

## **Draft Guidance on Lansoprazole**

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

**Form/Route:** Delayed Release Capsule/Oral

**Recommended studies:** 3 studies

1. Type of study: Fasting  
Design: Single-dose, two-way crossover in vivo  
Strength: 30 mg  
Subjects: Healthy males and nonpregnant females, general population.  
Additional Comments: Applicants may consider using a reference-scaled average bioequivalence approach for this drug product. If using this approach, the applicant should provide evidence of high variability in the bioequivalence parameters AUC and/or  $C_{max}$  (i.e., within-subject variability  $\geq 30\%$ ). For general information on this approach, please refer to Haidar et al., Bioequivalence Approaches for Highly Variable Drugs and Drug Products, Pharm. Res. 25:237-241(2008).

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2. Type of study: Fed  
Design: Single-dose, two-way crossover in vivo  
Strength: 30 mg  
Subjects: Healthy males and nonpregnant females, general population.  
Additional Comments: Please see comment above. Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies.

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3. Type of study: Fasting sprinkle-in-applesauce  
Design: Single-dose, two-way crossover in vivo  
Strength: 30 mg  
Subjects: Healthy males and nonpregnant females, general population.  
Additional Comments: Please administer the dose after sprinkling the entire contents of the capsule on a teaspoonful of applesauce in accordance with the approved labeling of the RLD. Please see comment above.

**Analytes to measure (in appropriate biological fluid):** Lansoprazole in plasma

**Bioequivalence based on (90% CI):** Lansoprazole

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**Waiver request of in vivo testing:** 15 mg based on (i) acceptable bioequivalence studies on the 30 mg strength, (ii) acceptable in vitro dissolution testing across all strengths, and (iii) proportional similarity of the formulations across all strengths. Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in vivo testing.

**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. 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 tube (16 French or greater). Please conduct the following in vitro comparative testing to compare the performance of the test product to that of the reference product to support NG tube administration

1. Please determine comparative sedimentation volume and particle size of granule dispersion using 12 units each of the test and the reference products, for both 15 mg and 30 mg strengths, in 40 ml of apple juice 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 40 mL of apple juice and gently rotate the syringe.
  - b) Place the syringe perpendicular to the bench with the tip up and record sedimentation volume at 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 min and record the sedimentation volume 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 volume. 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.

2. Please determine the comparative particle size of the granule dispersion using 12 units each of the test and reference products, 15 mg and 30 mg strengths, after delivery to the container through a combination of syringe and the 16 French nasogastric tube at 0 and 15 min 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 apple juice, shake the syringe gently and flush the system by pushing the fluid through the feeding tube into the container. 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 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 report flush volume used in these studies.

3. Please conduct comparative recovery studies to determine what percentage of the initial dose suspended in apple juice passes through the 16 French nasogastric tubes. Please use 12 units of both strengths of the test and the reference products in 40 ml apple juice and follow the process outlined in #2 (above). Please determine the percentage of lansoprazole recovered at the tube exit relative to the initial dose for both the test and the reference products at 0 and 15 min using a validated analytical method. The T/R recovery ratio and the 90% confidence interval of the T/R recovery ratio should be calculated. The DBII will set an interim specification based upon the review of the submitted data. If high variability is observed, you may increase the numbers of units used for this test.
4. Please conduct comparative acid resistance stability testing using 12 units of both strengths of the test and the reference products. Please use the following method:
  - a) Prepare the granule dispersion in 40 ml apple juice (hold for 15 min), and collect the contents of granule dispersion at the tube exit.
  - b) Transfer the contents of granule dispersion into dissolution vessel containing 500 mL of 0.1 N HCl maintained at  $37 \pm 0.5^\circ\text{C}$ .
  - c) Flush the nasogastric tube with additional apple juice 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. Analyze the amount of lansoprazole released at 60 minutes.
5. Please submit standard operating procedures for sedimentation, particle size, acid resistance and recovery testing. Please include details about types of juice, 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%) in all the testing. 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.