Contains Nonbinding Recommendations

Draft Guidance on Lansoprazole

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Delayed-release, orally disintegrating tablet; 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 nonpregnant females, general population
   Additional Comments: Applicant may consider using a reference-scaled average bioequivalence approach for lansoprazole. If using this approach, the applicant should provide evidence, from the bioequivalence studies, of high variability in the bioequivalence parameters AUC and/or Cmax (i.e., within-subject variability $\geq$ 30%).

---

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: See comments above.

Analytes to measure: Lansoprazole in plasma

Bioequivalence based on (90% CI): Lansoprazole

Waiver request of in-vivo testing: 15 mg based on (i) acceptable bioequivalence studies on the 30 mg strength, (ii) acceptable dissolution testing between both strengths, and (iii) proportional similarity in the formulations between both 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 both strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Product-specific testing conditions for in vitro feeding 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 in vitro feeding tube studies including comparative recovery testing with three repeated administrations, particle size distribution study, comparative acid resistance stability testing, and sedimentation volume testing. Refer to the details below for additional information of general procedures for in vitro feeding tube tests.

Testing tube: NG tube (8 French)

Testing strength: 15 mg, 30 mg

Dispersion medium: 15 mg strength in 4 mL and 30 mg strength in 10 mL water with different pH values (e.g., pH 5.5, 7.0 and 8.5)

Testing conditions for acid resistance stability testing: 500 mL of 0.1 N HCl maintained at 37 ± 0.5°C; USP Apparatus II at 75 rpm. Analyze the amount of lansoprazole released at 60 minutes.

General procedures for in vitro feeding tube studies:

Feeding tube preparation procedure: Prepare the feeding tube studies based on the procedure outlined in the most current FDA approved drug product labeling using 12 units each of the test (T) and reference (R) products dispersed in the dispersion medium for 0 minute and the maximum allowable incubation time (e.g., 15 minutes for lansoprazole delayed-release orally disintegrating tablet) as per the drug label, unless the product-specific testing conditions state otherwise. If the information provided in the drug label or the product-specific testing conditions is not sufficient to conduct comparative in vitro feeding tube tests, follow the procedure as below:

(a) Prepare the drug product (e.g., granules from capsule, tablet (crushed or not)) in the dispersion medium (e.g., water, apple juice, or milk), and rotate gently until the drug product is completely dispersed.

(b) Transfer the drug suspension into an oral syringe, connect the oral syringe to the feeding tube, and pass the suspension through the feeding tube into a collection container. After administration of the suspension using feeding tube, flush the feeding tube with an additional amount of the dispersion medium.

(c) Repeat the testing procedure described above with a fresh set of 12 units. However, after suspending the drug product in step (a), wait 15 minutes prior to injecting the contents into the feeding tube.

Risk assessment of administration conditions: Feeding tubes (e.g., NG, G) may be made with different materials (e.g., PVC, silicone, and polyurethane) which can impact the inner tube

diameter. Feeding tubes are also available with different designs (e.g., number of ports and/or eyes; retention balloons; open or closed distal end) which can impact the flow of material through the tube. The applicant should consider the design of the various feeding tubes that may be used for product administration, and test a representative selection (a minimum of 3 for both NG and G tubes) of tube designs to ensure complete delivery of the drug product in the recovery test. Note that for G tubes (if applicable), at least one tube should be tested with a balloon configuration. Evaluation of testing conditions should be made on the basis of recovery study (testing procedure as below) and visual analysis and documented with photographs and videos.

Various dispersion media such as water, apple juice, milk, and liquid nutritional supplement may be used as vehicles for administration and flush through feeding tubes as per the corresponding reference listed drug label. The properties of the dispersion media may vary between brands or formulations. Variations may include pH, concentration, ingredients, preparation method (e.g., reconstituted from frozen concentrate), etc. Therefore, the applicant should consider the different types and properties of vehicle that may be used for product administration by evaluating the risk due to potential variations in the dispersing media used. This analysis should form part of the basis for justifying the appropriateness of administration conditions selected for risk evaluation. In the case that water is used as the dispersion medium as per the drug labels, since the pH for different types of water (e.g., distilled, sterile and tap water) may generally vary between the range of 5.5 to 8.5, there is a concern that the process of dispersing some modified-release products (e.g., extended-release, delayed-release) in water with different pH within the preparation container, oral syringe, or a feeding tube might adversely impact the integrity of the enteric coating or dissolution of drug products containing pH-sensitive excipients. Therefore, water with different pH values (e.g., pH 5.5, 7.0 and 8.5) may be recommended for the in vitro feeding tube studies.

The following in vitro feeding tube tests may be recommended as per product-specific testing conditions:

1. Comparative recovery testing: Following the feeding tube preparation procedure outlined above, conduct comparative recovery studies to determine what percentage of the initial dose passes through a combination of an oral syringe and a feeding tube. Determine the percentage of drug recovered at the tube exit relative to the initial dose for both the T and R 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, the applicant may increase the number of units used for this test. Visually examine the tube and the syringe for any aggregation, adherence, clogging, etc.

   If the labeling indicates that the product may be administered multiple times per day, the applicant may need to consider repeated administration conditions in the recovery test (e.g., the same tube should be used for sequential administrations of the drug product).

2. Particle size distribution study: Following the feeding tube preparation procedure outlined above, determine the comparative particle size of the drug suspension before and after delivery to the feeding tube. Provide the particle size data at the D10, D50, and D90 levels.

Determine particle size using laser diffraction method or any validated method that is sufficiently reproducible and sensitive.

3. Comparative acid resistance stability testing: Following the feeding tube preparation procedure outlined above, conduct comparative acid resistance stability testing after recovery through a combination of an oral syringe and a feeding tube. Measure pH values of drug suspension before and after delivery through the feeding tube. After collection of the drug suspension at the feeding tube exit, transfer the suspension into a dissolution vessel using the testing conditions for acid resistance stability testing described in "Product-specific testing conditions." Analyze the amount of drug released at the specified time points.

4. Sedimentation volume testing: Following the feeding tube preparation procedure outline above, determine comparative sedimentation volume of the dispersion using 12 units each of the T and R products, if components of the drug product have the potential for sedimentation (e.g., insoluble excipients) which may increase the risk of clogging. Record the sedimentation volume. Markings on the syringe may be used for the measurement. 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.

Standard operating procedure submission: Submit standard operating procedures for the above in vitro feeding tube testing. Include details about the dispersion medium (e.g., type of water, the pH of water before and after dispersion, brand of apple juice), flush volume used in the studies, the tube and syringe used (e.g., material, brand, size, with or without balloon, etc.), holding position of the tube, shaking method, analytical site and testing dates, etc. for each of the studies. Provide explanation if additional pressure is needed to be applied during the testing to ensure complete recovery. Submit individual data, mean values, standard deviations, and coefficients of variation (CV %) in all the testing in an Excel file. Visually examine the tubing and the syringe for any aggregation, adherence, clogging, etc., and report all observations and supply supporting photographs. For recovery studies, videos may be provided to document the testing process and associated observations. Provide the pre-study and within-study assay validation report. Conduct all the above testing on unexpired T and R batches.