

Draft Guidance on Esomeprazole Strontium

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Esomeprazole Strontium

Form/Route: Delayed Release Capsule/Oral

Recommended studies: 3 studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 40 mg (40 mg esomeprazole eq. to 49.3 mg esomeprazole strontium)
Subjects: Healthy males and nonpregnant females, general population.

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2. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: 40 mg (40 mg esomeprazole eq. to 49.3 mg esomeprazole strontium)
Subjects: Healthy 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 in the bioequivalence parameters of AUC and/or C_{max} (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 Please refer to the Progesterone Capsule Draft Guidance for additional information regarding highly variable drugs.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: 40 mg (40 mg esomeprazole eq. to 49.3 mg esomeprazole strontium)
Subjects: Healthy 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 all strengths, and (iii) proportional similarity of the formulations across all strengths.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods 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. 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. 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 Vitro Comparative Nasogastric (NG) Tube Studies:

The approved labeling for the reference product states that the product may be administered by a nasogastric (NG) tube. Please conduct the following in vitro comparative testing using 16 French NG tube 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 studies.

1. Please determine comparative sedimentation depth (volume of sediment) and particle size of granule dispersion using 12 units each of the test and the reference products, for both 20 mg and 40 mg strengths, in 50 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 capsule and empty the contents of one capsule into the syringe. Insert the syringe plunger, draw up 50 mL of water and shake the syringe vigorously for 15 seconds. Please 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). Please remove the syringe plunger and determine the particle size of the granules in the syringe.
 - c) Using a new set of 12 units, please repeat the process described in step (a) to prepare the granule dispersion then incubate for 15 minutes and record the sedimentation depth and determine the particle size of granules.

Please 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. Please 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. Please provide a qualitative description, e.g., particle aggregation and particles adhering to the syringe walls. Please take photos of the contents of the syringe at various intervals throughout the testing process. Please determine particle size using laser diffraction method or any method that is sufficiently reproducible and sensitive.

2. Please determine the comparative particle size of the granule dispersion using 12 units each of the test and reference products, 20 mg and 40 mg strengths, after delivery to the container through a combination of syringe and the 16 French nasogastric 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, 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. Please 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) Please repeat the testing described above with a fresh set of 12 units. However, after suspending the capsule content in step a, wait 15 minutes prior to injecting the contents into the feeding tube.

Please repeat the testing described above with a fresh set of 12 units using water with each pH listed above (pH 5.5, 6.5, and 7.5). Please visually examine the tubing and the syringe for any aggregation, adherence, clogging, etc., and please report all the observations and supporting photographs. Please provide the particle size data at the D10, D50, and D90 levels and determine particle size using laser diffraction method or any method that is sufficiently reproducible and sensitive.

3. Please conduct the comparative recovery studies of the dispersed granules from the 16 French nasogastric tubes. Please use 12 units of the test and the reference products of both strengths in 50 ml water with different pH (pH 5.5, 6.5, and 7.5) and follow the process outlined in #2 (above). Please determine the percentage of esomeprazole recovered at the tube exit relative to the initial dose for both the test and the reference 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. Please conduct comparative acid resistance stability testing after recovery through a combination of oral syringe and 16 French NG tube using 12 units 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. Please use the following method:
- a) Prepare the granule dispersion in 50 ml water and collect the contents of granule dispersion at the tube exit. Please measure the initial pH of water and pH of the water after the dispersed granules are delivered through 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 nasogastric tube with additional water and transfer any remaining contents into the dissolution media mentioned above.
 - d) Acid resistance testing should be conducted using USP Apparatus II at 75 rpm. Measure esomeprazole and analyze the amount of esomeprazole released from the pellets of the DR capsule [not from the dissolution medium (0.1N HCl)] at 120 minutes.
 - e) Please repeat the testing described above with a fresh set of 12 units and hold for 15 minutes.

Please 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. Please submit standard operating procedures for sedimentation, particle size, acid resistance and recovery testing. Please 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. Please 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. Please also provide the pre-study and within-study assay validation report.

Please conduct all the above testing on unexpired test and reference batches.