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Draft Guidance on Carglumic Acid

October 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Carglumic acid

Dosage Form: Tablet, for suspension

Route: Oral

Strength: 200 mg

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. 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: Healthy males and non-pregnant, non-lactating females
   Additional comments: 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: 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 in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units for each of the test product and reference listed drug (RLD).[1] Specifications will be determined upon review of the abbreviated new drug application.

If any strength of 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 the most recent version of the FDA guidance for industry on *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*.[a]

Product-specific testing conditions for in vitro feeding tube studies: The approved labeling for the RLD product states that the product may be administered by a nasogastric (NG) or gastrostomy (G) tube. Conduct the in vitro feeding tube studies, including comparative recovery testing, sedimentation volume and redispersibility testing, and in-use stability in designated dispersion media (i.e., water). For general procedures of in vitro feeding tube studies, refer to the most recent version of the FDA guidance for industry on *Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations.*[a]

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).

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[1] If the RLD is not available, refer to the most recent version of the FDA guidance for industry on *Referencing Approved Drug Products in ANDA Submissions*.