

## **Draft Guidance on Cysteamine Bitartrate**

**March 2021**

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This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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This is a new draft product-specific guidance for industry on generic cysteamine bitartrate.

**Active Ingredient:** Cysteamine bitartrate

**Dosage Form; Route:** Delayed release granule; oral

**Recommended Studies:** Four studies

1. Type of study: Fasting

Design: Single-dose, two-treatment, two-period crossover in vivo

Strength: EQ 300 mg Base/packet

Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments: Females of reproductive potential should practice abstention or contraception during the study.

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2. Type of study: Fed

Design: Single-dose, two-treatment, two-period crossover in vivo

Strength: EQ 300 mg Base/packet

Subjects: Males and non-pregnant, non-lactating females, general population  
Additional comments: See comments above.

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3. Type of study: Fasting sprinkle  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: EQ 300 mg Base/packet  
Subjects: Males and non-pregnant, non-lactating females, general population  
Additional comments: See comments above. Sprinkle the intact granules and mix in 4 ounces of applesauce in accordance with the approved labeling of the reference product.
  
  4. Type of study: Fasting sprinkle  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: EQ 300 mg Base/packet  
Subjects: Males and non-pregnant, non-lactating females, general population  
Additional comments: See comments above. Sprinkle the intact granules into 4 ounces of orange juice in accordance with the approved labeling of the reference product.
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**Analyte to measure:** Cysteamine in plasma

**Bioequivalence based on (90% CI):** Cysteamine

**Additional strength:** Bioequivalence of the EQ 75 mg Base/packet strength to the corresponding reference product strength may be demonstrated based on principles described in the FDA guidance for industry, *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.

**Dissolution test method and sampling times:** For modified release drug products, applicants should develop specific discriminating dissolution methods. Alternatively, applicants may use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA's database, <http://www.accessdata.fda.gov/scripts/cder/dissolution/>, provided that applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed, submit the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for each strength of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

**Alcohol dose dumping studies:**

Due to concerns of dose dumping of cysteamine bitartrate from this product when taken with alcohol, conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium as follows:

Testing Conditions: 1000 mL, 0.1 N HCl, USP apparatus 1 (basket) at 75 rpm (EQ 75 mg Base) and 150 rpm (EQ 300 mg Base), with or without alcohol;

Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours

Test 2: 12 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: 12 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: 12 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

Conduct testing on both test and reference products accordingly, and provide data on individual unit, means, range and %CV.

#### **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 gastric (G) tube (14 French or larger). Conduct in vitro feeding tube studies including comparative recovery testing, particle size distribution study, and sedimentation volume testing. Refer to the draft guidance, *Lansoprazole Delayed-Release Orally Disintegrating Tablet*, for additional information regarding procedures of in vitro feeding tube studies.

Testing tube: G tube (14 French)

Testing strength: EQ 300 mg Base

Dispersion medium: Disperse the capsule contents in 4 ounces of applesauce, followed by flushing with 10 mL of fruit juice (except grapefruit juice)

Incubation times: 0 and 30 min

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