LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

1600 STEWART AVENUE, WESTBURY, NY 11590
(516) 222-6222 • FAX (516) 683-1887

May 8, 2018

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

Dear Sir or Madam:

The undersigned submits this petition, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR 10.30 and 21 CFR Sec. 314.93 on behalf of a client requesting the Commissioner of the Food and Drug Administration (FDA) to declare that Cysteine Hydrochloride Injection 5% containing 34.6 mg/mL of Cysteine base are suitable for consideration in an abbreviated new drug application (ANDA).

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration declare that, Cysteine Hydrochloride Injection 5% containing 34.6 mg/mL of Cysteine base are suitable for submission as an ANDA. The reference-listed drug product (RLD), upon which this petition is based, is Cysteine Hydrochloride Injection 7.25% in syringe which is subject of NDA 19-523 most recently held by Hospira, Inc. (Hospira), and initially approved on October 22, 1986, as designated in the Orange Book (see copy of the page from the current Electronic Edition of the *Approved Drug Products with Therapeutic Equivalence Evaluations* (Attachment 1). On June 4, 2010, the FDA announced its determination that Cysteine Hydrochloride Injection, USP, 7.25%, was not withdrawn from sale for reasons of safety or effectiveness. This determination allows FDA to approve abbreviated new drug applications (ANDAs) for Cysteine Hydrochloride if all other legal and regulatory requirements are met.

Statement of Grounds

The Federal Food, Drug, and Cosmetic Act provides for the submission of an Abbreviated New Drug Application for a drug product that differs in strength that of the listed drug provided the FDA has approved a petition that proposed filing such an application.

The RLD, held by Hospira is a sterile, nonpyrogenic solution of Cysteine Hydrochloride 7.25% containing 0.5 gram in 10 mL of water for injection. The petition is thus seeking a change in strength (total drug content) (from 0.5 g/container to 0.346 g/container) from that of the RLD.

Based on the original approved labeling for the RLD, for addition to amino acids solutions intended for use in newborn infants, it is recommended that 7.25% Cysteine Hydrochloride Injection, USP be added to the amino acids solution to provide cysteine at approximately 1.5% of the total amino acids. Hence, an infant receiving amino acids solutions at 2.5 g/kg/day should be provided 37.5 mg/kg/day of cysteine or 0.75 ml/kg/day of 7.25% Cysteine Hydrochloride Injection, USP. Similarly, an infant receiving amino acids solutions at 3 g/kg/day should be provided 45 mg/kg/day of cysteine or 0.9 ml/kg/day of 7.25% Cysteine Hydrochloride Injection, USP. For addition to amino acids solutions that are intended for use in adults, a dosage of 5 mg of cysteine per gram of amino acids can be used. For example, 6 ml of 7.25% Cysteine Hydrochloride Injection, USP added to 500 ml of 11.4% Amino Acids Injection will provide a final concentration of 60 mg cysteine per 100 ml of amino acids solution.

Therefore, for a strength for 5% Cysteine Hydrochloride Injection which will contain 34.6 mg/mL of Cysteine base, to provide 37.5 mg/kg/day for the first example given, administration 1.08 ml/kg/day will be needed instead of 0.75 ml/kg/day. The following table compares the adjustment in admixture that is needed to provide the same amount of drug for each scenario.

Dosage of Amino Acid	Patient population	Dosage of Cysteine	Amount of Cysteine Hydrochloride Injection Needed (7.25%)	Amount of Cysteine Hydrochloride Injection Needed (5%)
2.5 g/kg/day	Infant	37.5 mg/kg/day	0.75 mL/kg/day	1.09 mL/kg/day
3 g/kg/day	Infant	45 mg/kg/day	0.9 mL/kg/day	1.3 mL/kg/day
	Adult	60 mg/100 mL of amino acid	6 mL/500mL of amino acid	8.7 mL/500 mL amino acid

The proposed drug product will reduce the waste of unused drug based on the dosage recommendation in both infant and adult.

There are no proposed changes in labeling with the exception of the obvious changes in strength and amount to be admixed sought in this petition. The uses, indications, warnings and directions for use will remain the same as that of the RLD. Draft labeling for the proposed product is included in Attachment 2, and the RLD's approved labeling is provided in Attachment 3.

Therefore, the petitioner's request for the Commissioner to find that a change in strength (i.e., a change in total drug content) from 0.5 g to 0.346 g, for Cysteine Hydrochloride Injection should raise no questions of safety or effectiveness, and the Agency should approve the petition.

Applicability of Pediatric Research Equity Act

In September of 2007, Congress reauthorized the Pediatric Research Equity Act of 2003 (PREA) that amended the Federal Food, Drug, and Cosmetic Act to provide the Agency authority to require drug firms to study drugs in pediatric patients, if the Agency concludes that such study would provide beneficial health data for that patient population. The Act specifically requires that ANDAs submitted under an approved suitability petition under section 505(j)(2)(C) of the Act for changes in dosage form, route of administration, or new active ingredient in combination products are subject to the pediatric assessment requirements that PREA imposes. Since this petition is not seeking for a change in any of the changes listed and is limited to change in strength (total amount in a vial), requirement of PREA does not apply.

C. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31.

D. Economic Impact

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis, if requested by the Agency.

E. Certification

The undersigned certifies that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

Digitally signed by
s.ahmed@lachmanconsultants.com
Date: 2018.05.08 14:21:56 -04'00'

Sharif Ahmed
Principal Consultant

Attachments:
1. Approved Drug Products with Therapeutic Equivalence Evaluations, Electronic Orange Book listing, accessed 5/8/2018
2. Draft insert labeling for proposed product
3. Approved labeling for reference-listed drug, Cysteine Hydrochloride Injection 7.25%.

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Home | Back to Search Results

Product Details for NDA 019523

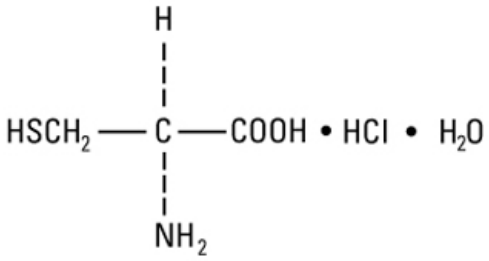
CYSTEINE HYDROCHLORIDE (CYSTEINE HYDROCHLORIDE)
7.25% **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons** Marketing Status: Discontinued

Active Ingredient: CYSTEINE HYDROCHLORIDE
Proprietary Name: CYSTEINE HYDROCHLORIDE
Dosage Form; Route of Administration: INJECTABLE; INJECTION
Strength: 7.25% **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**
Reference Listed Drug: Yes
Reference Standard: No
TE Code:
Application Number: N019523
Product Number: 001
Approval Date: Oct 22, 1986
Applicant Holder Full Name: HOSPIRA INC
Marketing Status: Discontinued
Patent and Exclusivity Information

5.0% Cysteine Hydrochloride Injection, USP (0.346 g Cysteine)

DESCRIPTION

5.0% Cysteine Hydrochloride Injection, USP (0.346 as the monohydrate), is a sterile, nonpyrogenic solution. Each 10 ml provides 0.346 g cysteine and 2.85 mEq of chloride in Water for Injection, USP. The pH range is 1.0 to 2.5. Cysteine is a sulfur-containing amino acid which is unstable when included in autoclaved solutions of amino acids. To avoid this problem, Cysteine Hydrochloride Injection is provided as an additive to use with amino acids solutions. The structural formula for cysteine hydrochloride is:



CLINICAL PHARMACOLOGY

In the adult, cysteine is synthesized from methionine via the trans-sulfuration pathway. However, in newborn infants maturation of the enzyme system needed to convert methionine to cysteine is not complete; therefore, cysteine is generally considered an essential amino acid in infants. In addition, adult and pediatric patients with severe liver disease may have an impairment of the enzymatic conversion of methionine to cysteine.

INDICATIONS AND USAGE

5.0% Cysteine Hydrochloride Injection, USP is indicated for use as an additive to amino acids solutions to meet nutritional requirements of newborn infants requiring total parenteral nutrition (TPN) and of adult and pediatric patients with severe liver disease who may have impaired enzymatic processes and require TPN. It can also be added to amino acids solutions to provide a more complete profile of amino acids tor protein synthesis.

CONTRAINDICATIONS

Due to the acidity of the solution, 5.0% Cysteine Hydrochloride Injection, USP should not be given by direct injection into a peripheral vein because phlebitis may result.

WARNINGS AND PRECAUTIONS

5.0% Cysteine Hydrochloride Injection, USP is a hypertonic solution and should be administered only as a component of an admixture of parenteral nutrients. It is only to be administered intravenously.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.