Contains Nonbinding Recommendations

Draft Guidance on Carglumic Acid

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two- treatment, two-period crossover in vivo
   Strength: 200 mg at the dose of 100 mg/kg*
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: None

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2. Type of study: Fed
   Design: Single-dose, two- treatment, two-period crossover in vivo
   Strength: 200 mg at the dose of 100 mg/kg*
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: None

*Note: Because carglumic acid tablet is supplied as 200 mg tablet, the dose for each subject should be calculated by multiplying the subject's weight by 100 mg/kg and then rounding up to the next 200 mg dose. The tablets should not be swallowed whole or crushed. Disperse carglumic acid tablets in water immediately before use per the labeling instruction. Carglumic acid tablets do not dissolve completely in water and un-dissolved particles of the tablet may remain in the mixing container. To ensure complete delivery of the dose, the mixing container should be rinsed with additional volumes of water and the contents swallowed immediately. The total volume of water should be 250 mL and the total calculated dose should be consumed. For data analysis, the dose administered should be included in the Analysis of Variance (ANOVA) statistical model. Dose normalization is not advised.

Analyte to measure (in appropriate biological fluid): Carglumic acid in plasma

Bioequivalence based on (90% CI): Carglumic acid

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 for each of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

If the tablet product has a functional score, additional dissolution profile testing should be conducted for each segment of the split tablet after manual and mechanical splitting as per Guidance for Industry on *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*.

Product-specific testing conditions for in vitro feeding tube studies:
The approved labeling for the reference product states that the product may be administered via a feeding tube. Conduct the in vitro feeding tube studies including comparative recovery testing and sedimentation volume testing. Refer to *the Lansoprazole Delayed-Release Orally Disintegrating Tablet Guidance* for additional information regarding procedures of in vitro feeding tube studies.

Testing tube: Nasogastric (NG) tube (6 French)

Testing strength: 200 mg*

Dispersion medium: Add about 2.5 mL of water into a small cup for each tablet followed by flushing immediately with 1 to 2 mL of additional water to clear the NG tube

Incubation time: 0 and 15 minutes

*Note: Consider conducting the comparative in vitro NG tube studies at a dose relevant to clinical use (e.g., dispersing 30 tablets in 75 mL water).