

Draft Guidance on Dexlansoprazole

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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: 60 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, please provide evidence of high variability, within the study, in the bioequivalence parameters 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 Please refer to the Progesterone Capsule Draft Guidance for additional information regarding highly variable drugs.

2. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: 60 mg
Subjects: Healthy males and nonpregnant females, general population
Additional Comments: Please see comments above.

3. Type of study: Fasting sprinkle-in-applesauce
Design: Single-dose, two-way crossover in vivo
Strength: 60 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 tablespoon of applesauce in accordance with the approved label of the RLD. Please see additional comments above.

Analytes to measure: Dexlansoprazole in plasma

Bioequivalence based on (90% CI): Dexlansoprazole

Waiver request of in vivo testing: 30 mg based on (i) acceptable bioequivalence studies on the 60 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional

similarity of the formulations across all strengths. Please refer to the Mirtazapine Draft Guidance for additional information regarding waivers of in vivo testing.

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 addition to the method above, for this product, dissolution profiles generated using USP Apparatus I at 100 rpm in at least three dissolution media (pH 4.5, 6 and 6.8) and water should be submitted to the Agency. This is to verify the release profiles of the dual releasing formulation. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Comparative dissolution profiles should include individual unit data as well as the mean, range, and %CV at each time point for twelve units. Specifications will be determined upon review of the data submitted in the application.

In Vitro Comparative Nasogastric Tube Studies:

The approved labeling for the reference product states that the product may be administered through a nasogastric (NG) tube (16 French). 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. Since the pH for different types of water (e.g., distilled, sterile, and tap water) may vary between 5.0 and 8.5, there is a concern that the process of dispersing a dexlansoprazole product in water with different pH within a syringe or an NG tube might adversely impact the integrity of the enteric coating. Therefore, water with different pH is recommended in the in vitro NG tube studies.

NG tubes may be made with different materials (e.g., PVC, silicone, and polyurethane), and dispersed granules and extragranular excipients may interact with tubing material differently. Therefore, the applicant should consider the dispersant pH, material of different kinds of NG tubes that may be used for product administration, and justify why the equivalence testing conducted below is sufficient for risk evaluation. Justification of testing conditions may be made on the basis of recovery studies (for testing procedure, see #3 below). Studies should be performed demonstrating the recovery of the granule dispersion through NG tubes and tested to determine the worst case scenario conditions (e.g. pH, tubing material) which will be used for the equivalence testing below.

1. Determine comparative sedimentation volume and particle size of granule dispersion, using 12 units each of the test and the reference products for both 30 mg and 60 mg strengths in water with different pH (pH 5.5, 6.5, and 7.5) as follows:
 - a) Place 20 mL of water into a clean container. Carefully open the capsule and empty the granules into the container of water. Use a 60 mL catheter-tip syringe to draw up the water and granule mixture.

- b) Place the syringe perpendicular to the bench with the tip up and record sedimentation volume 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 volume, and determine the particle size of granules.

Record the sedimentation volume 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 volume. 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 dispersed granules after tube delivery with 0 and 15 minutes incubation time, using 12 units each of the test and the reference products for both 30 mg and 60 mg strengths, in water with different pH (pH 5.5, 6.5, and 7.5) as follows:
 - a) Prepare the feeding tube (16 French) 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, and use the syringe plunger to push the granule dispersion through the syringe and the feeding tube into a collection container.
 - c) Rinse the delivery device with 10 mL of water followed by a second rinse with an additional 10 mL of water. Each time, swirl the syringe gently and flush the device by pushing the fluid through the feeding tube into the container. Perform particle size analysis of the collected fluid.
 - d) Repeat the testing described above with a new set of 12 units. However, after suspending the capsule content in the syringe as described in step (a), wait 15 minutes prior to injecting the contents into the feeding tube.

Visually examine the tubing and the syringe for any aggregation, adherence, clogging, etc. Report all the observations and submit supporting photographs. Provide the particle size data at D10, D50 and D90 levels.

3. Conduct the comparative recovery studies of the dispersed granules delivered through a combination of syringe and NG tube (16 French). Use 12 units of the test and the reference products for both 30 mg and 60 mg strengths in water with different pH (pH 5.5, 6.5, and 7.5) and follow the process outlined in Step 2 above. Incubate the granule dispersion in water for 0 minute and 15 minutes prior to delivering through the feeding tube. Determine the percentage of dexlansoprazole recovered at the tube exit relative to the initial dose for both the test and the reference products 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 number of units used for this test. Videos may be provided to document the testing process and associated observations.

4. Conduct comparative acid resistance stability testing on the capsule contents recovered after the delivery through a combination of syringe and NG tube, using 12 units of the test and the reference products for both 30 mg and 60 mg strengths in water with different pH (pH 5.5, 6.5, and 7.5). Incubate the granule dispersion in water for 0 minute and 15 minutes prior to delivering through the feeding tube. Use the following method:
 - a) Prepare the granule dispersion in 20 mL of water as described in Step 1 (a), and collect the contents of granule dispersion from the tube exit. Measure the pH of the water containing the granule dispersion before and after the tube delivery.
 - b) Transfer the granule dispersion into a dissolution vessel containing 500 mL of 0.1 N HCl maintained at $37 \pm 0.5^\circ\text{C}$.
 - c) Flush the nasogastric tube twice with 10 mL of water and transfer any remaining contents into the dissolution medium mentioned above.
 - d) Conduct the acid resistance testing using USP Apparatus I at 100 rpm. Analyze the amount of dexlansoprazole released at 120 minutes.
5. Submit standard operating procedures for sedimentation, particle size, recovery and acid resistance testing. Include details about the type of water, the pH of water, 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, coefficients of variation (CV%) of each study in an excel file. Submit photographs that are necessary 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.