer any remaining contents into the dissolution media mentioned above.
 - d) Acid resistance testing should be conducted using U.S. Pharmacopeia (USP) Apparatus II at 75 rpm. Measure esomeprazole and analyze the amount of esomeprazole released from the pellets of the Delayed Release packet [not from the dissolution medium (0.1N HCl)] at 120 minutes.

- e) Repeat the testing described above with a fresh set of 12 units and hold for 15 minutes.

Repeat the testing described above with a fresh set of 12 units using water with each pH (pH 5.5, 6.5, and 7.5).

- 5. Submit standard operating procedures for sedimentation, particle size, acid resistance, and recovery testing. Include details about the tube and syringe used (e.g., material, brand, size, etc.), holding positions of the tube, shaking method, analytical site and testing dates, etc. for each of the studies. Submit individual data, mean values, standard deviations, and coefficient of variation (CV%) of each study in an Excel file. The photographs should be submitted to support your observations and results. Provide the pre-study and within-study assay validation report.

Conduct all the above testing on unexpired test and reference batches.