

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**212535Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

**Memorandum**

DEPARTMENT OF HEALTH AND HUMAN  
SERVICES PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**Date:** December 12, 2019  
**From:** Hitesh Shroff, Ph.D.  
Application Technical Lead, Branch V  
Division of New Drug Products II  
Office of New Drug Products

**Through:** Moo-Jhong Rhee, Ph.D.  
Chief, Branch V  
Division of New Drug Products II  
Office of New Drug Products

**To:** CMC Review #1 of NDA 212535

**Subject:** Final Recommendation for NDA 212535

At the time when the CMC Review #1 was completed on November 22, 2019 it had noted the following pending issues:

The label/labeling issues have not been completely resolved.

Because of these deficiencies, the NDA was not recommended for approval from the OPQ perspective.

The applicant submitted the revised Prescribing Information (PI) and container/carton labels on December 11, 2019. The resubmitted CMC sections of the labeling/labels deemed acceptable. (See the Attachment 1)

The applicant submitted additional admixture stability studies results in the amendment dated December 6, 2019. Based on the admixture stability studies it is recommended that when Nouress is admixed with electrolytes e.g. (b) (4), etc. it should not be refrigerated. The admixture should be administered within 24 hours at room temperature. The unused portion should be discarded.

**Recommendation:**

This NDA is now recommended for Approval from the OPQ perspective.

**Application Technical Lead's Assessment and Signature**

The NDA is recommended for Approval from quality perspective.

Hitesh Shroff, Ph.D.  
Application Technical Lead,  
Branch V Division of New Drug Products II  
December 12, 2019

Hitesh N.  
Shroff -S

Digitally signed by Hitesh N.  
Shroff -S  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=2000  
348333, cn=Hitesh N. Shroff -S  
Date: 2019.12.12 15:48:05 -05'00'

## Attachment 1

**Memorandum**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**Date:** December 11, 2019

**From:** Hong Cai, Ph.D.  
Drug Product Reviewer  
Office of New Drug Products  
Branch IV/DNDP II

**Through:** Moo-Jhong Rhee, Ph.D.  
Chief, Branch IV  
Office of New Drug Products  
Branch IV/DNDP II

**To:** Drug Product/Labeling Review #1 of NDA212535  
for Nouress™ (cysteine hydrochloride injection)

**Subject:** Final Recommendation

The applicant submitted revised Prescribing Information, container/carton labels and a stability study report for TPN admixture on December 11, 2019 (SN0042) and December 6, 2019 (SN0040), respectively, after the completion of the Labeling Review #1 on 9/12/19 and Drug Product Review #1 on November 22, 2019.

The updated Prescribing Information (PI), container and carton labels have been satisfactorily revised as were recommended in the Labeling Review #1.

In the admixture stability studies, the applicant excluded two electrolyte components, (b) (4) from the TPN admixture containing Nouress unlike the previous in vitro studies. The ratio of Nouress to Amino Acids (AAs) is kept as 22 mg to 1 gram based on the recommended dosage of Nouress for neonate (See Section 2.5 of PI). In this study, the applicant included an additional arm using the approved drug ELCYS for side by side comparison with Nouress. The study protocol is CON-FS-0598 Rev00 and the study report is FEA-AR-19-0028 Rev.01. The study results are summarized as the following:

1. No visual particulate matters observed in the study TPN admixture containing Nouress after the storage period of 24-hour at room temperature or 24-hour room temperature post 24-hour refrigeration. This suggests the visual particles observed after the refrigeration in the previous study is most likely due to the addition of the two electrolytes.
2. The assay values of cysteine and the impurity (b) (4) are comparable between Nouress and the approved drug ELCYS. Detailed data is shown in the table below. It is noted that the assay values of Nouress are in the range of (b) (4) % (b) (4) immediately after mixing with AAs and Glucose (initial time point). This is

lower than expected. Although the exact causes have not been thoroughly investigated yet due to the time constraint since the action date is December 15, 2019, however, similar observation occurred with the approved drug ELCYS ( (b) (4) ). This suggests that the low assay value at the initial time points may not be Nouress specific. Further, there is a decrease of assay values over storage. The decrease could be more than (b) (4) % from initial time point. It is difficult to trend for the assay of the post refrigeration samples due to the analytical method variation and the failure of the system suitability testing for 24-hour time point samples. Nevertheless, the decrease of assay value of cysteine is not unexpected based on our previous experience with the approved drug ELCYS. Additionally, the amount of impurity (b) (4) did not increase significantly over storage although those values are for information only due to the failure of the analytical method validation. Moreover, cysteine hydrochloride injection has a long history of human use since LD product from Hospira was approved in 1986. Therefore, the study results are acceptable for the intended purpose.

Cysteine Assay Values (% (b) (4))					
Store at RT			Nouress		ELCYS
# of Replicates	1	2	3	Ave.	1
0hr	(b) (4)				
12hr	(b) (4)				
24hr	(b) (4)				
Store at RT post 24 hr Refrigeration			Nouress		ELCYS
# of Replicates	1	2	3	Ave.	1
0hr	(b) (4)				
6 hr	(b) (4)				
12hr	(b) (4)				
24hr	(b) (4)				
RT: Room Temperature					
Impurity (b) (4), Assay % (b) (4)					
Store at RT			Nouress		ELCYS
# of Replicates	1	2	3	Ave.	1
0hr	(b) (4)				
12hr	(b) (4)				
24hr	(b) (4)				
Store at RT post 24 hr Refrigeration			Nouress		ELCYS
# of Replicates	1	2	3	Ave.	1
0hr	(b) (4)				
6 hr	(b) (4)				
12hr	(b) (4)				
24hr	(b) (4)				
RT: Room Temperature					

**Recommendation:**

The PI and labels are now deemed satisfactory from the CMC perspective, and from the drug product perspective, the stability of the TPN admixture with Nouress is also deemed acceptable, if it is kept under refrigeration up to 24 hours after mixing and being used within 24 hours under room temperature.

Therefore, with the revised final PI and labels, and acceptable admixture stability data, this application is now recommended for approval from the drug product and CMC labeling perspectives.

Hong Cai, Ph.D.  
Drug Product Reviewer  
Branch IV, Division II, ONDP

Moo-Jhong Rhee, Ph.D.  
Branch Chief  
Branch IV, Division II, ONDP

**Attachment-1:**

**Sections related to CMC in Prescribing Information submitted on December 11, 2019 (SN0042):**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use NOURESS™ safely and effectively. See full prescribing information for NOURESS.

NOURESS (cysteine hydrochloride injection), for intravenous use  
Initial U.S. Approval: 1971

————— **DOSAGE FORMS AND STRENGTHS** —————

Injection: 500 mg/10 mL (50 mg/mL) cysteine hydrochloride, USP in a single-dose vial. (3)

**Full Prescribing Information:**

**Admixture Stability and Storage in Section 2.3**

Stability and Storage

- For single use only. Discard unused portion of the vial of NOURESS.
- Use parenteral nutrition solution containing NOURESS promptly after mixing. Any storage of the admixture should be under refrigeration at 2°C to 8°C (36°F to 46°F) and

limited to a brief period of time, no longer than 24 hours. After removal from refrigeration, inspect for precipitates, use promptly, and complete the infusion within 24 hours. Discard if any precipitates are observed.

- Discard any remaining admixture.
- Protect parenteral nutrition solution from light.

### 3 DOSAGE FORMS AND STRENGTHS

Injection: 500 mg/10 mL (50 mg/mL) cysteine hydrochloride, USP as a clear, colorless, sterile solution in a single-dose vial.

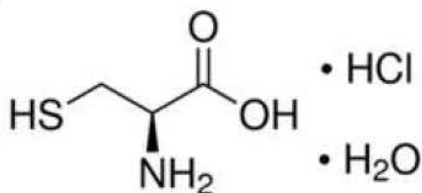
#### 11 DESCRIPTION

NOURESS (cysteine hydrochloride injection) is a sterile, nonpyrogenic solution for intravenous use supplied as 500 mg/10 mL cysteine hydrochloride, USP in a single-dose vial.

Each mL of NOURESS contains 50 mg of cysteine hydrochloride, (equivalent to 34.5 mg of cysteine), and 0.006 mL of hydrochloric acid (6M) in water for injection. Sodium hydroxide and/or hydrochloric acid are used as needed to adjust the pH. The pH range of NOURESS is 1.0 to 1.5.

The active ingredient is cysteine hydrochloride. The chemical name of cysteine hydrochloride is L-cysteine hydrochloride monohydrate. Its molecular formula is  $C_3H_7NO_2S \cdot HCl \cdot H_2O$  and molecular weight is 175.63. The chemical structure of L-cysteine hydrochloride monohydrate is depicted below:

8



Cysteine hydrochloride is a white crystalline powder soluble in water. Cysteine is a sulfur-containing amino acid and is prone to oxidation when exposed to air in aqueous solution, which may convert cysteine to insoluble cystine resulting in precipitation over time.

NOURESS contains no more than 145 mcg/L of aluminum.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

NOURESS (cysteine hydrochloride injection) is a clear, colorless, sterile and nonpyrogenic solution supplied as follows:

500 mg/10 mL (50 mg/mL) of cysteine hydrochloride, USP in single-dose vials (NDC 76014-006-05), packaged as 5 vials per carton (NDC 76014-006-05)

Store NOURESS at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Protect from light. Avoid excessive heat. Protect from freezing. If accidentally frozen, discard the vial.

Vial stoppers are not made with natural rubber latex.

For storage of admixed solution see *Dosage and Administration (2.3)*

Manufactured for:

Avadel Legacy Pharmaceuticals, LLC

Chesterfield, MO 63005

Rev. 12/19



**Attachment II:**  
**Copy of the Carton and Container Labels submitted on December 11, 2019, SN0042.**

**Carton Label:**



**Container (Vial Label):**





Hong  
Cai

Digitally signed by Hong Cai  
Date: 12/11/2019 11:33:58AM  
GUID: 55919d6500e16bdaad5825645e4f22ff



Moo Jhong  
Rhee

Digitally signed by Moo Jhong Rhee  
Date: 12/11/2019 11:41:40AM  
GUID: 502d0913000029f9798ca689a802fa55



**Hitesh  
Shroff**

Digitally signed by Hitesh Shroff

Date: 12/12/2019 04:05:14PM

GUID: 502d1ab500002afd219fd67e3b9c99c8



# QUALITY ASSESSMENT



**Recommendation: As of this review, this 505 (b)(2) NDA is *not* ready for Approval in its present form per 21 CFR 314.125(b)(6).**

## NDA 212535

### OPQ Review #1

Drug Name/Dosage Form	Cysteine Hydrochloride Injection, for intravenous use
Strength	500 mg/10 mL (50 mg/mL)
Route of Administration	Injection
Rx/OTC Dispensed	Rx
Applicant	Flamel Ireland Limited dba Avadel Ireland, Ireland
US agent, if applicable	Marla Scarola, The Weinberg Group, Washington, DC

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	Mar 15, 2019	OPQ
Amendment	Apr 24, 2019	ONDP
Amendment	May 17, 2019	ONDP
Amendment	Jun 10, 2019	ONDP
Amendment	Jun 14, 2019	ONDP
Amendment	Jun 21, 2019	OPF
Amendment	Jul 5, 2019	OPF
Amendment	Jul 15, 2019	ONDP
Amendment	Jul 19, 2019	ONDP
Amendment	Jul 24, 2019	ONDP
Amendment	Jul 25, 2019	OPF
Amendment	Aug 1, 2019	ONDP
Amendment	Aug 15, 2019	ONDP
Amendment	Aug 19, 2019	OPF
Amendment	Sep 5, 2019	ONDP
Amendment	Sep 6, 2019	ONDP
Amendment	Sep 16, 2019	ONDP
Amendment	Sep 18, 2019	ONDP
Amendment	Oct 2, 2019	ONDP
Amendment	Oct 15, 2019	ONDP
Amendment	Oct 18, 2019	ONDP
Amendment	Nov 11, 2019	ONDP

**Quality Review Team**

DISCIPLINE	REVIEWER	Secondary Assessment
Drug Substance	Larry Perez	Donna Christner
Drug Product, Labeling and Environmental Assessment	Hong Cai	Moo-Jhong Rhee
Process and Facilities	Qin Liang	Tianhong Tim Zhao
Microbiology	Dupez Palmer	Marla Stevens-Riley
Biopharmaceutics	Vincent Li	Tapash Ghosh
Regulatory Business Process Manager	Oumou Barry	N/A
Application Technical Lead	Hitesh Shroff	N/A

**Quality Review Data Sheet**

**1. RELATED/SUPPORTING DOCUMENTS**

**A. DMFs:**

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	L-Cysteine Hydrochloride Monohydrate	Active	Reviewed by Lawrence Perez on June 5, 2019	LOA: Oct 2, 2018
	Type III		(b) (4)	Active	Not reviewed, Information provided in NDA	LOA Oct 17, 2018
	Type III			Active	Not reviewed, Information provided in NDA	LOA Dec 11, 2015
	Type III			Active	Not reviewed, Information provided in NDA	LOA April 19, 2005

**B. Other Documents: IND, RLD, or sister applications**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	132382	From the same applicant and for same indications
NDA	019523	<ul style="list-style-type: none"> <li>Reference Listed Drug (RLD): Cysteine Hydrochloride Injection, 72 mg/mL from Hospira Inc., IL</li> <li>Discontinued on Jun 6, 2006 for reasons other than safety and efficacy</li> </ul>

**2. CONSULTS: None**

<b>DISCIPLINE</b>	<b>STATUS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			

## Executive Summary

### I. Recommendations and Conclusion on Approvability

The applicant has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed Nouress (cysteine hydrochloride injection) 500 mg/10 mL (50 mg/mL).

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The Office of Process and Facilities (OPF) has made a final overall “Approval” recommendation for the facilities involved in this application.

The label/labeling issues have *not* been satisfactorily resolved as of this review.

Therefore, from the OPQ perspective, this NDA is *not* deemed ready for approval in its present form per CFR 314.125(b)(6), until above mentioned issues are satisfactorily resolved. (see the **List of Deficiencies**)

### II. Summary of Quality Assessments

#### A. Product Overview

Nouress (cysteine hydrochloride injection) 500 mg/10 mL (50 mg/mL) is a sterile, nonpyrogenic solution for intravenous use. Each 10 mL of Nouress contains 500 mg of Cysteine Hydrochloride, USP (b) (4) mL of hydrochloric acid (6 Molar) in Water for Injection, USP. The pH of the solution is adjusted to 1.0 to 1.5 with hydrochloric acid or sodium hydroxide. There are no preservatives or anti-oxidants in this formulation. (b) (4)

Nouress is supplied as a single-dose vials. Nouress must be diluted and used as an admixture in parenteral nutrition solutions.

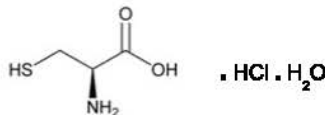
<p align="center"><b>Proposed Indication(s) including Intended Patient Population</b></p>	<p>Nouress (b) (4) indicated for use as an additive to amino acids solutions to meet nutritional requirements of neonates (preterm and term infants less than one month of age) requiring total parenteral nutrition.</p>
<p align="center"><b>Duration of Treatment</b></p>	<p>As needed</p>
<p align="center"><b>Maximum Daily Dose</b></p>	<p><u>Recommended Dosage:</u></p> <ul style="list-style-type: none"> <li>(b) (4)</li> <li>The recommended dosage in neonates is based upon the recommended daily protein (amino acid) requirements: 22 mg NOURESS/g amino acids. The corresponding volume is 0.44 mL NOURESS/g amino acids.</li> </ul>

Alternative Methods of Administration

N/A

**B. Quality Assessment Overview**

**Drug Substance:** The active ingredient in Nouress (cysteine hydrochloride injection) 500 mg/ 10mL is L-cysteine hydrochloride monohydrate. The drug substance is a white crystalline powder. It is hygroscopic and very soluble in water (b) (4). Cysteine hydrochloride monohydrate is a natural amino acid. It is a chiral naturally occurring amino acid with a molecular weight of 175.63 g/mol and a molecular formula of C<sub>3</sub>H<sub>7</sub>NO<sub>2</sub>S.HCl.H<sub>2</sub>O.



**Manufacturing:** It is manufactured by (b) (4) under cGMP conditions (b) (4). The complete CMC information regarding raw materials, manufacturing, purification, characterization, stability, storage and container closure is provided in DMF (b) (4). A Letter of Authorization was also submitted by the manufacturer.

The overall quality of L-cysteine hydrochloride monohydrate is controlled by its specification, which includes appearance, identification test (b) (4) (b) (4)

The drug substance meets the USP specification. The biopharmaceutical classification (BCS), particle size and polymorphism of the drug substance are not important because the drug product is an injection for intravenous administration.

The applicant provided satisfactory certificates of analysis of four batches of the drug substance used in the manufacture of the drug product. The proposed re-test period of (b) (4) deemed acceptable. The DMF (b) (4) was reviewed by Dr. Lawrence Perez and was deemed adequate from the CMC perspective. (See the Drug Substance review)

The API, L-cysteine hydrochloride monohydrate, manufactured by (b) (4) (b) (4) is controlled to conform to the requirements (specification) to produce Nouress (cysteine hydrochloride injection) 500 mg/ 10mL.

**Drug Product:** Nouress (cysteine hydrochloride injection) 500 mg/10 mL (50 mg/mL) is clear, colorless, sterile and nonpyrogenic solution. Each mL of the drug product contains 50 mg of L-cysteine hydrochloride monohydrate (equivalent to 34.5 mg of L-cysteine). The pH range of the drug product is 1.0 to 1.5. The drug product is not for direct intravenous infusion, it must be diluted and admixed with a TPN solution prior to intravenous administration. As there are no preservatives or anti-oxidants in the drug product formulation, it is a single-dose drug product and the unused portion should be discarded. The drug product is supplied as 10 mL USP (b) (4) clear glass vial, closed with a stopper and sealed with a brown flip-off cap.



The drug product specification includes appearance, identity tests, assay for strength, impurities by validated HPLC methods as well as bacterial endotoxin per USP <85> for purity; pH, particulate matter per USP <788>, extractable volume per USP <697>, aluminum content tests for quality and sterility per USP <71>. The elemental impurities per USP <232>, USP <233> and ICH Q3D are not included in the drug product specification because no elemental impurities were detected above (b) (4) % of PDE in historical batches.

The drug product strength is the only difference between the reference listed drug (LD) from Hospira (72.5 mg/mL) and the proposed drug product (50 mg/mL). Due to the lower strength of the proposed drug product, a slightly larger volume is required compared to the LD to achieve the same amount of cysteine in the admixture. Based on the comparative physico-chemical properties of the to-be administered dosage form, the FDA determined that a biobridge has been established between the proposed and the listed drug product as per 21 CFR 320.24 (b)(6) to assure similar *in-vivo* disposition of cysteine. Thus, an additional *in vivo* bioequivalence (BE) bridging study is not needed. (see the **Biopharmaceutics** review)

The Cysteine Hydrochloride Injection compatibility study was conducted with commonly used in typically used TPNs and diluents e.g. 10% Dextrose Injection, TrophAmine, Calcium Gluconate Injection and Potassium Phosphate Injection. In the compatibility study, appearance, pH, osmolality, viscosity, assay, related substances, particulate matter and in-use stability were assessed. The admixtures appear to be stable up to 24 hours at 25°C, but some particulate matters were observed when, after admixing, it was stored at 5°C. Based on this observation, it was recommended not to refrigerate after admixing of this product, unless admixed with just nutritional TPN (b) (4).

The stability testing of the drug product batches was performed in accordance with ICH Q3A(R2). Based on the satisfactory 12-month long-term stability in upright and inverted positions at 25°C and 6-month accelerated stability data at 40°C from three primary registration batches, the proposed **24-month of expiration dating period** is granted when stored at 25°C in the proposed container closure system. (see the **Drug Product** review).

**Manufacturing:**

Nouress (cysteine hydrochloride injection) 500 mg/10 mL (50 mg/mL) is manufactured, tested and released by (b) (4). The manufacturing process involves (b) (4).

[Redacted text block]

(b) (4)

(b) (4)

This NDA is recommended for approval based on drug product sterility assurance from the microbiological perspective. (See the **Microbiology review**)

**Facilities:**

The Office of Process and Facilities (OPF) has made an “Adequate” recommendation for all drug substance and drug product manufacturing and testing facilities. (See the **Manufacturing Integrated Assessment review**)

**Environmental Assessment:**

In accordance with 21 CFR 25.15(d), Avadel affirms that the requested action, approval of the NDA for Cysteine Hydrochloride Injection, USP qualifies for a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.31(a). Action on the NDA will not increase the use of the active moiety. In addition, to the applicant’s knowledge there are no extraordinary circumstances indicating that the proposed action would significantly affect the quality of the human environment (21 CFR 25.21).

Therefore, claim of a categorical exclusion from the requirements of an environmental assessment (EA) in accordance with 21 CFR Part 25.31(a) and 21 CFR Part 25.15 (d), was deemed acceptable. (See the **Drug Product review**)

**Labeling:** As of this review, the labels and labeling issues are *not* satisfactorily resolved from the CMC perspective according to the labeling/label review. (See the **List of Deficiencies** below and **Labeling review**).

**C. Post Approval Commitment:** None

**D. Lifecycle Management Considerations:** None

**E. Special Product Quality Labeling Recommendations:** None

**F. Final Risk Assessment (see Attachment)**

**G. List of Deficiencies:**

The following labeling deficiencies should be resolved with the applicant:

**A. Regarding Labels****For the 5x10ml vial carton label:**

1. Provide the lot number and expiration date information on the carton label.
2. Include “See package insert for the dosage information” on the carton label.

**For All Labels (carton and vial):**

1. The product title on cartons and vials should be revised to the following:  
*Nouress™*  
*(cysteine hydrochloride injection), USP*
2. Add the strength equivalency statement of cysteine hydrochloride to cysteine free base to the side panel per USP salt policy:  
*50 mg/mL of cysteine hydrochloride, (equivalent to 34.5 mg/mL of cysteine)*
3. Add the quantitative ingredient of the drug product in the carton label. The statement should be consistent with the statement in section 11, description of PI. The recommended statement is as the following:  
*"Each mL of Nouress contains 50 mg of cysteine hydrochloride (equivalent to 34.5 mg of cysteine), and 0.006 mL of hydrochloric acid (6M) in water for injection. Sodium hydroxide and/or hydrochloric acid are used as needed to adjust the pH. The pH range is 1.0 to 1.5."*  
This statement should be included in the vial label if the space is permitted.
4. The statement of the storage condition should be consistent with the statement in Section 16 of PI. The admixture storage condition per Section 2.3 of PI should also need to be included in the carton label.
5. Add the statement: "*Sterile*"
6. Add the barcode.

***Application Technical Lead Name and Date:***

Hitesh Shroff, Ph.D.  
Application Technical Lead, Branch V  
Division of New Drug Products II  
November 22, 2019

Hitesh N.  
Shroff -S

Digitally signed by Hitesh N. Shroff -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S  
Date: 2019.11.22 18:18:06 -05'00'

## CHAPTER IV: LABELING

### 1.0 PRESCRIBING INFORMATION

#### 1.1 Highlights of Prescribing Information

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use (b) (4) safely and effectively. See full prescribing information for (b) (4).

(b) (4) (Cysteine-cysteine Hydrochloride hydrochloride Injection) (b) (4) for intravenous use  
 Initial U.S. Approval: 1971

**DOSAGE FORMS AND STRENGTHS**

Injection: 500 mg/10 mL (50 mg/mL) cysteine hydrochloride, USP in a (b) (4) (b) (4) single-dose (b) (4) vial (b) (4) (3)

Item	Information Provided in NDA	Reviewer's Assessment
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))		
Proprietary name and established name	(b) (4) (Cysteine Hydrochloride Injection, USP)	<p style="text-align: center;"><b>Not Satisfactory</b></p> <p>Revise the product title to one of the following formats: Once the format is selected, the entire PI document should be revised to have the consistent format for the presentation of established name.</p> <p>“Tradename (cysteine hydrochloride) Injection, for intravenous use” or                      “Tradename (cysteine hydrochloride injection), for intravenous use”.</p> <p style="text-align: right;">(b) (4)</p>

Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	<p>(b) (4)</p> <p><b>Not Satisfactory</b></p> <p>Revise to:          “Injection: 500 mg/10 mL (50 mg/mL) cysteine hydrochloride, USP in a (b) (4) (b) (4) single-dose vial .”</p>

**\*Cysteine Hydrochloride is defined in USAN as a monohydrate substance.**

## 1.2 Full Prescribing Information

### 1.2.1 Section 2 (Dosage and Administration)

Note: Only the following content in Section 2.3 related to storage condition of the admixture will be reviewed.

Stability and Storage

For single use only. Discard used container of (b) (4)

The amino acids admixture should be refrigerated until ready for use and used within 24 hours of the time of mixing.

Use (b) (4) solution containing (b) (4) mixing. Any storage of the admixture should be under refrigeration and limited to a brief period of time, no longer than 24 hours. After removal from refrigeration, use promptly and complete the infusion within 24 hours. Discard any remaining admixture.

Protect (b) (4) solution from light.

Item	Information Provided in NDA	Reviewer’s Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c) (12))		
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	<p><u>Stability and Storage</u></p> <p>(b) (4)</p>	<p><b>Not Satisfactory</b></p> <p>The review of this section is on-going pending applicant IR response.</p>

**3 DOSAGE FORMS AND STRENGTHS**

Injection: 500 mg/10 mL (50 mg/mL) cysteine hydrochloride, USP as a clear, colorless, sterile solution in a (b) (4) single-dose (b) (4)

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))		
Available dosage forms	Not provided	<b>Not Satisfactory</b> Add the dosage form "Injection".
Strengths: in metric system	50 mg/mL	<b>Not Satisfactory</b> <ul style="list-style-type: none"> <li>The strength of the total content in the vial is not defined.</li> <li>The strength is not clearly defined as "cysteine hydrochloride".</li> </ul> Revise to "500 mg/10 ml (50 mg/mL) cysteine hydrochloride as a clear, colorless, sterile solution in a (b) (4) single-dose vial."
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Not provided.	<b>Not Satisfactory</b> See the revision comment in the section "Strengths: in metric system".

**1.2.3 Section 11 (Description)**

**11 DESCRIPTION**

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c) (12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))		
Proprietary name and established name	(b) (4)	<p><b>Not Satisfactory</b> Revise to (b) (4)</p> <p>Also see the comment in Highlights Section for product title.</p>
Dosage form and route of administration		<p><b>Not Satisfactory</b> Revised to "Tradename (cysteine hydrochloride injection) is a sterile, nonpyrogenic solution for intravenous use."</p>
Active moiety expression of strength with equivalence statement (if applicable)	Not provided.	<p><b>Not Satisfactory</b> Add the following statement: Each 10 mL of Tradename contains (b) (4) mg of cysteine hydrochloride (equivalent to (b) (4) mg of cysteine), and (b) (4) hydrochloric acid (6M) in water for injection.</p>
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	(b) (4)	<p><b>Not Satisfactory</b> Revise to the following: (b) (4)</p>



Pharmacological/ therapeutic class	Not provided.	<b>Not Satisfactory</b> Add “Cysteine is a sulfur-containing amino acid.”
Chemical name, structural formula, molecular weight	(b) (4)	<b>Not Satisfactory</b> Revise to (b) (4)
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	Not provided.	<b>Not Satisfactory</b> Add the following: Cysteine hydrochloride is a white crystalline powder soluble in water. (b) (4) (b) (4) (b) (4) may convert to insoluble cystine (b) (4) precipitation over time.

### 1.2.4 Section 16 (How Supplied/Storage and Handling)

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4) (cysteine hydrochloride injection) is a clear, colorless (b) (4) sterile solution (b) (4) supplied as follows:

500 mg/10 mL (50 mg/mL) of cysteine hydrochloride, USP in (b) (4) single-dose vials (NDC 76014-006-05), packaged as 5 vials per carton (NDC XXXXX-XXX-XX)

(b) (4)

(b) (4) Store (b) (4) at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Avoid excessive heat. Protect from freezing. If accidentally frozen, discard the vial. (b) (4)

Vial stoppers are not made with natural rubber latex.

For storage of admixed solution see *Dosage and Administration* (2.3)

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c) (17))		
Strength of dosage form	50 mg/mL 10 mL vial	<p><b>Not Satisfactory</b> Revise to: “Tradename (cysteine hydrochloride injection), is supplied as follows: 500mg /10 mL (50 mg/mL) of cysteine hydrochloride”</p>
Available units (e.g., bottles of 100 tablets)	(b) (4), for single use (supplied in packages of 5)	<p><b>Not Satisfactory</b> Revise to: “500mg /10 mL (50 mg/mL) of cysteine hydrochloride is a clear, colorless, sterile and nonpyrogenic solution in (b) (4)”</p>
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Not provided	<p><b>Not Satisfactory</b> Add the description of the formulation: “is a clear, colorless, sterile and nonpyrogenic solution.” Add NDC number</p>
Special handling (e.g., protect from light)	(b) (4)	<p><b>Not Satisfactory</b> Add the following statement for this parental SVP: “<i>If accidentally frozen, discard the vial.</i>”</p>
Storage conditions	Store (b) (4) at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. (b) (4)	<p><b>Not Satisfactory</b> Add the admixture storage condition as the following: “<i>For storage of admixed solutions see Dosage and Administration (2.3).</i>”</p>

**Reviewer's Assessment of Package Insert: *Inadequate***

Review comments are made on the Prescribing Information which is based on the submission dated June 7, 2019 (SN0006).

As of this review, the Prescribing Information is not deemed satisfactory from the CMC labeling perspective (See “**List of the deficiencies**” at the end of this review).

**1.2.5 Other Sections of Labeling: N/A****1.2.6 Manufacturing Information after Section 17 (for drug products)**

— Manufactured for:  
Avadel Legacy Pharmaceuticals, LLC  
Chesterfield, MO 63005

Rev. XX/XX

**2.0 Patient Labeling****3.0 Carton and Container Labels****3.1 Container (vial) Label (SN0015 submitted on July 24, 2019):**

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	Nouress™ (Cysteine Hydrochloride Injection, USP)	<b>Not Satisfactory</b> Revise to “Tradename (cysteine hydrochloride injection) USP” Refer to the reviewer comments in PI for the product title presentation.
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	500mg/10 mL (50 mg/mL)	<b>Not Satisfactory</b> In the side panel, add the following statement per USP salt policy: 50 mg of cysteine hydrochloride (equivalent to 34.5 mg of cysteine)
Net quantity of dosage form	500 mg/10 ml 10 mL Single-Dose Vial	<b>Satisfactory</b>
“Rx only” displayed prominently on the main panel	Rx Only	<b>Satisfactory</b>
Lot number and expiration date	Lot Exp	<b>Satisfactory</b>
Storage conditions Special handling, e.g., “Dispense in tight and light resistant container as defined in USP”.	Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature]. (b) (4) (b) (4)	<b>Satisfactory</b> This is due to the space limitation consideration.
Bar code (21CFR 201.25)	Not provided	<b>Not Satisfactory</b> Provide the barcode
NDC number (21 CFR 207.35(b)(3)(i))	NDC 76014-006-33	<b>Satisfactory</b>
Manufacturer/distributor's name	Mfd. For Avadel Lgcy Phrm, LLC	<b>Satisfactory</b>

<p>Quantitative ingredient information (injectables)</p>	<p>Not provided.</p>	<p><b>Not Satisfactory</b> Revise to: Each 10 mL of Tradename contains (b) (4) mg of cysteine hydrochloride, USP (equivalent to (b) (4) mg of cysteine), and (b) (4) mL of hydrochloric acid (6M) in water for injection. Sodium hydroxide and/or hydrochloric acid are used as needed to adjust the pH. The pH range is 1.0 to 1.5.</p>
<p>Statement of being sterile (if applicable)</p>	<p>Not Provided</p>	<p><b>Not Satisfactory</b> Add in "Sterile"</p>
<p>Statement of Maximum level of aluminum present at expiry of all SVP's used in the preparation of TPN solutions per 21. CFR 201.323 (c).</p>	<p>Not provided</p>	<p><b>Not Satisfactory</b> Add the statement: Contains no more than 145 mcg/L of aluminum.</p>

### 3.2 Carton Label (SN0015, submitted on July 24, 2019)



(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	Nouress (Cysteine Hydrochloride Injection, USP)	<p><b>Not Satisfactory</b></p> <p>Revise to either of these two options:            Tradename (cysteine hydrochloride) injection, USP, or            Tradename (cysteine hydrochloride injection), USP</p> <p>Refer to the reviewer comments in the PI regarding the product title presentation.</p>
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	500 mg/ 10mL (50 mg/mL)	<p><b>Not Satisfactory</b></p> <p>In the side panel, add the cysteine hydrochloride to cysteine free base equivalence statement. Such as 50 mg/mL of cysteine hydrochloride, (equivalent to 34.5 mg/mL of cysteine)</p>
Net quantity of dosage form	500 mg/10mL (50 mg/mL) 5x10 mL Single-Dose Vials	<b>Satisfactory</b>
"Rx only" displayed prominently on the main panel	Rx only	<b>Satisfactory</b>
Lot number and expiration date	Not provided	<p><b>Not Satisfactory</b></p> <p>Provide the lot number and expiration date</p>
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store at 20°C – 25°C (68°F – 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP for Controlled Room Temperature]. Protec from freezing.	<p><b>Not Satisfactory</b></p> <p>Revise the admixture storage condition to be consistent with the statement in Section #2.3 (stability and storage) of the approved PI.</p>



Manufacturer/distributor's name	Avadel™ Manufactured for Avadel Legacy Pharmaceuticals, LLC Chesterfield, MO 63005	<b>Satisfactory</b>
“See package insert for dosage information”	Not Provided.	<b>Not Satisfactory</b> Add the statement: “See package insert for dosage information.”
Quantitative ingredient information (injectables)	Each mL contains 50 mg L-Cysteine Hydrochloride Monohydrate in Water for Injection adjusted to pH 1.0-1.5	<b>Satisfactory</b> Revise to: “Each mL of Tradename contains 50 mg of cysteine hydrochloride (equivalent to 34.5 mg of cysteine), and 0.006 mL of hydrochloric acid (6M) in water for injection. Sodium hydroxide and/or hydrochloric acid are used as needed to adjust the pH. The pH range is 1.0 to 1.5.”
Statement of being sterile (if applicable)	Not Provided.	<b>Not Satisfactory</b> Add the statement of “sterile”

**Reviewer’s Assessment of Labels: *Inadequate from CMC perspective***

The above review comments for the container and closure labels are based on the submission of NDA212535 on July 24, 2019 (SN0015), and as of this review, the labels for container and cartons are not deemed satisfactory from CMC perspective (see the following **List of deficiencies**).

***List of Deficiencies:***

***A. Regarding Prescribing Information:***

5. **Manufacturer information followed Section #17 “Patient Counseling Information”.**
6. **The content of “Stability and Storage” in Section 2.3 (Preparation Instructions for Admixing Using a Parenteral Nutrition Container) is not reviewed at this time. This is due to pending the applicant response for the admixture stability study report. The review will be amended once the report is submitted and reviewed.**

## **B. Regarding Labels**

### **For the 5x10ml vial carton label:**

1. *Provide the lot number and expiration date information on the carton label.*
2. *Include “See package insert for the dosage information” on the carton label.*

### **For All Labels (carton and vial):**

1. *The product title on cartons and vials should be revised to the following:  
Nouress™  
(cysteine hydrochloride injection), USP*
2. *Add the strength equivalency statement of cysteine hydrochloride to cysteine free base to the side panel per USP salt policy: 50 mg/mL of cysteine hydrochloride, (equivalent to 34.5 mg/mL of cysteine).*
3. *Add the quantitative ingredient of the drug product in the carton label. The statement should be consistent with the statement in section 11, description of PI. The recommended statement is as the following:  
“Each mL of Tradename contains 50 mg of cysteine hydrochloride (equivalent to 34.5 mg of cysteine), and 0.006 mL of hydrochloric acid (6M) in water for injection. Sodium hydroxide and/or hydrochloric acid are used as needed to adjust the pH. The pH range is 1.0 to 1.5.” This statement should be included in the vial label if the space is permitted.*
4. *The statement of the storage condition should be consistent with the statement in Section 16 of PI. The admixture storage condition per Section 2.3 of PI should also need to be included in the carton label.*
5. *Add the statement: “Sterile”.*
6. *Add the barcode.*

## **Overall Assessment and Recommendation:**

From the ONDP perspective, this application is **not** deemed ready for approval in its present form per 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

**Primary Labeling Reviewer Name and Date:**



## QUALITY ASSESSMENT



I agree with Dr. Cai's assessment on the labeling and labels, and therefore, concur with her recommendation that this application is **not ready for approval** as of this review until the deficiencies in the **List of Deficiencies** are satisfactorily resolved.

*Moo-Jhong Rhee, Ph.D.*

*Chief*

*Branch V/DNDP II/ONDP/OPQ*



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## CHAPTER VII: MICROBIOLOGY

<b>Product Information</b>	
<b>NDA Number</b>	212535
<b>Assessment Cycle Number</b>	1
<b>Drug Product Name/ Strength</b>	Cysteine Hydrochloride Injection, USP 50 mg/mL (b) (4)
<b>Route of Administration</b>	Intravenous injection
<b>Applicant Name</b>	Flamel Ireland Limited dba Avadel Ireland
<b>Therapeutic Classification/ OND Division</b>	DGEIP, additive for total parenteral nutrition
<b>Manufacturing Site</b>	(b) (4)
<b>Method of Sterilization</b>	(b) (4)

**Assessment Recommendation: Adequate**

**Assessment Summary:**

**List Submissions being assessed (table):**

<b>Document(s) Assessed</b>	<b>Date Received</b>
<b>Original submission (eCTD: 0001)</b>	<b>03/15/2019</b>
<b>Quality Response to Information Request (eCTD: 0004)</b>	<b>05/17/2019</b>
<b>Quality Response to Information Request (eCTD: 0009)</b>	<b>06/21/2019</b>
<b>Quality Response to Information Request (eCTD: 0019)</b>	<b>08/18/2019</b>

**Highlight Key Issues from Last Cycle and Their Resolution: N/A**

**Remarks:** The drug product is (b) (4).  
 (b) (4) The first cycle review was conducted by Andrew Pike, PhD; who is no longer with the Agency. A teleconference was held between the FDA and representatives of Avadel and (b) (4) on 6/17/19 to discuss their media fill program. Additional information is provided on page 22 of this document.

**Concise Description of Outstanding Issues: None**

**Supporting Documents:**

- DMF (b) (4)

**S DRUG SUBSTANCE**

The drug product will be sterilized during production. Therefore, the drug substance was not reviewed.

**P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT**

- **Description of the drug product** – The drug product is a sterile, nonpyrogenic solution packaged into 10 mL/20 mm glass vials and closed with 20 mm rubber stoppers. Each glass vial will contain 10 mL.
- **Drug product composition** – The drug product composition is displayed in the table below from Section 3.2.P.1 Description and Composition of the Drug Product pg. 1 of 1.

Component	Function	Standard	Concentration	Amount per 10 mL vial
L-Cysteine HCl Monohydrate	API	USP	50 mg/mL	0.5 g
WFI	(b) (4)		(b) (4)	q.s.
Hydrochloric acid (6 M)	pH adjustment		0.06 mL	
Hydrochloric acid			q.s.	q.s. to pH 1.0-1.5
Sodium hydroxide				
(b) (4)				

- **Description of the container closure system** – The drug product will be packaged into (b) (4) glass vials, closed with 20 mm (b) (4) stoppers, and sealed with 20 mm brown flip-off seals. Vials will be purchased from (b) (4) (Section 3.2.P.7 Container Closure System pg. 1 of 8).

**Adequate**

**Assessment:** The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

**P.2 PHARMACEUTICAL DEVELOPMENT**

**P.2.5 MICROBIOLOGICAL ATTRIBUTES**

*Container/Closure and Package Integrity*

Section 3.2.P.2 Report 18-044-A-0-Container Closure Integrity (10 mL/20mm Vial and 20mm Stopper) and Microbiological Attributes

The drug product is labeled as single-dose.

(b) (4)



Post-Approval Commitments

N/A

**MICROBIOLOGY LIST OF DEFICIENCIES**

None

*Primary Microbiology Assessor Name and Date:* Dupeh Palmer, PhD; 8/21/19

*Secondary Assessor Name and Date (and Secondary Summary, as needed):*  
Marla Stevens-Riley, PhD; 8/21/19

## CHAPTER VI: BIOPHARMACEUTICS

<b>Product Information</b>	L-Cysteine HCl Injection, USP, 50 mg/mL
<b>NDA Number</b>	212535
<b>Assessment Cycle Number</b>	1
<b>Drug Product Name/ Strength</b>	L-Cysteine HCl Injection, USP, 50 mg/mL
<b>Route of Administration</b>	Intravenous
<b>Applicant Name</b>	Flamel Ireland Limited
<b>Therapeutic Classification/ OND Division</b>	ODEIII/DGIEP
<b>RLD/RS Number</b>	NDA 019523
<b>Proposed Indication</b>	For use as an additive to (b) (4), meet (b) (4) nutritional requirements of neonates receiving total parenteral nutrition

**Assessment Recommendation: Adequate**

**Assessment Summary:**

The proposed drug product, L-Cysteine Hydrochloride Injection, USP is a clear solution intended for administration by intravenous (IV) injection for TPN (total parenteral nutrition). The reference listed drug (RLD) is Hospira Inc.'s Cysteine Hydrochloride Injection, USP (NDA No. 019523), which was approved on 10/22/1986, but discontinued on 06/16/2006 for reasons other than safety and efficacy. A recent NDA 210660, 50 mg/mL by Exela Pharma Sciences, LLC, was approved on April 3, 2019.

NDA 212535 was submitted on 03/15/17 under 505(b)(2). The composition of the Test and Reference drug products is shown in Table 1. The proposed test drug product has the same active ingredient, dosage form, route of administration, preparation for administration, and indications as the RLD, except that the active ingredient concentration in the RLD is 72.5 mg/mL whereas the proposed Cysteine Hydrochloride Injection, USP is 50 mg/mL.



The proposed product has the same Cysteine Hydrochloride concentration as the recently approved NDA product (NDA 210660).

**Table 1. A comparison of Flamel L-Cysteine Hydrochloride Injection, USP with the RLD product**

**Table 4: Formulation of Avadel and Hospira Products**

	Avadel's Cysteine Hydrochloride Injection, USP	Hospira's Cysteine Hydrochloride Injection, USP <sup>a</sup>
CHM	50 mg/mL	72.5 mg/mL
Cysteine	34.5 mg/mL	(b) (4)
WFI	q.s.	q.s.
pH	1.0-1.5 (use NaOH and/or HCl to adjust pH)	Range per label: 1.0-2.5
Osmolality	501-752 mOsm/kg	Not available <sup>b</sup>

<sup>a</sup> Source: Hospira's Cysteine Hydrochloride Injection, USP label (NDA 19523)

**Table 5: Osmolality Comparison of Avadel and Unapproved Marketed Products**

	Avadel's Cysteine Hydrochloride Injection, USP	Sandoz
Batch/Expiry	Laboratory Batch AV-17-008	Batch GN 4912 (Exp. Sep 2018)
pH	1.24	1.26
Osmolality	589 ± 2 mOsm/kg <sup>a</sup>	577 mOsm/kg <sup>b</sup>

<sup>a</sup> Mean ± SD

<sup>b</sup> Single measure

**CHM = cysteine hydrochloride Monohydrate**

The proposed product is for admixing use only. Not for direct infusion.

<b>CQAs</b>	<b>Initial Risk Ranking</b>	<b>Comments</b>	<b>Updated Risk Ranking after Assessment Cycle #</b>	<b>Comments</b>
pH	low	To be marketed product has a pH of 1.0 to 1.5	low	pH specification is tighter than that of the RLD (1.0 to 2.5). Moreover, pH of the admixture prior to administration is governed by the

				amino acid solution diluent.
Osmolality	low	To be marketed product has an osmolality of 589 mOsm/kg	low	Comparable to the currently marketed Sandoz product.

**List Submissions being assessed (table):**

Document(s) Assessed	Date Received
<a href="#">Application 212535 - Sequence 0001 - 0001 (1) 03/15/2019 ORIG-1 /Multiple Categories/Subcategories</a>	3/15/2019

**Highlight Key Issues from Last Cycle and Their Resolution:** Not Applicable

**Concise Description of Outstanding Issues (List bullet points with key information and update as needed):**  
None

**B.12 BRIDGING OF FORMULATION**

The applicant provided bridging justification in Module 2.7.1. The reference listed drug product (72.5 mg/mL) by Hospira has been discontinued on 06/16/2006. The proposed drug product has the same concentration of cysteine and composition as the recently approved product NDA 210660 (approved on April 3, 2019). The applicant provided comparative testing data between the proposed drug product and an in-house prepared surrogated Hospira's product following mixing with total parenteral solutions. The comparative testing data included appearance, pH, osmolality, viscosity and buffer capacity. The comparative test results showed that the final cysteine concentration and physicochemical properties are comparable.

**Assessment: Adequate**

The only differences between the proposed drug product and the reference listed product are concentration of cysteine HCL and primary package. The acceptance of the primary package of the primary package will be reviewed by the Drug Product Reviewer.

The proposed drug product has a cysteine HCl concentration of 50 mg/mL and the reference listed product has a cysteine HCl concentration of 72.5 mg/mL. The lower concentration of the proposed product requires a larger volume relative to the reference listed product to be mixed with the total parenteral solution(s) to achieve the same cysteine to amino acids ratio in the admixture. The additional volume of the proposed drug product needed is relatively small relative to the final volume of the admixture. Hence, it will not affect the physicochemical properties of the admixture. The osmolality of the admixture mixed with a surrogated 72.5 mg/mL RLD product has the same osmolality as that of the proposed drug product in the admixture after diluting with the same total parenteral solutions. Hence, the same physicochemical properties and concentration of cysteine between the proposed product and the RLD product before administration suggest that there is unlikely to have any difference between the biopharmaceutics of the proposed product and the RLD products. Moreover, the proposed drug product has the same cysteine concentration and composition as the recently approved NDA 210660.

Based on the comparative physico-chemical properties and nature of final to be administered dosage form, the FDA determined that a biobridge has been established between the proposed and the listed product as per 21 CFR 320.24 (b)(6) to assure similar *in-vivo* disposition of cysteine. Thus, an additional *in vivo* bioequivalence (BE) bridging study is not needed.

## **B. 13 BIOWAIVER REQUEST**

### **Assessment: Adequate**

The firm did not submit a biowavier request. However, a biobridge has been established between the proposed and the listed product as per 21 CFR 320.24 (b)(6) to assure similar *in-vivo* disposition of cysteine.

## **R. REGIONAL INFORMATION**

### Comparability Protocols

**Assessment:** Not applicable. The applicant did not submit any comparability protocol.

### Post-Approval Commitments

**Assessment:** None

### Lifecycle Management Considerations

None

## **BIOPHARMACEUTICS LIST OF DEFICIENCIES**

None

***Primary Biopharmaceutics Assessor's Name and Date:***  
***Vincent Li, Ph.D., 6/27/2019***

***Secondary Assessor Name and Date (and Secondary Summary, as needed):***  
***Tapash Ghosh, Ph.D.,***

**ATTACHMENT I: Final Risk Assessments**

**A. Final Risk Assessment – NDA 212535**

**a) Drug Product: Nouress (cysteine hydrochloride injection) 500 mg/10 mL (50 mg/mL)**

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay, impurities and precipitates	(b) (4)	L to H	During the aseptic vial filling process, the head space is (b) (4)	Precipitates were not observed in the vials on storage.	Low
Precipitates in admixtures with TPN	Potential formation (b) (4)	H to M	Precipitates were assessed by visual examination.	No precipitates observed during the admixture in-use stability testing.  Low	None
Particulate Matter in admixtures with TPN	Potential formation (b) (4)	H to M	Particulate matter was controlled in admixture specification per USP <788>.	Particulate matter remained within acceptable range during the admixture in-use stability testing.  Low	None
Bioburden	Manufacturing environment and processes	M	(b) (4)	Bioburden is controlled in the drug product at release and stability.  Low	None
Sterility	Sterilization	M	(b) (4)	Sterility is controlled in drug product at release and stability.  The drug product is supplied as single-use vials.  Low	None



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