UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ETON PHARMACEUTICALS, INC.,

Petitioner

v.

EXELA PHARMA SCIENCES, LLC,

Patent Owner

U.S. PATENT NO. 10,583,155

DECLARATION OF MADAN CHILAKURI

1. My name is Madan Chilakuri. I am over 21 years of age. I submit this declaration on behalf of Eton Pharmaceuticals, Inc. (hereinafter "Eton") in connection with the above-captioned matter. I am not being compensated for this Declaration or for the time spent in preparing it.

2. Based on my personal knowledge, I am informed and understand that the facts stated in this Declaration are true.

3. I hold a M.S. and R.Ph. in State of Wisconsin and am currently President at Pharma Regulatory Consultants LLC ("PRC"). I have been employed by PRC since May 2017.

4. In the May-July 2017 time frame, PRC was engaged in providing consulting work to Eton. As part of that engagement, on July 11, 2017, I electronically submitted a Freedom of Information Act ("FOIA") request to the Federal Drug Administration ("FDA") for the Approval History for New Drug Application (NDA) 019523. A true and correct screen shot copy of that request is attached as Exhibit A.

5. On July 12, 2017, I received an electronic confirmation of my request from FDA. A true and correct copy of that confirmation is attached as Exhibit B.

6. Prior to or on July 28, 2017, I received a copy of the Approval History for NDA 019523 from the FDA via mail on a CD. A true and correct copy of the CD is attached as Exhibit C and a true and correct copy of the Approval History

for NDA 019523 that was contained on the CD is attached as Exhibit D.

7. On July 28, 2017, I sent via email a copy of the above-mentioned Approval History for NDA 019523 to Eton. A true and correct copy of my email communication and the Approval History for NDA 019523 attachment is attached as Exhibit E.

8. I hereby declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, and that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. I understand that willful false statements are punishable by fine or imprisonment or both. *See* 18 U.S.C. § 1001.

Date: 06-04-2020

Respectfully submitted,

Madan Chilakuri

Exhibit A

U.S. Food and Drug Administration

FOIA Request Confirmation

Confirmation Number: FDA1736172

Requester:

General

Description of Requester:	**Commercial user**
Max Amount Willing to Pay:	**$500.00**

Organization

Organization Name:	**Pharma Regulatory Consultants LLC**				
Primary Phone:	**207-756-4065**	Other Phone:		Email:	**mc@pharmaregllc.com**

Mailing Address

Address 1:	**2829 Glenarye Dr**
Address 2:	
City:	**Lindenhurst**
State:	**IL**
Zip Code:	**60046**

Billing Address

Address 1:	**2829 Glenarye Dr**
Address 2:	
City:	**Lindenhurst**
State:	**IL**
Zip Code:	**60046**

Details

Requester Name:	**Approval History for New Drug Application (NDA) 019523**		
Requester File #:		Request Letter:	
Requested Date From:		Requested Date To:	
Subject of Request:	**Dear sir/madam, We are requesting approval history of Cysteine Hydrochloride, NDA # 019523, sponsor Hospira, Inc. We request information**		

Waiver of Fees

Justification:	

Expedited Processing

Reason:	
Justification:	

Print Create Another Request Close

Within one business day of the submission of your online request, you will receive by electronic mail an FOIA Control Number. If you need to communicate with FDA regarding your request, please refer to this Control Number. Requests received after 4:00 P.M. E.S.T. will be considered to have been received on the following business day.

If your informational needs change, and you need to cancel your request, please contact the Division of Freedom of Information by telephone, mail, or fax. Please include your control number in the correspondence. For contact information, please see FDA's FOIA page.

Exhibit B

Gmail

Madan Chilakuri <mc@pharmaregllc.com>

FDA Receipt of FOI Request

1 message

FDA_FOI@fda.gov <FDA_FOI@fda.gov> Wed, Jul 12, 2017 at 6:31 AM
To: mc@pharmaregllc.com

Note: Do NOT reply directly to this E-mail

Pharma Regulatory Consultants LLC Approval History for New Drug Application (NDA) 019523

Re: Confirmation # FDA1736172
In Reply refer to: 2017-6052

The Food and Drug Administration (FDA) has received your Freedom of Information Act (FOIA) request for records regarding:

NDA 019523

Original Subject: Dear sir/madam, We are requesting approval history of Cysteine Hydrochloride, NDA # 019523, sponsor Hospira, Inc. We request information including Approval Letter(s), Printed Labeling,Summary Review,Medical Review(s), Chemistry Review(s) , Pharmacology Review(s), Clinical Pharmacology Biopharmaceutics Review(s),Other Review(s) (PDF), and Label for NDA # 019523. Thanking you, Sincerely, Madan Chilakuri M.S, R.Ph. 207-756-4065 mc@pharmaregllc.coom

We will respond as soon as possible and may charge you a fee for processing your request. If your informational needs change, and you no longer need the requested records, please contact us to cancel your request, as charges may be incurred once processing of your request has begun. For more information on processing fees, please see http://www.fda.gov/RegulatoryInformation/FOI/FOIAFees/default.htm. If you have any questions about your request, please call Rochelle A. Coleman, Information Technician at (301) 796-8982 or write to us at:

Division of Freedom of Information, U.S. Food and Drug Administration
5630 Fishers Lane, Room 1035
Rockville, MD 20857
Fax:(301)827-9267

You also have the right to seek dispute resolution services from:

FDA FOIA Public Liaison
Office of the Executive Secretariat
5630 Fishers Lane, Room 1050
Rockville, MD 20857

E-Mail: FDAFOIA@fda.hhs.gov and/or:

Office of Government Information Services
National Archives and Administration
8601 Adelphi Road ? OGIS
College Park, MD 20740-6001

Telephone: 202-741-5770
Toll-Free: 1-877-684-6448
E-mail: ogis@nara.gov
Fax: 202-741-5769

Exhibit C

U.S. FOOD & DRUG ADMINISTRATION

July 12, 2017

In Response Refer to File: 2017-6052

Madan Chilakuri M.S., R.Ph.
Pharma Regulatory Consultants LLC
2829 Glenarye Dr.
Lindenhurst, IL 60046

Dear Requester,

This is in response to your Freedom of Information Act request dated July 12, 2017, in which you requested a copy of the approval information for Cysteine Hydrochloride, NDA 19523. Your request was received in the Center for Drug Evaluation and Research on July 12, 2017.

The releasable documents are enclosed. Portions of the documents are exempt from disclosure under FOIA. Please see http://www.fda.gov/RegulatoryInformation/FOI/ucm390370.htm for a complete list of FOIA exemptions.

The following charges may be included in a monthly invoice:

Reproduction: $0.00 Search: $11.50 Review: $0.00 Other: $1.00 (CD) TOTAL: $12.50

The above total may not reflect final charges for this request.

PLEASE DO NOT SEND PAYMENT UNLESS YOU RECEIVE AN INVOICE FOR THE TOTAL MONTHLY FEE.

This concludes the response for the Center for Drug Evaluation and Research. If we can be of further assistance to you, please do not hesitate to contact Cynthia Durant at 301-796-3501.

Sincerely,

Guruprasad S. Udapi -S

Digitally signed by Guruprasad S. Udapi -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000680608, cn=Guruprasad S. Udapi -S
Date: 2017.07.12 11:42:17 -04'00'

Guruprasad S. Udapi
Lead Regulatory Counsel
Division of Information Disclosure Policy
Office of Regulatory Policy
Center for Drug Evaluation and Research

You have the right to appeal this determination. By filing an appeal, you preserve your rights under FOIA and give the agency a chance to review and reconsider your request and the agency's decision.

Your appeal must be mailed within 90 days from the date of this response, to:

Ms. Catherine Teti
Deputy Agency Chief FOIA Officer
U.S. Department of Health and Human Services
Office of the Assistant Secretary for Public Affairs
Room 729H
200 Independence Avenue SW
Washington, DC 20201

Please clearly mark both the envelope and your letter "Freedom of Information Act Appeal."

You may also contact the FDA FOIA Public Liaison for assistance at:

FDA FOIA Liaison
Office of the Executive Secretariat
5630 Fishers Lane Room 1050
Rockville, MD 20857
E-mail: FDAFOIA@fda.hhs.gov

If you are unable to resolve your FOIA dispute through our FOIA Public Liaison, the Office of Government Information Services (OGIS), the Federal FOIA Ombudsman's office, offers mediation services to help resolve disputes between FOIA requesters and Federal agencies. The contact information for OGIS is:

Office of Government Information Services
National Archives and Records Administration
8601 Adelphi Road – OGIS
College Park, MD 20740-6001
Telephone: 202-741-5770
Toll-Free: 1-877-684-6448
E-mail: ogis@nara.gov
Fax: 202-741-5769

Enclosure: NDA 19523

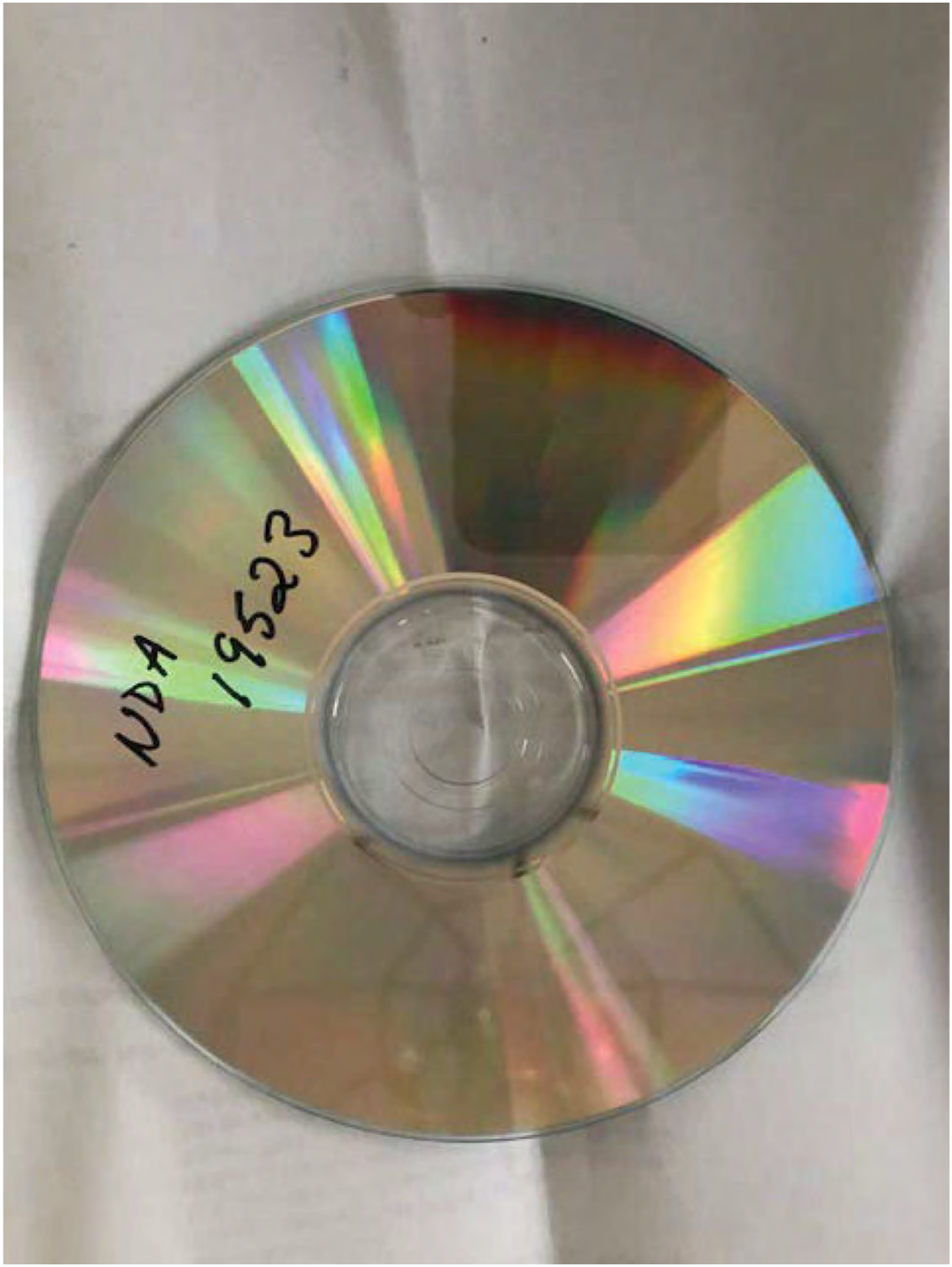

NDA
19523

Exhibit D

NDA
19523

NDA
19523
AP GTR.

NDA

KabiVitrum, Inc.
[illegible] Harbor Bay Parkway
Alameda, CA 94501

Attention: Ronald G. Leonardi, Ph.D.

Gentlemen:

Reference is made to your new drug application dated August 30, 1995, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for 7.25% Cysteine Hydrochloride Injection, USP.

We also acknowledge receipt of your amendment dated September 11, 1996.

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling, dated October 7, 1996. Accordingly, the application is approved, effective on the date of this letter.

Please submit one market package of the drug when available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

Patricia M. Russell, M.D.
Director
Division of Surgical-Dental
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

APPROVAL

NDA

19523

FPL

Rev. 10/7/86, NDA 19-523
7.25% Cysteine HCl

Approved by: [signature] 4.c.-1

PACKAGE INSERT

excessive heat. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product. Solution that has been frozen must not be used.

NDC 0601-0473-10
(Mar 1986)

APPROVED [illegible] 22

Distributed by
KabiVitrum, Inc.
Alameda, CA 94501 USA

PACKAGE INSERT

INDICATIONS AND USAGE

7.25% 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 for protein synthesis.

CONTRAINDICATIONS

Due to the acidity of the solution, 7.25% Cysteine Hydrochloride Injection, USP should not be given by direct injection into a peripheral vein because phlebitis may result.

WARNINGS AND PRECAUTIONS

7.25% 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.

Pregnancy Category C

Animal reproduction studies have not been conducted with 7.25% Cysteine Hydrochloride Injection, USP. It is also not known whether 7.25% Cysteine Hydrochloride Injection, USP can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. 7.25% Cysteine Hydrochloride Injection, USP should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

No adverse reactions to Cysteine Hydrochloride Injection have been reported at the recommended dosage levels.

DOSAGE AND ADMINISTRATION

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 being supplied. 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. An infant receiving 3.0 g/kg/day of amino acids should be provided 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 Novamine™ 11.4% Amino Acids Injection will provide a final concentration of 60 mg cysteine/100 mL of amino acids solution.

These amino acids admixtures should then be aseptically diluted with appropriate caloric substrates calculated to supply the patient with adequate energy. The admixture should be refrigerated until ready for use and used within 24 hours of the time of mixing.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

7.25% Cysteine Hydrochloride Injection, USP (0.5 g cysteine) is supplied in a 10 mL additive syringe.

Exposure of pharmaceutical products to heat should be minimized. Avoid

APPROVED [redacted]22

Reviewed by: [illegible] 4.c.-1

PACKAGE INSERT

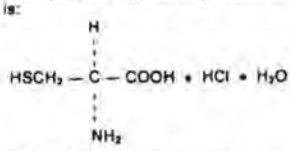
■ ■ ■

747310-0
(Mar 1986)

7.25% Cysteine Hydrochloride Injection, USP, in 10 mL Additive Syringe

DESCRIPTION

7.25% Cysteine Hydrochloride Injection, USP (0.725 g as the monohydrate), is a sterile, nonpyrogenic solution. Each 10 mL provides 0.5 g cysteine and 4.13 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:



$$HSCH_2 - \underset{NH_2}{\overset{H}{C}} - COOH \cdot HCl \cdot H_2O$$

APPROVED [illegible]

CLINICAL PHARMACOLOGY

In the adult, cysteine is synthesized from methionine via the transsulfuration 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.

Rev. 10/7/86, NDA 19-523
7.25% Cysteine HCl

Labeling: [illegible]
NDA No: [illegible] Rec'd. [illegible]
Reviewed by: [illegible] 10/24/86

4.a.-2

UNIT CARTON

NDC 0601-0473-10

7.25% Cysteine Hydrochloride Injection, USP (0.5 g Cysteine)

For Intravenous Use After Dilution

Sterile — Nonpyrogenic Single Dose Container

CAUTION: U.S. Federal law prohibits dispensing without prescription.

Code
473-10 10 mL

CAUTION: MUST BE DILUTED BEFORE USE.
Recommended storage: room temperature (25°C/77°F).
Avoid excessive heat. Solution that has been frozen must not be used.
Each 10 mL contains 0.725 g Cysteine Hydrochloride, USP (0.5 g Cysteine) in Water for Injection, [illegible] providing 4.13 mEq of chloride.
Use only if solution is clear and syringe undamaged.
473100

Distributed by
KabiVitrum, Inc.
Alameda, CA 94501 USA

APPROVED

Labeling: Circ
NDA No: 19-523 Rec'd. 10-7-86.
Reviewed by: GD 10/20/86

SYRINGE LABEL

10 ML NDC 0801-0475-10

7.25% CYSTEINE HYDROCHLORIDE
INJECTION, USP
(0.5 G CYSTEINE)

STERILE - - NONPYROGENIC SINGLE DOSE CONTAINER
FOR INTRAVENOUS USE AFTER DILUTION
SEE PACKAGE INSERT
CAUTION: U.S. FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION
047310-0

DISTRIBUTED BY
KabiVitrum, Inc.
Alameda, CA 94501 USA

CODE
473-10

EXP DATE LOT

UNIT CARTON

APPROVED 10-22-86

NDC 0601-0473-10

7.25% Cysteine Hydrochloride Injection, USP (0.5 g Cysteine)

For Intravenous Use After Dilution

Sterile — Nonpyrogenic Single Dose Container

CAUTION: U.S. Federal law prohibits dispensing without prescription.

Code
473-10 10 mL

CAUTION: MUST BE DILUTED BEFORE USE
Recommended storage: room temperature (25°C/77°F).
Avoid excessive heat. Solution that has been frozen must not be used.
Each 10 mL contains 0.725 g Cysteine Hydrochloride, USP (0.5 g Cysteine) in Water for Injection, USP, providing 4.13 mEq of chloride.
Use only if solution is clear and syringe undamaged.
447310-0

Distributed by
KabiVitrum, Inc.
Alameda, CA 94501 USA

SYRINGE LABEL

APPROVED 10-22-86

10 ML NDC 0601-0473-10

7.25% CYSTEINE HYDROCHLORIDE
INJECTION, USP
(0.5 G CYSTEINE)

STERILE — NONPYROGENIC SINGLE DOSE CONTAINER
FOR INTRAVENOUS USE AFTER DILUTION
SEE PACKAGE INSERT
CAUTION: U.S. FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION 0473-10

DISTRIBUTED BY
KabiVitrum, Inc.
Alameda CA 94501 USA

CODE
473-10

EXP DATE LOT

NDA
19523
MOR

NDA 19-523(A-Az) Completed: 5/30/86

MEDICAL OFFICER'S REVIEW OF NDA SUPPLEMENT

Sponsor: KabiVitrum

Drug: 7.25% Cysteine HCL Injection, USP in 10 ml Additive Syringe

Category: Amino Acid as Nutritional Supplement

Dosage Form: Sterile non-pyrogenic Aqueous Solution

Route of Administration: I.V. Infusion

Indications: Parenteral Nutritional Supplementation

Submitted: 5/7/86
Received: 5/9/86
Assigned: 5/20/86

Type of Submission: NDA supplement in response to not approvable notice.

Background:

The original NDA for this product was submitted 8/30/85. The sponsor was notified that it was not approvable 1/24/86.

Most of the deficiencies involved Chemistry and Microbiology problems. The product was thought to be clinically approvable with labeling revisions. The present submission addresses all cited deficiencies.

Revised Package Insert Review:

The requested revisions in the sections of "Clinical Pharmacology" and Indications and Usage" have been made and they are satisfactory. The remainder of the p.i. is as previously submitted and is satisfactory.

Recommendations

NDA 19-523 is clinically approvable.

John C. Kenealy, M.D.

JUN 19

NDA 19-523

MEDICAL OFFICER'S REVIEW OF ORIGINAL NDA

DATE COMPLETED: 9/25/85

NAME OF SPONSOR: KabiVitrum Inc.
Alameda, CA

NAME OF DRUG: Cysteine hydrochloride, 7.25%

PHARMACOLOGY CATEGORY: Parenteral nutrient (amino acid)

CLASSIFICATION: 5 CU

DOSAGE FORM: Additive to amino acid infusion during total parenteral nutrition

ROUTE OF ADMINISTRATION: Intravenous Infusion

DATE OF SUBMISSION: 8/30/85

DATE RECEIVED: 8/30/85

DATE ASSIGNED: 9/20/85

TYPE OF SUBMISSION: Original NDA

This NDA seeks approval of a cysteine additive for amino acid infusions during TPN. Cysteine has not been considered to be an essential amino acid for normal adults or children. However, there is evidence that the enzyme system responsible for the synthesis of cysteine from methionine becomes active only at term or very shortly thereafter. For this reason, many neonatologists consider cysteine an essential nutrient for pre-term neonates.

The sponsor presents no new clinical data with this NDA. Reference is made to NDA 18-792 (Neopham 6.5% Amino Acids Injections) for evidence of clinical safety and effectiveness. Published and unpublished reports of pre-clinical and clinical studies of cysteine containing amino acid solutions from this country and Europe are summarized.

Reference is made to the approved and commercially available Abbott Laboratories Inc. product, cysteine hydrochloride 0.5 gm.

The bulk of the remainder of this submission is concerned primarily with manufacturing and control data and will be reviewed by chemistry. Evidence of compatibility of this additive with various amino acid solutions commercially available should be considered by Chemistry and Pharmacology.

Drafts of the proposed labeling and of the package insert are submitted.

OCT 24 1985

PACKAGE INSERT REVIEW

Description - Satisfactory

Clinical Pharmacology - This section states that "... adults and pediatric patients with severe liver disease often have an impairment of the enzymatic conversion of methionine to cysteine." The sponsor should be requested to submit references from the literature to support this broad statement. (See recommendations.)

Unsatisfactory

Indications and Usage - In this section, the statement is made that this product is indicated to meet the nutritional requirements "... of adults and pediatric patients with severe liver disease who have impaired enzymatic processes and require TPN." Substantiation of this statement from published reports should be submitted (see recommendations).

Unsatisfactory

Contraindications - Satisfactory

Warnings and Precautions - Satisfactory

Adverse Reactions - Satisfactory

Dosage and Administration - Satisfactory

RECOMMENDATIONS

This NDA is clinically approvable pending the following.

1. Assessment of evidence of compatibility of this additive with all commercially available amino acid solutions by Chemistry and Pharmacology.

2. The following comments should be addressed to the sponsor concerning the package insert.

   a. Clinical Pharmacology - In this section, the last sentence states, "In addition, adults and pediatric patients with severe liver disease often have an impairment of the enzymatic conversion of methionine to cysteine." Please submit appropriate references to substantiate this statement. Otherwise, please revise the statement to read as follows: "In addition, adult and pediatric patients with severe liver disease may have an impairment of the enzymatic conversion of methionine to cysteine."

b. Indications and Usage - In this section, please modify the statement "... adults and pediatric patients with severe liver disease who have impaired enzymatic conversion ..." to read "... adults and pediatric patients with severe liver disease who may have impaired enzymatic conversion ...," unless appropriate references are sited as above requested.

John C. Kenealy, M.D.

NDA 19-523
HFN-160
HFN-340
R/D JKenealy 9/25/85
R/D Init. by PGWalters 9/25/85
FT OLA 2046N A0121N 10/22/85
Doc. Room 160

NDA
19523
Chem
Rev

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE Aug 26, 1986
FROM: C.P. Hoiberg, Supv Chem		OFFICE HFN-160
TO: NDA 19-523(Kabi-Vitrum) File for 7.25% Cys Inj.		DIVISION
SUBJECT: Chem Review(Dr. Sir) #2 Dated Aug 8, 1986		

SUMMARY

From chemistry standpoint, the application should be approved.

cc:Dr. Si[illegible]-160

AUG 2 8 1986

FCW/HR 8/26/86

SIGNATURE

DOCUMENT NUMBER

FORM FD 2034 (6/74)

NDA
19523

Pharm
Rev

NDA 19-523

Applicant: KabiVitrum, Inc.
Alameda, CA 94501

Review #1

Review Date: November 7, 1985

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary
Date Received - August 30, 1985

Drug: 7.25% Cysteine Hydrochloride Injection, USP

Formulation:

	gm/10 ml additive syringe
Cysteine Hydrochloride, USP	0.725 (equivalent to 0.5 gm Cysteine)
Water for Injection, USP	q.s.

Category: Fluid and Nutrient Replenisher - Additive to Amino Acids Solutions During Total Parenteral Nutrition

Related
NDAs: 18-792 - Neopham, 6.5% Amino Acids Injection

Marketing Indication: Additive to amino acid infusions to meet nutritional requirements of newborn infants requiring total parenteral nutrition (TPN) and of adults and pediatric patients with severe liver disease who have impaired enzymatic processes and require TPN.

For newborn infants, 7.25% Cysteine Hydrochloride Injection, USP should be added to the amino acid solution to provide cysteine at approximately 1.5% of the total amino acids being supplied (e.g. an infant receiving amino acid infusions at 2.5 gm/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). For adults, a dosage of 5 mg cysteine/gm of amino acids can be used.

NOV 22 1985

New Preclinical Studies: None.

Applicant refers to preclinical data in NDA 18-792 and to support this NDA. is also used in support of this NDA.

Reference is made to the pharmacology review (7-15-82) by James E. Wilson, Ph.D. in NDA 18-792. Preclinical data are summarized in the Evaluation section.

Evaluation:

This NDA is for 7.25% Cysteine Hydrochloride Injection, USP, supplied in a 10 ml additive glass barrel syringe. Each 10 ml provides 0.5 gm cysteine and 4.13 mEq of chloride in Water for Injection, USP. Cysteine is to be used as an additive to amino acid infusions to meet nutritional requirements of newborn infants requiring total parenteral nutrition (TPN) and of adults and pediatric patients with severe liver disease who have impaired enzymatic processes and require TPN. For infants it is recommended that 7.25% Cysteine Hydrochloride Injection, USP be added to the amino acid solution to provide cysteine at approximately 1.5% of the total amino acids being supplied. For example, an infant receiving an amino acid infusion at 2.5 gm/kg/day should be provided 37.5 mg/kg/day of cysteine while 5 mg cysteine/gm of amino acids can be used for an adult. This drug is chemically and pharmacologically related to 5% Cysteine Hydrochloride Monohydrate Injection marketed by Abbott Laboratories.

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 be used with amino acid solutions.

Cysteine is generally considered an essential amino acid in infants and young children due to the absence of inadequate levels of the hepatic enzyme cystathionase. This enzyme system converts methionine to cysteine in normal adults; however, the age at which methionine conversion to cysteine becomes adequate is unknown. Additionally, patients with severe liver disease may have an impairment of the enzymatic conversion of methionine to cysteine.

No new preclinical data were submitted. Reference is made to NDA 18-792 (Neopham 6.5% Amino Acids Injection) and and for preclinical data to support this NDA. Animal safety studies of Neopham, submitted to NDA 18-792, included 28 and 56 day subchronic toxicity studies in rats and dogs, respectively, which were conducted by Vitrum Ltd., Stockholm, Sweden.

England, conducted animal safety studies of the silicone fluid for the lubrication of medical devices.

HRC conducted USP XX Biological Test Procedures for Elastomeric Closures for Injection. These studies were considered pivotal and adequate.

Neopham, 6.5% Amino Acids Injection, formulated with 18 amino acids, including L-cysteine 1.0 gm/liter, in a pattern similar to the amino acid pattern in the proteins of human breast milk, demonstrated a low order of toxicity in acute intravenous toxicity studies in four species (mice, rats, rabbits and dogs). In mice, the intravenous LD_{50} values of Neopham ranged from 108-282 ml/kg/day. The clinical dosage ranges from 15-23 ml/kg/day (1-1.5 gm/kg/day)

A 28 day intravenous toxicity study of Neopham, infused at different dosages over 20 hour periods, was conducted in the rat. Animals infused with 290 (2.7 gm N) ml/kg/day on a nitrogen-free diet lost more weight during an adaptation period than parallel control rats given an oral casein plus 0.6% methionine diet. These animals had a mean significant increase in the relative organ weights of kidney and spleen, but the increases could not be correlated with any histopathological abnormalities or changes in blood chemistry. Some differences were observed in the total protein, globulin fractions and albumin between the infused and non-infused groups, but these were explained by the varied nutritional intakes.

A 56 day intravenous toxicity study of Neopham (15 or 45 ml/kg infused at 9 ml/kg/hr for 5 hours) in dogs caused emesis at the higher dosage, particularly when the infusion rate was excessive.

A subcutaneous toxicity study of Neopham administered to neonatal rats from days 10-14 of life showed no difference in the level of DNA in the brain compared to rats similarly treated with 5% dextrose. There were some sex differences when each sex was examined alone, but the deviations were in the opposite direction and counterbalanced each other. Higher levels of cholesterol in the cerebrum and cerebellum for both sexes were observed at 21 and 31 days in the amino acid group than in the dextrose controls. At 60 days, the cerebellar level of cholesterol in females was significantly higher than the control value. Investigators theorized that treatment of the neonates with the amino acid mixture may have simulated the myelination process. Some neonates which were allowed to mature and intermate showed no differences between the two groups in terms of fertility, litter size, number of stillbirths or survival of progeny to weaning.

silicone fluid for the lubrication of medical devices
passed requirements for acute toxicity, intracutaneous reactivity, tissue reaction, pyrogenicity, 90 day implant and cell culture test.

formulation passed the USP XX Biological Test Procedures for Elastomeric Closures for Injection (acute systemic and intracutaneous reactivity tests in mice and rabbits, respectively).

Labeling is considered satisfactory.

Conclusion

This NDA is considered approvable from the standpoint of pharmacology.

Clyde G. Oberlander
Pharmacologist

cc:

NDA 19-523

Applicant: KabiVitrum, Inc.
Alameda, CA 94501

Review #2

Date of Review: May 16, 1986

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
A-AZ - May 7, 1986

5-14-86

Drug: 7.25% Cysteine Hydrochloride Injection, USP

Category: Fluid and Nutrient Replenisher - Additive to Amino Acids Solutions During Total Parenteral Nutrition

Evaluation

This amendment responds to our letter of January 24, 1986 concerning chemistry and labeling deficiencies. Labeling is satisfactory by pharmacology.

Conclusion

This NDA is considered approvable from the standpoint of pharmacology.

Clyde G. Oberlander
Pharmacologist

cc:

MAY 2[illegible] 1986

Admixture Concentration (Per Liter)

	7740	7528	7741	7529	7742	7530	7743	7531
Dextrose, Monohydrate USP(g)	50	50	250	250	100	100	250	250
Isoleucine, USP (g)	2.31	2.31	2.31	2.31	2.80	2.80	2.80	2.80
Leucine, USP (g)	3.50	3.50	3.50	3.50	4.25	4.25	4.25	4.25
Lysine (as acetate) USP (g)	3.68	3.68	3.68	3.68	4.46	4.46	4.46	4.46
Methionine, USP (g)	0.60	0.60	0.60	0.73	0.73	0.73	0.73	0.73
Phenylalanine,USP(g)	1.04	1.04	1.04	1.26	1.26	1.26	1.26	1.26
Threonine, USP (g)	1.40	1.40	1.40	1.40	1.70	1.70	1.70	1.70
Tryptophan, USP (g)	0.70	0.70	0.70	0.70	0.85	0.85	0.85	0.85
Valine, USP (g)	1.75	1.75	1.75	1.75	2.12	2.12	2.12	2.12
N-Acetyl-L-Tyrosine(g)	0.94	0.94	0.94	0.94	1.15	1.15	1.15	1.15
Alanine, USP (g)	3.48	3.48	3.48	3.48	4.22	4.22	4.22	4.22
Arginine, USP (g)	3.56	3.56	3.56	3.56	4.32	4.32	4.32	4.32
Glycine, USP (g)	1.75	1.75	1.75	1.75	2.12	2.12	2.12	2.12
Proline, USP (g)	2.52	2.52	2.52	2.52	3.07	3.07	3.07	3.07
Histidine, USP (g)	1.05	1.05	1.05	1.05	1.28	1.28	1.28	1.28
Serine, USP (g)	1.86	1.86	1.86	1.86	2.25	2.25	2.25	2.25
Glutamic Acid (g)	2.58	2.58	2.58	2.58	3.14	3.14	3.14	3.14
Aspartic Acid (g)	2.45	2.45	2.45	2.45	2.98	2.98	2.98	2.98
Total Amino Acids (g)	35	35	35	35	42.5	42.5	42.5	42.5
Sodium Hydrosulfite(g)	0.30	---	0.30	---	0.30	---	0.30	---
Potassium Metabisulfite(g)	---	0.30	---	0.30	---	0.30	---	0.30
Sodium (mEq)	41*	38	40*	35.7	43.7*	40	42*	38.5
Potassium (mEq)	13	15.7**	33	35.7**	13	15.7**	33	35.7**
Chloride (mEq)	36.5	36.5	43	43	36.5	36.5	43	43
Magnesium (mEq)	3	3	5	5	3	3	5	5
Phosphorous (mM)	3.5	3.5	15	15	3.5	3.5	15	15
Acetate (mEq)	25.1	25.1	25.1	25.1	30.5	30.5	30.5	30.5
Osmolarity (mOsm)	616	616	1420	1420	919	919	1438	1438
pH (approx.)	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8

*Includes sodium from antioxidant
**Includes potassium from antioxidant

CONTAINER CHARACTERISTICS:

Upper chamber contains 500 ml of the amino acid formulation at a concentration that this twice the final admixture. Lower chamber contains 500 ml of dextrose again at twice the concentration of the final admixture.

Abbott's Nutrimix Dual-Chamber is fabricated from the firm's CR3 polyester.

Additive port and rubber sleeve stopper are identical to that used currently on approved polyvinyl chloride containers. Cyclohexamone is used as a solvent sealant for attaching administration and additive port assemblies to their respective exit tubes.

RELATED DMFs:

RELATED NDAs: 19-437, 19-438, 19-491, 19-493, 19-504, 19-505, and 19-506.

DOSAGE:

AMINOSYN II with electrolytes in dextrose injection may be infused through a central or peripheral vein. AMINOSYN II 3.5% with Electrolytes in 25% Dextrose Injection and AMINOSYN II 4.25% with electrolytes in 25% Dextrose Injection are hypertonic and may not be administered by peripheral vein. AMINOSYN II 4.25%M, in 10% Dextrose Injection is also hypertonic, and may be administered by peripheral vein only if lipid emulsion is administered simultaneously.

The infusion rate for central vein AMINOSYN II with electrolytes in dextrose injection should be 2 ml/min initially and may be gradually increased.

Adults: The daily nutrient requirements of the average adult patient are about 30 kcal/kkg, 12 to 18 grams of nitrogen total and between 2500 to 3000 ml total of fluids per day. In depleted and severely traumatized patients the requirements are significantly higher. In such cases 4000 calories and 25 grams of nitrogen or more may be required daily. Infusion rate of the admixtures should be 2 ml/min initially and may be gradually increased.

Pediatric: Infants generally receive a 2 to 2.5% amino acid solution, but older pediatric patients can tolerate amino acids in concentrations of up to 5%. Dosage is prescribed as follows: infants, 2 to 3g/kg/day; ages 1 to 3 years, 2 to 2.5 g/kg/day; ages 4 to 12 years, 2 g/kg/day; ages 13 to 15 years, 1.7 g/kg/day; ages 16 and above, 1.5g/kg/day.

LITERATURE REFERENCES

1. Oral versus subcutaneous toxicity of glutamate at several ages in mice.---

Age (Days)	Oral LED* (mg/g)	SC LED* (mg/g)
10	0.50	0.35
21	1.00	0.80
45	1.50	1.25
60	2.00	1.50

*The lowest effective dose (LED) at any given age was established by administration of glutamate either orally or SC to mice over a range of doses and determining histologically the lowest dose which in >50% of the animals treated at that dose (n=6), produced 5 necrotic neuronal profiles in a representative section cut through the arcuate hypothalamic nucleus at its point of maximal damage (Olney, Neurobehav. Toxicol. Teratol. 6: 455-462, 1984).

2. Correlation of oral glutamate dose and neuronal necrosis to plasma amino acid levels in young mice. Plasma glutamate levels of 24 to 50 micromoles/dl produced no neuronal lesions, levels of from 50-52 micromoles/dl produced small lesions, and levels greater than 52 micromoles/dl produced significant degree of necrosis. Experiments with control animals indicated that normal glutamate levels were 6-12 micromoles/dl. The threshold value for minimum neuronal damage was 50-52 micromoles/dl and at this level only 1 of 12 animals showed neuronal damage. Experiments with 25-day-old mice indicated that glutamate susceptibility decreases with age (Stegnik et al, Toxicology 2: 285-99, 1974).

3. Correlation of oral aspartate dose and neuronal necrosis to plasma amino acid levels in infant mice. Eight-day-old mice were given single oral doses of sodium aspartate by gavage.

Aspartate Dose (mmoles/kg)	Mean Peak Plasma Level (Micromol/dl) ASP	GLU	GLU+ASP	Affected Animals	NN/S
0	4.3	11	15	0/10	0
3.76	87	64	127	0/20	0
4.89	158	69	227	3/10	7.3
5.64	235	94	329	12/12	46
7.52	311	119	430	18/18	81

Abbreviations used: ASP, aspartate; GLU, glutamate; NN/S, number of necrotic neurons/section of maximal damage.

Reference: Finklestein et al, Toxicology 29: 109-119, 1983

4. Additive toxic effect of glutamate and aspartate in infant mice. Mice, 10 to 12 days old, were given single oral doses of monosodium glutamate (MSG) or monosodium asparate (MSA) alone and in combination.

Test Compound	Dose (g/kg)	Number Treated	Number Affected	Necrotic Hypothalamic Neurones
None	--	10	0	0
MSG	0.50	23	12	7
MSG	1.00	19	19	25
MSG	1.00	4	4	26
MSG/MSA	0.50/0.50	8	8	2

A mixture of MSG (0.5 g/kg) and monosodium aspartate (0.5g/kg) developed a degree of hypothalamic damage characteristically seen in animals treated with either agent at 1g/kg (Olney and HO, Nature 227:609-11, 1970).

5. Dicarboxylic amino acid concentration in plasma of human infants. Eight infants (1.2 to 2.8 kg) were fed parenterally 180 kcal/kg/day) with two regimens containing dextrose (15g/kg/day), amino acids (2g/kg/day), and lipid 2g/kg/day), for successive 3-day periods in a cross-over design. Regimen I was NEOPHAM (KabiVitrum) and Regimen II was TRAVASOL (Travenol Laboratories). NEOPHAM contains aspartate and glutamate whereas TRAVASOL does not.

Mean Plasma Concentration (Micromoles per DL)

Treatment Regimen	Aspartate	Glutamate
Dextrose Only	1.9	5.0
Regimen I (NEOPHAM)	3.4	8.7
Regimen II (TRAVASOL)	2.7	6.7
Normal Orally Fed Controls	2.6	10.7

Regimen I provided a mean of 226 mg (1.537 mmol) of glutamate and 130 mg 0.977 mmol) of aspartate per kg per day. Regimen II provided no glutamate or aspartate.

Reference: Bell et al., Am. J. Clin. Nutr. 37: 99-107, 1983.

EVALUATION:

AMINOSYN II, one of the proposed solutions in the firm's Nutrimix Dual-Chamber Container has the same number and the same ratio of amino acids as that found in the firm's approved NDA 19-437 AMINOSYN II with Electrolytes (An Amino Acid Injection) in Abbovac glass bottles. Other NDAs containing AMINOSYN II and approved by the reviewing pharmacologist are 19-491, 19-493, 19-504, 19-505, and 19-506. Highest concentration of sodium hydrosulfite is 0.60 g/L in NDAs 19-491 and 19-493. In the others either sodium hydrosulfite or potassium metabisulfite may be used in concentrations ranging from 0.20-0.30 g/L. The value selected for the present NDA is 0.30 g/L. AMINOSYN II has all the amino acids of marketed AMINOSYN with the exception of tyrosine which has been deleted. Added to AMINOSYN II are L-aspartic acid, L-glutamic acid, and N-acetyl-L-tyrosine. Attention will be directed mainly towards these last three compounds in this review.

Glutamate and aspartate cause hypothalamic neuronal necrosis when administered orally or parenterally to newborn rodents in large doses. Adult rodents, on the other hand, are less sensitive to the neurotoxic effects of these dicarboxylic amino acids. The necrosis occurs in or near certain brain regions that lack blood brain barriers (circumventricular organs, CVO). The newborn mouse, the most susceptible of all species that have been examined, tolerates plasma glutamate plus aspartate concentrations up to 50 micromol/dl (approximately four times normal) without evidence of neuronal necrosis. Neuronal necrosis only occurs when the mean plasma glutamate plus aspartate concentration exceeds 60 micromol/dl (Bell et al Aeta Chirurgia Scand. 517(s): 29-37, 1983).

The reference by Olney (Item 1 in LITERATURE REFERENCES) states that while some neurotoxic agents are much more effective when administered parenterally than orally, this is not the case for either glutamate or aspartate. These agents are about 75% as effective by the oral route when compared with administration by the subcutaneous route. Several species in which brain damage following oral administration of glutamate includes rats, mice, guinea pigs, and monkeys. There is good agreement, according to Olney, among laboratories that glutamate or aspartate is effective in destroying CVO neurons in either infant mice or rats beginning at an oral dose of 0.5g/kg.

Oral glutamate tolerance tests (Olney, Reference 1 above) have been conducted on both infant and adult mice and monkeys over a wide range of loading doses (100-2000 mg/kg) and on adult humans with the top loading dose restricted to 200 mg/kg (comparable data on human young are nonexistent). The dose-response profile is more similar for monkeys and mice than for humans. Mice are less tolerant than monkeys (higher plasma glutamate values from a given load). Infants of either species are less tolerant than adults and the adult human is far less tolerant than either mice or monkeys of any age. It is believed that a similar age differential might exist for the human, such that the slope of the response curve for the human infant would be steeper than for the human adult.

In spite of the low tolerance to oral doses of glutamate (high plasma values from a load dose), the human infant may be more resistant to necrosis of hypothalamic neurons than non-humanm primates and rodents. Unfortunately the delayed sequelae such as obesity and subtle disturbances in the neuroendocrine status of the human infant or child would not be evident until adolescence or perhaps early adulthood, approximately twenty years later.

Oddly enough, human breast milk contains no glutamic acid or aspartic acid but does contain N-acetyl-L-tyrosine. The presence of this last compound in milk, in this reviewer's opinion, is supportative evidence of safety for the amino acid derivative. Even breast milk, as stated by one authority, is insufficient for long term total parenteral nutrition in the premature infant.

For approximately 20 years prior to 1969, the amount of glutamate added to a single 4 1/2 oz. jar of baby food was up to 25X that found in a 4 1/2 oz. feeding of mother's milk. On a mg/kg body weight basis, one jar of baby food provided a human infant with 1/4 the oral load of glutamate known to destroy hypothalmic neurons in infant animal brain. Although glutamate is not added to baby foods today, babies and young children are exposed to large loads of glutamate through adult foods.

One author (Olney, Neurotoxicology 2:163-192, 1980) points out a popular trend to regard both asparate and glutamate as promising ingredients in "health tonics" which are dry-base beverages distributed primarily through health food stores. One packet of "C-Pop" which is intended to make a 6 oz serving of beverage, contains 313 mg of free aspartate. If aspartame is added as a sweetener, the concentration of aspartate would increase further.

This reviewer feels that in light of the slow infusion rate of AMINOSYN II and the small increases in mean plasma concentrations of aspartate and glutamate when 2g/kg/day of amino acids was infused into infants as NEOPHAM, the risks of parenteral administration of dicarboxylic amino acids is probably less than that associated with certain infant foods. As this reviewer has pointed out in the past, safety in total parenteral nutrition depends upon adequate clinical monitoring. In this regard the package insert warns that administration of amino acid solutions to a person with hepatic insufficiency may result in serum amino acid imbalances, metabolic alkalosis, prerenal azotemia, hyperammonemia, stupor, and coma. The measurement of blood ammonia levels in infants is stressed because of possible mental retardation from hyperammonemia.

The CR3 polyester container is the same Nutrimix Dual-Chember container as approved in related NDA 19-118 AMINOSYN 3.5% (crystalline amino acid solution) with 25% Dextrose in Flexible Container, related NDA 19-119 AMINOSYN 4.25% (crystalline amino acid solution) with 25% Dextrose in Flexible Container, and related N . 19-120 AMINOSYN 3.5% (crystalline amino acid solution with 5% Dextrose in Flexible Container. Likewise, NDAs 19-504, 19-505, and 19-506 utilize the Nutrimix Dual-Chamber Container and have beedn approved from the standpoint of pharmacology Safety information on Abbott's CR3 polyester container is in the phmacologist's review of the three approved NDAs.

CONCLUSION:

Application is approvable from the standpoint of preclinical animal studies.

Labeling was examined for conformity with the Labeling Format Revision Program, and found adequate from the standpoint of pharmacology.

J.E. Wilson, Ph.D.
6/19/86

cc: NDA 19-564
HFN 160, HFN 340
Doc Room 160
HFN 102 Glocklin
R/D JEWilson,5/19/86
R/D init. JKInscoe,5/20/86
FT/jb,W5016P,D3638P,5/21/86

NDA
19523
Micro
Rev

Division of Surgical-Dental Drug Products

Microbiologist's Review No. 2

July 1, 1986

A. 1. NDA: 19-523

Applicant: KabiVitrum, Inc.
1311 Harbor Bay Parkway
Alameda, CA 94501

2. Product Name: 7.25% Cysteine Hydrochloride Injection, USP

3. Dosage Form: sterile solution in 10 ml additive syringe

4. Pharmacological Category and/or Principle Indication:

Additive for use with amino acids solutions in parenteral nutrition.

B. 1. Initial Submission: August 30, 1985

2. Amendments: October 15, 1985
May 7, 1986 (subject of this review)
received for review 6/4/86.

3. Supporting Documents:

4. Related Documents:

NDA 17-673/S-006 Abbott Laboratories

C. Remarks:

JUL 7 1986

D. Conclusions:

Recommend approval on the basis of sterility assurance.

Peter H. Cooney

Peter H. Cooney, PhD.

cc:
NDA 19-523
HFN-160, Doc Rm 160
HFN-160/PHCooney:7/1/86
R/D init. by CPHoibery:7/1/86/PHRussell:7/2/86
f/t deg: 7/2/86 #2651X/00035

Exhibit E

From: **Madan Chilakuri** <mc@pharmaregllc.com>
Date: Fri, Jul 28, 2017 at 5:07 PM
Subject: L-Cysteine HCl Hospira NDA approval History
To: Michael Major <mwm@mppgroupllc.com>, Sean Brynjelsen <brynjelsen@gmail.com>, Rosen, Barry <barry.rosen@advocatehealth.com>

Dear All,

Please find the attached NDA019523 approval history received from the FDA for L-Cystine HCl Injection held by Hospira.

According to the approval history, the RLD product concentration is 7.25% L-cysteine Hydrochlore

Regards,
Madan

Pharma Regulatory Consultants LLC
Ph: 207-756-4065 fx: 224-372-5396
mc@pharmaregllc.com

NDA
19523

NDA
19523
AP CTR.

NDA

KabiVitrum, Inc.
2211 Harbor Bay Parkway
Alameda, CA 94501

Attention: Ronald G. Leonardi, Ph.D.

Gentlemen:

Reference is made to your new drug application dated August 30, 1995, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for 7.25% Cysteine Hydrochloride Injection, USP.

We also acknowledge receipt of your amendment dated September 11, 1996.

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling, dated October 7, 1996. Accordingly, the application is approved, effective on the date of this letter.

Please submit one market package of the drug when available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

Patricia M. Russell, M.D.
Director
Division of Surgical-Dental
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

APPROVAL

NDA

19523

FPL

Rev. 10/7/86, NDA 19-523
7.25% Cysteine HCl

Approved by: [signature] 10/21/86 4.c.-1

PACKAGE INSERT

excessive heat. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product. Solution that has been frozen must not be used.

NDC 0601-0473-10
(Mar 1986)

APPROVED [illegible] 22

Distributed by
KabiVitrum, Inc.
Alameda, CA 94501 USA

Rev. 10/7/86, NDA 19-523
7.25% Cysteine HCl

[redacted] 4.c.-1

PACKAGE INSERT

INDICATIONS AND USAGE

7.25% 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 for protein synthesis.

CONTRAINDICATIONS

Due to the acidity of the solution, 7.25% Cysteine Hydrochloride Injection, USP should not be given by direct injection into a peripheral vein because phlebitis may result.

WARNINGS AND PRECAUTIONS

7.25% 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.

Pregnancy Category C

Animal reproduction studies have not been conducted with 7.25% Cysteine Hydrochloride Injection, USP. It is also not known whether 7.25% Cysteine Hydrochloride Injection, USP can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. 7.25% Cysteine Hydrochloride Injection, USP should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

No adverse reactions to Cysteine Hydrochloride Injection have been reported at the recommended dosage levels.

DOSAGE AND ADMINISTRATION

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 being supplied. 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. An infant receiving 3.0 g/kg/day of amino acids should be provided 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 Novamine™ 11.4% Amino Acids Injection will provide a final concentration of 60 mg cysteine/100 mL of amino acids solution.

These amino acids admixtures should then be aseptically diluted with appropriate caloric substrates calculated to supply the patient with adequate energy. The admixture should be refrigerated until ready for use and used within 24 hours of the time of mixing.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

7.25% Cysteine Hydrochloride Injection, USP (0.5 g cysteine) is supplied in a 10 mL additive syringe.

Exposure of pharmaceutical products to heat should be minimized. Avoid

APPROVED [redacted]2

[redacted]

PACKAGE INSERT

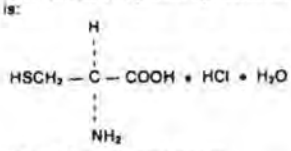
■ ■ ■

747310-0
(Mar 1986)

7.25% Cysteine Hydrochloride Injection, USP, in 10 mL Additive Syringe

DESCRIPTION

7.25% Cysteine Hydrochloride Injection, USP (0.725 g as the monohydrate), is a sterile, nonpyrogenic solution. Each 10 mL provides 0.5 g cysteine and 4.13 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:



$$HSCH_2 - \underset{\displaystyle NH_2}{\overset{\displaystyle H}{\underset{|}{\overset{|}{C}}}} - COOH \cdot HCl \cdot H_2O$$

APPROVED ... 22

CLINICAL PHARMACOLOGY

In the adult, cysteine is synthesized from methionine via the transsulfuration 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.

Rev. 10/7/86, NDA 19-523
7.25% Cysteine HCl

Labeling: [illegible]
NDA No: [illegible] Rec'd. [illegible]
Reviewed by: [illegible] 10/24/86

4.a.-2

UNIT CARTON

NDC 0601-0473-10

7.25% Cysteine Hydrochloride Injection, USP (0.5 g Cysteine)

For Intravenous Use After Dilution

Sterile — Nonpyrogenic Single Dose Container

CAUTION: U.S. Federal law prohibits dispensing without prescription.

Code
473-10 10 mL

CAUTION: MUST BE DILUTED BEFORE USE.
Recommended storage: room temperature (25°C/77°F).
Avoid excessive heat. Solution that has been frozen must not be used.
Each 10 mL contains 0.725 g Cysteine Hydrochloride, USP (0.5 g Cysteine) in Water for Injection, [illegible] providing 4.13 mEq of chloride.
Use only if solution is clear and syringe undamaged.
473100

Distributed by
KabiVitrum, Inc.
Alameda, CA 94501 USA

APPROVED

Labeling: Circ
NDA No: 19-523 Rec'd. 10-7-86
Reviewed by: GD 10/20/86

SYRINGE LABEL

10 ML NDC 0801-0475-10

7.25% CYSTEINE HYDROCHLORIDE
INJECTION, USP
(0.5 G CYSTEINE)

STERILE - - NONPYROGENIC SINGLE DOSE CONTAINER
FOR INTRAVENOUS USE AFTER DILUTION
SEE PACKAGE INSERT
CAUTION: U.S. FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION
047310-0

DISTRIBUTED BY CODE
KabiVitrum, Inc. 473-10
Alameda, CA 94501 USA

EXP DATE LOT

UNIT CARTON

APPROVED 10-22-86

NDC 0601-0473-10

7.25% Cysteine Hydrochloride Injection, USP (0.5 g Cysteine)

For Intravenous Use After Dilution

Sterile — Nonpyrogenic Single Dose Container

CAUTION: U.S. Federal law prohibits dispensing without prescription.

Code
473-10 10 mL

CAUTION: MUST BE DILUTED BEFORE USE
Recommended storage: room temperature (25°C/77°F).
Avoid excessive heat. Solution that has been frozen must not be used.
Each 10 mL contains 0.725 g Cysteine Hydrochloride, USP (0.5 g Cysteine) in Water for Injection, USP, providing 4.13 mEq of chloride.
Use only if solution is clear and syringe undamaged.
447310-0

Distributed by
KabiVitrum, Inc.
Alameda, CA 94501 USA

SYRINGE LABEL

APPROVED 10-22-86

10 ML NDC 0601-0473-10

7.25% CYSTEINE HYDROCHLORIDE
INJECTION, USP
(0.5 G CYSTEINE)

STERILE — NONPYROGENIC SINGLE DOSE CONTAINER
FOR INTRAVENOUS USE AFTER DILUTION
SEE PACKAGE INSERT
CAUTION: U.S. FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION

0473-10

DISTRIBUTED BY
KabiVitrum, Inc.
Alameda CA 94501 USA

CODE
473-10

EXP DATE LOT

NDA
19523
MOR

NDA 19-523(A-Az) Completed: 5/30/86

MEDICAL OFFICER'S REVIEW OF NDA SUPPLEMENT

Sponsor: KabiVitrum

Drug: 7.25% Cysteine HCL Injection, USP in 10 ml Additive Syringe

Category: Amino Acid as Nutritional Supplement

Dosage Form: Sterile non-pyrogenic Aqueous Solution

Route of Administration: I.V. Infusion

Indications: Parenteral Nutritional Supplementation

Submitted: 5/7/86
Received: 5/9/86
Assigned: 5/20/86

Type of Submission: NDA supplement in response to not approvable notice.

Background:

The original NDA for this product was submitted 8/30/85. The sponsor was notified that it was not approvable 1/24/86.

Most of the deficiencies involved Chemistry and Microbiology problems. The product was thought to be clinically approvable with labeling revisions. The present submission addresses all cited deficiencies.

Revised Package Insert Review:

The requested revisions in the sections of "Clinical Pharmacology" and Indications and Usage" have been made and they are satisfactory. The remainder of the p.i. is as previously submitted and is satisfactory.

Recommendations

NDA 19-523 is clinically approvable.

John C. Kenealy, M.D.

JUN 1986

NDA 19-523

MEDICAL OFFICER'S REVIEW OF ORIGINAL NDA

DATE COMPLETED: 9/25/85

NAME OF SPONSOR: KabiVitrum Inc.
Alameda, CA

NAME OF DRUG: Cysteine hydrochloride, 7.25%

PHARMACOLOGY CATEGORY: Parenteral nutrient (amino acid)

CLASSIFICATION: 5 CU

DOSAGE FORM: Additive to amino acid infusion during total parenteral nutrition

ROUTE OF ADMINISTRATION: Intravenous Infusion

DATE OF SUBMISSION: 8/30/85

DATE RECEIVED: 8/30/85

DATE ASSIGNED: 9/20/85

TYPE OF SUBMISSION: Original NDA

This NDA seeks approval of a cysteine additive for amino acid infusions during TPN. Cysteine has not been considered to be an essential amino acid for normal adults or children. However, there is evidence that the enzyme system responsible for the synthesis of cysteine from methionine becomes active only at term or very shortly thereafter. For this reason, many neonatologists consider cysteine an essential nutrient for pre-term neonates.

The sponsor presents no new clinical data with this NDA. Reference is made to NDA 18-792 (Neopham 6.5% Amino Acids Injections) for evidence of clinical safety and effectiveness. Published and unpublished reports of pre-clinical and clinical studies of cysteine containing amino acid solutions from this country and Europe are summarized.

Reference is made to the approved and commercially available Abbott Laboratories Inc. product, cysteine hydrochloride 0.5 gm.

The bulk of the remainder of this submission is concerned primarily with manufacturing and control data and will be reviewed by chemistry. Evidence of compatibility of this additive with various amino acid solutions commercially available should be considered by Chemistry and Pharmacology.

Drafts of the proposed labeling and of the package insert are submitted.

OCT 24 1985

PACKAGE INSERT REVIEW

Description - Satisfactory

Clinical Pharmacology - This section states that "... adults and pediatric patients with severe liver disease often have an impairment of the enzymatic conversion of methionine to cysteine." The sponsor should be requested to submit references from the literature to support this broad statement. (See recommendations.)

Unsatisfactory

Indications and Usage - In this section, the statement is made that this product is indicated to meet the nutritional requirements "... of adults and pediatric patients with severe liver disease who have impaired enzymatic processes and require TPN." Substantiation of this statement from published reports should be submitted (see recommendations).

Unsatisfactory

Contraindications - Satisfactory

Warnings and Precautions - Satisfactory

Adverse Reactions - Satisfactory

Dosage and Administration - Satisfactory

RECOMMENDATIONS

This NDA is clinically approvable pending the following.

1. Assessment of evidence of compatibility of this additive with all commercially available amino acid solutions by Chemistry and Pharmacology.

2. The following comments should be addressed to the sponsor concerning the package insert.

   a. Clinical Pharmacology - In this section, the last sentence states, "In addition, adults and pediatric patients with severe liver disease often have an impairment of the enzymatic conversion of methionine to cysteine." Please submit appropriate references to substantiate this statement. Otherwise, please revise the statement to read as follows: "In addition, adult and pediatric patients with severe liver disease may have an impairment of the enzymatic conversion of methionine to cysteine."

b. Indications and Usage - In this section, please modify the statement "... adults and pediatric patients with severe liver disease who have impaired enzymatic conversion ..." to read "... adults and pediatric patients with severe liver disease who may have impaired enzymatic conversion ...," unless appropriate references are sited as above requested.

John C. Kenealy, M.D.

NDA 19-523
HFN-160
HFN-340
R/D JKenealy 9/25/85
R/D Init. by PGWalters 9/25/85
FT OLA 2046N A0121N 10/22/85
Doc. Room 160

NDA
19523
Chem
Rev

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE Aug 26, 1986
FROM: C.P. Hoiberg, Supv Chem		OFFICE HFN-160
TO: NDA 19-523(Kabi-Vitrum) File for 7.25% Cys Inj.		DIVISION
SUBJECT: Chem Review(Dr. Sir) #2 Dated Aug 8, 1986		

SUMMARY

From chemistry standpoint, the application should be approved.

cc:Dr. Si[illegible]-160

AUG 2 8 1986

FCH/HR 8/26/86

SIGNATURE

DOCUMENT NUMBER

FORM FD 2034 (6/74)

NDA
19523

Pharm
Rev

NDA 19-523

Applicant: KabiVitrum, Inc.
Alameda, CA 94501

Review #1

Review Date: November 7, 1985

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary
Date Received - August 30, 1985

Drug: 7.25% Cysteine Hydrochloride Injection, USP

Formulation:

	gm/10 ml additive syringe
Cysteine Hydrochloride, USP	0.725 (equivalent to 0.5 gm Cysteine)
Water for Injection, USP	q.s.

Category: Fluid and Nutrient Replenisher - Additive to Amino Acids Solutions During Total Parenteral Nutrition

Related
NDAs: 18-792 - Neopham, 6.5% Amino Acids Injection

Marketing Indication: Additive to amino acid infusions to meet nutritional requirements of newborn infants requiring total parenteral nutrition (TPN) and of adults and pediatric patients with severe liver disease who have impaired enzymatic processes and require TPN.

For newborn infants, 7.25% Cysteine Hydrochloride Injection, USP should be added to the amino acid solution to provide cysteine at approximately 1.5% of the total amino acids being supplied (e.g. an infant receiving amino acid infusions at 2.5 gm/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). For adults, a dosage of 5 mg cysteine/gm of amino acids can be used.

NOV 22 1985

New Preclinical Studies: None.

Applicant refers to preclinical data in NDA 18-792 and to support this NDA. is also used in support of this NDA.

Reference is made to the pharmacology review (7-15-82) by James E. Wilson, Ph.D. in NDA 18-792. Preclinical data are summarized in the Evaluation section.

Evaluation

This NDA is for 7.25% Cysteine Hydrochloride Injection, USP, supplied in a 10 ml additive glass barrel syringe. Each 10 ml provides 0.5 gm cysteine and 4.13 mEq of chloride in Water for Injection, USP. Cysteine is to be used as an additive to amino acid infusions to meet nutritional requirements of newborn infants requiring total parenteral nutrition (TPN) and of adults and pediatric patients with severe liver disease who have impaired enzymatic processes and require TPN. For infants it is recommended that 7.25% Cysteine Hydrochloride Injection, USP be added to the amino acid solution to provide cysteine at approximately 1.5% of the total amino acids being supplied. For example, an infant receiving an amino acid infusion at 2.5 gm/kg/day should be provided 37.5 mg/kg/day of cysteine while 5 mg cysteine/gm of amino acids can be used for an adult. This drug is chemically and pharmacologically related to 5% Cysteine Hydrochloride Monohydrate Injection marketed by Abbott Laboratories.

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 be used with amino acid solutions.

Cysteine is generally considered an essential amino acid in infants and young children due to the absence of inadequate levels of the hepatic enzyme cystathionase. This enzyme system converts methionine to cysteine in normal adults; however, the age at which methionine conversion to cysteine becomes adequate is unknown. Additionally, patients with severe liver disease may have an impairment of the enzymatic conversion of methionine to cysteine.

No new preclinical data were submitted. Reference is made to NDA 18-792 (Neopham 6.5% Amino Acids Injection) and and for preclinical data to support this NDA. Animal safety studies of Neopham, submitted to NDA 18-792, included 28 and 56 day subchronic toxicity studies in rats and dogs, respectively, which were conducted by Vitrum Ltd., Stockholm, Sweden.

England, conducted animal safety studies of the silicone fluid for the lubrication of medical devices.

HRC conducted USP XX Biological Test Procedures for Elastomeric Closures for Injection. These studies were considered pivotal and adequate.

Neopham, 6.5% Amino Acids Injection, formulated with 18 amino acids, including L-cysteine 1.0 gm/liter, in a pattern similar to the amino acid pattern in the proteins of human breast milk, demonstrated a low order of toxicity in acute intravenous toxicity studies in four species (mice, rats, rabbits and dogs). In mice, the intravenous LD_{50} values of Neopham ranged from 108-282 ml/kg/day. The clinical dosage ranges from 15-23 ml/kg/day (1-1.5 gm/kg/day)

A 28 day intravenous toxicity study of Neopham, infused at different dosages over 20 hour periods, was conducted in the rat. Animals infused with 290 (2.7 gm N) ml/kg/day on a nitrogen-free diet lost more weight during an adaptation period than parallel control rats given an oral casein plus 0.6% methionine diet. These animals had a mean significant increase in the relative organ weights of kidney and spleen, but the increases could not be correlated with any histopathological abnormalities or changes in blood chemistry. Some differences were observed in the total protein, globulin fractions and albumin between the infused and non-infused groups, but these were explained by the varied nutritional intakes.

A 56 day intravenous toxicity study of Neopham (15 or 45 ml/kg infused at 9 ml/kg/hr for 5 hours) in dogs caused emesis at the higher dosage, particularly when the infusion rate was excessive.

A subcutaneous toxicity study of Neopham administered to neonatal rats from days 10-14 of life showed no difference in the level of DNA in the brain compared to rats similarly treated with 5% dextrose. There were some sex differences when each sex was examined alone, but the deviations were in the opposite direction and counterbalanced each other. Higher levels of cholesterol in the cerebrum and cerebellum for both sexes were observed at 21 and 31 days in the amino acid group than in the dextrose controls. At 60 days, the cerebellar level of cholesterol in females was significantly higher than the control value. Investigators theorized that treatment of the neonates with the amino acid mixture may have simulated the myelination process. Some neonates which were allowed to mature and intermate showed no differences between the two groups in terms of fertility, litter size, number of stillbirths or survival of progeny to weaning.

silicone fluid for the lubrication of medical devices
passed requirements for acute toxicity, intracutaneous reactivity, tissue reaction, pyrogenicity, 90 day implant and cell culture test.

formulation passed the USP XX Biological Test Procedures for Elastomeric Closures for Injection (acute ystemic and intracutaneous reactivity tests in mice and rabbits, respectively).

Labeling is considered satisfactory.

Conclusion

This NDA is considered approvable from the standpoint of pharmacology.

Clyde G. Oberlander
Pharmacologist

cc:

NDA 19-523

Applicant: KabiVitrum, Inc.
Alameda, CA 94501

Review #2

Date of Review: May 16, 1986

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
A-AZ - May 7, 1986

Drug: 7.25% Cysteine Hydrochloride Injection, USP

Category: Fluid and Nutrient Replenisher - Additive to Amino Acids Solutions During Total Parenteral Nutrition

Evaluation

This amendment responds to our letter of January 24, 1986 concerning chemistry and labeling deficiencies. Labeling is satisfactory by pharmacology.

Conclusion

This NDA is considered approvable from the standpoint of pharmacology.

Clyde G. Oberlander
Pharmacologist

cc:

MAY 2[illegible] 1986

	Admixture Concentration (Per Liter)							
	7740	7528	7741	7529	7742	7530	7743	7531
Dextrose, Monohydrate USP(g)	50	50	250	250	100	100	250	250
Isoleucine, USP (g)	2.31	2.31	2.31	2.31	2.80	2.80	2.80	2.80
Leucine, USP (g)	3.50	3.50	3.50	3.50	4.25	4.25	4.25	4.25
Lysine (as acetate) USP (g)	3.68	3.68	3.68	3.68	4.46	4.46	4.46	4.46
Methionine, USP (g)	0.60	0.60	0.60	0.73	0.73	0.73	0.73	0.73
Phenylalanine,USP(g)	1.04	1.04	1.04	1.26	1.26	1.26	1.26	1.26
Threonine, USP (g)	1.40	1.40	1.40	1.40	1.70	1.70	1.70	1.70
Tryptophan, USP (g)	0.70	0.70	0.70	0.70	0.85	0.85	0.85	0.85
Valine, USP (g)	1.75	1.75	1.75	1.75	2.12	2.12	2.12	2.12
N-Acetyl-L-Tyrosine(g)	0.94	0.94	0.94	0.94	1.15	1.15	1.15	1.15
Alanine, USP (g)	3.48	3.48	3.48	3.48	4.22	4.22	4.22	4.22
Arginine, USP (g)	3.56	3.56	3.56	3.56	4.32	4.32	4.32	4.32
Glycine, USP (g)	1.75	1.75	1.75	1.75	2.12	2.12	2.12	2.12
Proline, USP (g)	2.52	2.52	2.52	2.52	3.07	3.07	3.07	3.07
Histidine, USP (g)	1.05	1.05	1.05	1.05	1.28	1.28	1.28	1.28
Serine, USP (g)	1.86	1.86	1.86	1.86	2.25	2.25	2.25	2.25
Glutamic Acid (g)	2.58	2.58	2.58	2.58	3.14	3.14	3.14	3.14
Aspartic Acid (g)	2.45	2.45	2.45	2.45	2.98	2.98	2.98	2.98
Total Amino Acids (g)	35	35	35	35	42.5	42.5	42.5	42.5
Sodium Hydrosulfite(g)	0.30	---	0.30	---	0.30	---	0.30	---
Potassium Metabisulfite(g)	---	0.30	---	0.30	---	0.30	---	0.30
Sodium (mEq)	41*	38	40*	35.7	43.7*	40	42*	38.5
Potassium (mEq)	13	15.7**	33	35.7**	13	15.7**	33	35.7**
Chloride (mEq)	36.5	36.5	43	43	36.5	36.5	43	43
Magnesium (mEq)	3	3	5	5	3	3	5	5
Phosphorous (mM)	3.5	3.5	15	15	3.5	3.5	15	15
Acetate (mEq)	25.1	25.1	25.1	25.1	30.5	30.5	30.5	30.5
Osmolarity (mOsm)	616	616	1420	1420	919	919	1438	1438
pH (approx.)	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8

*Includes sodium from antioxidant
**Includes potassium from antioxidant

CONTAINER CHARACTERISTICS:

Upper chamber contains 500 ml of the amino acid formulation at a concentration that this twice the final admixture. Lower chamber contains 500 ml of dextrose again at twice the concentration of the final admixture.

Abbott's Nutrimix Dual-Chamber is fabricated from the firm's CR3 polyester.

Additive port and rubber sleeve stopper are identical to that used currently on approved polyvinyl chloride containers. Cyclohexamone is used as a solvent sealant for attaching administration and additive port assemblies to their respective exit tubes.

RELATED DMFs:

RELATED NDAs: 19-437, 19-438, 19-491, 19-493, 19-504, 19-505, and 19-506.

DOSAGE:

AMINOSYN II with electrolytes in dextrose injection may be infused through a central or peripheral vein. AMINOSYN II 3.5% with Electrolytes in 25% Dextrose Injection and AMINOSYN II 4.25% with electrolytes in 25% Dextrose Injection are hypertonic and may not be administered by peripheral vein. AMINOSYN II 4.25%M, in 10% Dextrose Injection is also hypertonic, and may be administered by peripheral vein only if lipid emulsion is administered simultaneously.

The infusion rate for central vein AMINOSYN II with electrolytes in dextrose injection should be 2 ml/min initially and may be gradually increased.

Adults: The daily nutrient requirements of the average adult patient are about 30 kcal/kkg, 12 to 18 grams of nitrogen total and between 2500 to 3000 ml total of fluids per day. In depleted and severely traumatized patients the requirements are significantly higher. In such cases 4000 calories and 25 grams of nitrogen or more may be required daily. Infusion rate of the admixtures should be 2 ml/min initially and may be gradually increased.

Pediatric: Infants generally receive a 2 to 2.5% amino acid solution, but older pediatric patients can tolerate amino acids in concentrations of up to 5%. Dosage is prescribed as follows: infants, 2 to 3g/kg/day; ages 1 to 3 years, 2 to 2.5 g/kg/day; ages 4 to 12 years, 2 g/kg/day; ages 13 to 15 years, 1.7 g/kg/day; ages 16 and above, 1.5g/kg/day.

LITERATURE REFERENCES

1. Oral versus subcutaneous toxicity of glutamate at several ages in mice.---

Age (Days)	Oral LED* (mg/g)	SC LED* (mg/g)
10	0.50	0.35
21	1.00	0.80
45	1.50	1.25
60	2.00	1.50

*The lowest effective dose (LED) at any given age was established by administration of glutamate either orally or SC to mice over a range of doses and determining histologically the lowest dose which in >50% of the animals treated at that dose (n=6), produced 5 necrotic neuronal profiles in a representative section cut through the arcuate hypothalamic nucleus at its point of maximal damage (Olney, Neurobehav. Toxicol. Teratol. 6: 455-462, 1984).

2. Correlation of oral glutamate dose and neuronal necrosis to plasma amino acid levels in young mice. Plasma glutamate levels of 24 to 50 micromoles/dl produced no neuronal lesions, levels of from 50-52 micromoles/dl produced small lesions, and levels greater than 52 micromoles/dl produced significant degree of necrosis. Experiments with control animals indicated that normal glutamate levels were 6-12 micromoles/dl. The threshold value for minimum neuronal damage was 50-52 micromoles/dl and at this level only 1 of 12 animals showed neuronal damage. Experiments with 25-day-old mice indicated that glutamate susceptibility decreases with age (Stegnik et al, Toxicology 2: 285-99, 1974).

3. Correlation of oral aspartate dose and neuronal necrosis to plasma amino acid levels in infant mice. Eight-day-old mice were given single oral doses of sodium aspartate by gavage.

Aspartate Dose (mmoles/kg)	Mean Peak Plasma Level (Micromol/dl) ASP	GLU	GLU+ASP	Affected Animals	NN/S
0	4.3	11	15	0/10	0
3.76	87	64	127	0/20	0
4.89	158	69	227	3/10	7.3
5.64	235	94	329	12/12	46
7.52	311	119	430	18/18	81

Abbreviations used: ASP, aspartate; GLU, glutamate; NN/S, number of necrotic neurons/section of maximal damage.

Reference: Finklestein et al, Toxicology 29: 109-119, 1983

4. Additive toxic effect of glutamate and aspartate in infant mice. Mice, 10 to 12 days old, were given single oral doses of monosodium glutamate (MSG) or monosodium asparate (MSA) alone and in combination.

Test Compound	Dose (g/kg)	Number Treated	Number Affected	Necrotic Hypothalamic Neurones
None	--	10	0	0
MSG	0.50	23	12	7
MSG	1.00	19	19	25
MSG	1.00	4	4	26
MSG/MSA	0.50/0.50	8	8	27

A mixture of MSG (0.5 g/kg) and monosodium aspartate (0.5g/kg) developed a degree of hypothalamic damage characteristically seen in animals treated with either agent at 1g/kg (Olney and HO, Nature 227:609-11, 1970).

5. Dicarboxylic amino acid concentration in plasma of human infants. Eight infants (1.2 to 2.8 kg) were fed parenterally 180 kcal/kg/day) with two regimens containing dextrose (15g/kg/day), amino acids (2g/kg/day), and lipid 2g/kg/day), for successive 3-day periods in a cross-over design. Regimen I was NEOPHAM (KabiVitrum) and Regimen II was TRAVASOL (Travenol Laboratories). NEOPHAM contains aspartate and glutamate whereas TRAVASOL does not.

Mean Plasma Concentration (Micromoles per DL)

Treatment Regimen	Aspartate	Glutamate
Dextrose Only	1.9	5.0
Regimen I (NEOPHAM)	3.4	8.7
Regimen II (TRAVASOL)	2.7	6.7
Normal Orally Fed Controls	2.6	10.7

Regimen I provided a mean of 226 mg (1.537 mmol) of glutamate and 130 mg 0.977 mmol) of aspartate per kg per day. Regimen II provided no glutamate or aspartate.

Reference: Bell et al., Am. J. Clin. Nutr. 37: 99-107, 1983.

EVALUATION:

AMINOSYN II, one of the proposed solutions in the firm's Nutrimix Dual-Chamber Container has the same number and the same ratio of amino acids as that found in the firm's approved NDA 19-437 AMINOSYN II with Electrolytes (An Amino Acid Injection) in Abbovac glass bottles. Other NDAs containing AMINOSYN II and approved by the reviewing pharmacologist are 19-491, 19-493, 19-504, 19-505, and 19-506. Highest concentration of sodium hydrosulfite is 0.60 g/L in NDAs 19-491 and 19-493. In the others either sodium hydrosulfite or potassium metabisulfite may be used in concentrations ranging from 0.20-0.30 g/L. The value selected for the present NDA is 0.30 g/L. AMINOSYN II has all the amino acids of marketed AMINOSYN with the exception of tyrosine which has been deleted. Added to AMINOSYN II are L-aspartic acid, L-glutamic acid, and N-acetyl-L-tyrosine. Attention will be directed mainly towards these last three compounds in this review.

Glutamate and aspartate cause hypothalamic neuronal necrosis when administered orally or parenterally to newborn rodents in large doses. Adult rodents, on the other hand, are less sensitive to the neurotoxic effects of these dicarboxylic amino acids. The necrosis occurs in or near certain brain regions that lack blood brain barriers (circumventricular organs, CVO). The newborn mouse, the most susceptible of all species that have been examined, tolerates plasma glutamate plus aspartate concentrations up to 50 micromol/dl (approximately four times normal) without evidence of neuronal necrosis. Neuronal necrosis only occurs when the mean plasma glutamate plus aspartate concentration exceeds 60 micromol/dl (Bell et al Aeta Chirurgia Scand. 517(s): 29-37, 1983).

The reference by Olney (Item 1 in LITERATURE REFERENCES) states that while some neurotoxic agents are much more effective when administered parenterally than orally, this is not the case for either glutamate or aspartate. These agents are about 75% as effective by the oral route when compared with administration by the subcutaneous route. Several species in which brain damage following oral administration of glutamate includes rats, mice, guinea pigs, and monkeys. There is good agreement, according to Olney, among laboratories that glutamate or aspartate is effective in destroying CVO neurons in either infant mice or rats beginning at an oral dose of 0.5g/kg.

Oral glutamate tolerance tests (Olney, Reference 1 above) have been conducted on both infant and adult mice and monkeys over a wide range of loading doses (100-2000 mg/kg) and on adult humans with the top loading dose restricted to 200 mg/kg (comparable data on human young are nonexistent). The dose-response profile is more similar for monkeys and mice than for humans. Mice are less tolerant than monkeys (higher plasma glutamate values from a given load). Infants of either species are less tolerant than adults and the adult human is far less tolerant than either mice or monkeys of any age. It is believed that a similar age differential might exist for the human, such that the slope of the response curve for the human infant would be steeper than for the human adult.

In spite of the low tolerance to oral doses of glutamate (high plasma values from a load dose), the human infant may be more resistant to necrosis of hypothalamic neurons than non-humanm primates and rodents. Unfortunately the delayed sequelae such as obesity and subtle disturbances in the neuroendocrine status of the human infant or child would not be evident until adolescence or perhaps early adulthood, approximately twenty years later.

Oddly enough, human breast milk contains no glutamic acid or aspartic acid but does contain N-acetyl-L-tyrosine. The presence of this last compound in milk, in this reviewer's opinion, is supportative evidence of safety for the amino acid derivative. Even breast milk, as stated by one authority, is insufficient for long term total parenteral nutrition in the premature infant.

For approximately 20 years prior to 1969, the amount of glutamate added to a single 4 1/2 oz. jar of baby food was up to 25X that found in a 4 1/2 oz. feeding of mother's milk. On a mg/kg body weight basis, one jar of baby food provided a human infant with 1/4 the oral load of glutamate known to destroy hypothalmic neurons in infant animal brain. Although glutamate is not added to baby foods today, babies and young children are exposed to large loads of glutamate through adult foods.

One author (Olney, Neurotoxicology 2:163-192, 1980) points out a popular trend to regard both asparate and glutamate as promising ingredients in "health tonics" which are dry-base beverages distributed primarily through health food stores. One packet of "C-Pop" which is intended to make a 6 oz serving of beverage, contains 313 mg of free aspartate. If aspartame is added as a sweetener, the concentration of aspartate would increase further.

This reviewer feels that in light of the slow infusion rate of AMINOSYN II and the small increases in mean plasma concentrations of aspartate and glutamate when 2g/kg/day of amino acids was infused into infants as NEOPHAM, the risks of parenteral administration of dicarboxylic amino acids is probably less than that associated with certain infant foods. As this reviewer has pointed out in the past, safety in total parenteral nutrition depends upon adequate clinical monitoring. In this regard the package insert warns that administration of amino acid solutions to a person with hepatic insufficiency may result in serum amino acid imbalances, metabolic alkalosis, prerenal azotemia, hyperammonemia, stupor, and coma. The measurement of blood ammonia levels in infants is stressed because of possible mental retardation from hyperammonemia.

The CR3 polyester container is the same Nutrimix Dual-Chember container as approved in related NDA 19-118 AMINOSYN 3.5% (crystalline amino acid solution) with 25% Dextrose in Flexible Container, related NDA 19-119 AMINOSYN 4.25% (crystalline amino acid solution) with 25% Dextrose in Flexible Container, and related N . 19-120 AMINOSYN 3.5% (crystalline amino acid solution with 5% Dextrose in Flexible Container. Likewise, NDAs 19-504, 19-505, and 19-506 utilize the Nutrimix Dual-Chamber Container and have beedn approved from the standpoint of pharmacology Safety information on Abbott's CR3 polyester container is in the phmacologist's review of the three approved NDAs.

CONCLUSION:

Application is approvable from the standpoint of preclinical animal studies.

Labeling was examined for conformity with the Labeling Format Revision Program, and found adequate from the standpoint of pharmacology.

J.E. Wilson, Ph.D.
6/19/86

cc: NDA 19-564
HFN 160, HFN 340
Doc Room 160
HFN 102 Glocklin
R/D JEWilson,5/19/86
R/D init. JKInscoe,5/20/86
FT/jb,W5016P,D3638P,5/21/86

NDA
19523
Micro
Rev

Division of Surgical-Dental Drug Products

Microbiologist's Review No. 2

July 1, 1986

A. 1. NDA: 19-523

Applicant: KabiVitrum, Inc.
1311 Harbor Bay Parkway
Alameda, CA 94501

2. Product Name: 7.25% Cysteine Hydrochloride Injection, USP

3. Dosage Form: sterile solution in 10 ml additive syringe

4. Pharmacological Category and/or Principle Indication:

Additive for use with amino acids solutions in parenteral nutrition.

B. 1. Initial Submission: August 30, 1985

2. Amendments: October 15, 1985
May 7, 1986 (subject of this review)
received for review 6/4/86.

3. Supporting Documents:

4. Related Documents:

NDA 17-673/S-006 Abbott Laboratories

C. Remarks:

JUL 7 1986

D. Conclusions:

Recommend approval on the basis of sterility assurance.

Peter H. Cooney

Peter H. Cooney, PhD.

cc:
NDA 19-523
HFN-160, Doc Rm 160
HFN-160/PHCooney:7/1/86
R/D init. by CPHoidery:7/1/86/PHRussell:7/2/86
f/t deg: 7/2/86 #2651X/00035