

Draft Guidance on Cysteamine Bitartrate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Delayed-released capsules; oral

Recommended Studies: Four in vivo studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: EQ 75 MG BASE at a dose of 600 mg (8xEQ 75 MG BASE)
Subjects: Health males and nonpregnant females, general population
Additional comments: Female subjects should not be pregnant or lactating, and, if applicable, should practice abstention or contraception during the study
2. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: EQ 75 MG BASE at a dose of 600 mg (8xEQ 75 MG BASE)
Subjects: Health males and nonpregnant females, general population
Additional comments: Same as comments above
3. Type of study: Sprinkle
Design: Single-dose, two-way crossover in vivo
Strength: EQ 75 MG BASE at a dose of 600 mg (8xEQ 75 MG BASE)
Subjects: Healthy males and nonpregnant females, general population
Additional comments: a. See comments above. b. Fasting study, with content sprinkled over 4 ounces (1/2 cup) of applesauce in accordance with the approved labeling of the reference listed drug (RLD)
4. Type of study: Sprinkle
Design: Single-dose, two-way crossover in vivo
Strength: EQ 75 MG BASE at a dose of 600 mg (8xEQ 75 MG BASE)
Subjects: Healthy males and nonpregnant females, general population
Additional comments: a. See comments above. b. Fasting study, with content sprinkled in 4 ounces (1/2 cup) of either orange juice or apple juice in accordance with the approved labeling of the RLD

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

Bioequivalence based on (90% CI): Cysteamine

Waiver request of in vivo testing: EQ 25 MG BASE strength based on (i) acceptable bioequivalence studies on the EQ 75MG BASE strength, (ii) proportionally similar formulation across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths

Dissolution test method and sample 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 the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

In Vitro Comparative Recovery Feeding Tube Studies:

The approved labeling for the RLD states that the product may be administered for patients who have a 12 French or larger gastrostomy (G)-tube in place. The following in vitro comparative testing using a 12-French feeding tube to compare the performance of the test product (T) to that of the reference product (R) to support feeding tube administration should be conducted.

- a. Prepare the 12-French feeding tube according to the manufacturer's directions.
- b. 12 units each of the test and reference products should be used for this comparative recovery test. As per the RLD labeling, open each capsule and mix intact granules into approximately 4 ounces (1/2 cup) of applesauce, administer mixture via feeding tube within 30 minutes, flush with approximately 8 ounces (1 cup) of orange juice or apple juice to clear the tube.
- c. Collect the content from the flush-out from the feeding tube on each unit in the designated container.
- d. Wait for 45 minutes before centrifuging.
- e. Measure the drug released in the supernatant.
- f. Submit standard operating procedures for the comparative recovery study, including details about the tube used (e.g., material, brand, size, etc.), holding positions of the tube, analytical site and testing dates, etc., for each of the studies. Submit individual data, mean values, standard deviations, and coefficient of variation (%CV) of each study in an Excel file. Photographs should be submitted to support the observations and results. Provide the pre-study and within-study assay validation report.

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

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: 1000 mL 0.1N HCl; apparatus 1 (Basket)@75 rpm; with and without the 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

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