

Draft Guidance on Dexlansoprazole

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 30 mg
Subjects: Healthy males and non-pregnant, non-lactating females, general population
Additional comments: Applicants may consider using a reference-scaled average bioequivalence approach. For the method of statistical analysis using the reference-scaled average bioequivalence approach, refer to the Progesterone Capsule Guidance.

2. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: 30 mg
Subjects: Healthy males and non-pregnant, non-lactating females, general population
Additional comments: See comments above.

Analytes to measure (in appropriate biological fluid): Dexlansoprazole in plasma

Bioequivalence based on (90% CI): Dexlansoprazole

Waiver request of in vivo testing: Not applicable

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 (NG) Tube Studies:

The approved labeling for the reference product states that the product may be administered by a nasogastric (NG) tube (8 French or greater). 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 from 5.0 to 8.5, there is a concern that the process of dispersing a

dexlansoprazole product in water with different pH within an NG tube might adversely impact the integrity of the enteric coating. Therefore, water with different pH is recommended in the in vitro NG 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 #4 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. Disintegration time: Determine the disintegration time of orally disintegrating tablets in water using 12 units each of the test and the reference products in water with different pH different pH (pH 5.5, 6.5, and 7.5).
2. Determine comparative sedimentation volume and particle size of microgranule dispersion using 12 units each of the test and the reference products in 20 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, and place one tablet in an oral syringe. Insert the syringe plunger, draw up 20 mL of water and gently swirl the syringe.
 - b. Place the syringe perpendicular to the bench with the tip up and record sedimentation volume at 0 min. Remove the syringe plunger and determine the particle size of the microgranules in the syringe.
 - c. Repeat the process described in step (a) using a new set of 12 units to prepare the microgranule dispersion then incubate for 15 mins and record the sedimentation volume and determine the particle size of microgranules.

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

3. Determine the comparative particle size of the microgranule dispersion using 12 units each of the test and reference products after delivery to the container through a combination of syringe and the 8 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 microgranule dispersion.
 - b. Attach the syringe to the feeding tube, using the syringe plunger push the microgranule dispersion through the syringe and the feeding tube into a collection container.
 - c. The delivery device is rinsed 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 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.

Repeat the above procedure with a fresh set of 12 units using different pH of water (pH 5.5, 6.5 and 7.5). Examine visually the tubing and the syringe for any aggregation, adherence, clogging, etc., and report all the observations and supporting photographs. Provide the particle size data at the D10, D50, and D90 levels and report flush volume used in these studies.

4. Conduct the comparative recovery studies to determine what percentage of the initial dose suspended in water passes through from the 8 French nasogastric tubes. Use 12 units of both strengths of the test and the reference products in 20 mL water with different pH (pH 5.5, 6.5, and 7.5) and follow the process outlined in #2 (above). Determine the percentage of dexlansoprazole recovered at the syringe exit and 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. Specifications will be determined upon review of the ANDA. If high variability is observed, you may increase the numbers of units used for this test. Videos may be provided to document the testing process and associated observations.
5. Conduct comparative acid resistance stability testing after recovery through a combination of oral syringe and 8 French nasogastric tube using 12 units of the test and the reference products in water with different pH (pH 5.5, 6.5, and 7.5) at 0 minute and 15 minutes. Use the following method:
 - a. Prepare the tablet dispersion in 20 ml water (hold for 15 min), and collect the contents of the dispersion from the the tube exit. Measure the initial pH of water and pH of the water after the dispersed tablet is delivered.
 - b. Transfer the contents of the tablet 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 twice with 10 mL of water and transfer any remaining contents into the dissolution media mentioned above.

- d. Acid resistance testing should be conducted using USP Apparatus I at 100 rpm. Analyze the amount of dexlansoprazole released 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 different pH (pH 5.5, 6.5, and 7.5).

6. Submit standard operating procedures for sedimentation, particle size, acid resistance and recovery testing. Include details about types of water, pH of the 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, coefficient of variation (CV%) of each study in an excel file. Submit photographs that are necessary to support your observations and results. Also provide the pre-study and within-study assay validation report.

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

Alcohol Dose Dumping Studies:

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: Volume: 500 mL 0.1N HCl, USP apparatus 1 (basket) @100 rpm, with and without alcohol:

Test 1: Twelve units tested according to the proposed method, with data collected every 15 minutes for a total of 2 hours

Test 2: Twelve units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 3: Twelve units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 4: Twelve units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

After completion of the acid stage testing, each sample should be transferred to the corresponding buffer stage medium containing the same level of ethanol as the acid stage. The pH of the buffer media should be adjusted to pH 7.2 after adding the ethanol.

Testing Conditions: Volume: 900 mL 50 mmol/L phosphate buffer (pH 7.20) containing 5 mmol/L sodium lauryl sulfate, USP apparatus 1 (basket) @100 rpm, with and without alcohol.

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV on all strengths.