

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**212535Orig1s000**

**MULTI-DISCIPLINE REVIEW**

**Summary Review**

**Office Director**

**Cross Discipline Team Leader Review**

**Clinical Review**

**Non-Clinical Review**

**Statistical Review**

**Clinical Pharmacology Review**

NDA/BLA Multi-disciplinary Review and Evaluation for **NDA 212535** Nouress (cysteine hydrochloride)

**NDA/BLA Multi-Disciplinary Review and Evaluation**

<b>Application Type</b>	NDA
<b>Application Number(s)</b>	212535
<b>Priority or Standard</b>	Priority
<b>Submit Date(s)</b>	3/15/2019
<b>Received Date(s)</b>	3/15/2019
<b>Filing and Priority Review</b>	5/13/2019
<b>Extension Letter</b>	7/31/2019
<b>PDUFA Goal Date</b>	9/15/2019 (original); 12/15/2019 (new date after extension)
<b>Division/Office</b>	Division of Gastroenterology and Inborn Errors Products (DGIEP)
<b>Review Completion Date</b>	12/13/2019
<b>Established/Proper Name</b>	Cysteine Hydrochloride
<b>(Proposed) Trade Name</b>	Nouress
<b>Pharmacologic Class</b>	Sulfur-containing amino acid
<b>Applicant</b>	Avadel Legacy Pharmaceuticals LLC
<b>Dosage form</b>	Injection
<b>Applicant proposed Dosing Regimen</b>	50 mg/mL
<b>Applicant Proposed Indication(s)/Population(s)</b>	Use as an additive to amino acid (AA) solutions to meet the nutritional requirements of neonates requiring total parental nutrition (TPN)
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	Use as an additive to AA solutions to meet nutritional requirements of neonates (preterm and term infants less than one month of age) requiring total parenteral nutrition
<b>Recommended Dosing Regimen</b>	50 mg/mL

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NDA/BLA Multi-disciplinary Review and Evaluation for **NDA 212535** Nouress (cysteine hydrochloride)

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OPQ=Office of Pharmaceutical Quality  
 OPDP=Office of Prescription Drug Promotion  
 OSE=Office of Surveillance and Epidemiology  
 SRPM=Safety Regulatory Project Manager  
 DEPI=Division of Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DPV=Division of Pharmacovigilance  
 DPMH=Division of Pediatric and Maternal Health  
 RPM=Regulatory Project Manager  
 PBPM=Regulatory Business Project Manager  
 ATL=Application Technical Lead  
 DP=Drug Product  
 DS=Drug Substance

## Glossary

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AA	amino acid
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AET	analytical evaluation threshold
ANDA	abbreviated new drug application
BLA	biologics license application
CFR	Code of Federal Regulations
cys	cysteine
DGIEP	Division of Gastroenterology and Inborn Errors Products
DMF	drug master file
ECG	electrocardiogram
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GC/MS DI	Gas Chromatography/Mass Spectrometry Direct Injection
ICH	International Council on Harmonization
HS	Headspace
ICP-MS	Inductively Coupled Plasma / Mass Spectrometry
IND	Investigational New Drug
LC/DAD/MS	Liquid Chromatography/Diode Array Detector/Mass Spectrometry
LD	listed drug
LOQ	limits of quantitation
NDA	new drug application
NDC	national drug code
NMT	not more than
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PDE	permitted daily exposure
PK	pharmacokinetics
PN	parenteral nutrition
PLR	Physician Labeling Rule
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
RRT	relative retention time
RSD	relative standard deviation
TDI	total daily intake
TPN	total parenteral nutrition
TTC	threshold for toxicological concern
USP	United States Pharmacopeia
WRO	Written Response Only

## **1. Executive Summary**

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### **1.1. Product Introduction**

Nouress (cysteine hydrochloride injection) is a sulfur-containing amino acid (AA) supplement administered through parenteral nutrition. The Applicant's proposed indication is used as an additive to AA solutions to meet the nutritional requirements of neonates (preterm and term Infants less than one month of age) requiring total parental nutrition (TPN). The recommended dose for Nouress is 22 mg/gram AAs, providing 15 mg of cysteine/gram AAs. The corresponding volume is 0.44 mL Nouress/g AAs.

During the review cycle for Nouress, on April 16, 2019, Elcys™ (cysteine hydrochloride injection) was approved for use to meet the nutritional requirements of newborn infants requiring TPN; and of adult and pediatric patients with severe liver disease who may have impaired enzymatic processes and require TPN. Elcys is currently the only approved cysteine product on the market.

### **1.2. Conclusions on the Substantial Evidence of Effectiveness**

As a 505(b)(2) application, the efficacy of Nouress is established through reliance on the effectiveness of the listed drug (LD), 7.25% Cysteine Hydrochloride (NDA 019523, held by Hospira, Inc.). At this time, there are insufficient direct data and information to fully support the proposed indication of "meeting the nutritional requirements...". Although the essential need for cysteine in select populations of patients who require parenteral nutrition (PN) has been widely accepted as reflected by clinical practice guidelines and the current market demand, the specific evidentiary support for the nutritional requirement of cysteine in the Applicant's proposed target population, as demonstrated by subsequent clinical benefit relating to "how a patient feels, functions, and survives" is inadequate to support a complete assessment of Nouress' ability to meet "nutritional requirements." This is due to a lack of knowledge regarding the exact daily nutritional requirement for cysteine, which contributes to inadequate information on optimal dosing, as well as an absence of high-quality randomized controlled trials in the published literature to provide evidence of effectiveness for cysteine in promoting growth, impacting a patient's clinical course, or providing additional clinical benefit.

Despite these limitations, generally accepted scientific knowledge, (i.e., "AAs are building blocks of protein synthesis," "supply of AAs promotes growth," and "parenteral nutrition that provides a full profile of AAs is optimal"), together with the historical approval and subsequent safety and efficacy determinations of the LD for this 505(b)(2) application and the evidence available from current widespread clinical use of cysteine support a finding of substantial evidence of effectiveness for Nouress for the recommended indication as source of cysteine.

### 1.3. Benefit-Risk Assessment

#### Benefit-Risk Summary and Assessment

The NDA for the proposed product relies upon the Agency's findings of safety and efficacy for 7.25% Cysteine Hydrochloride, initially approved in 1986. Of note, although the listed drug (LD) has been withdrawn from the market, it was determined not to have been withdrawn due to reasons of efficacy or safety (see Section 3.1).

Cysteine Hydrochloride 5% carries a comparable benefit-risk potential to 7.25% Cysteine Hydrochloride. Parenterally-administered cysteine products are effective sources of the conditionally essential amino acid (AA) cysteine, as evidenced by the increased plasma cysteine and taurine concentration following supplementation with these products. A meta-analysis of small published trials demonstrated that cysteine supplementation led to a positive nitrogen balance; however, no significant effect on growth in neonates was reported with the administration of parenteral cysteine products. In clinical practice, addition of cysteine to the total parenteral nutrition (TPN) causes acidification of the admixture, which improves calcium and phosphate solubility, thereby enhancing delivery of these important nutritional components.

No new safety data were submitted in this application using the proposed drug product, and no new safety signals were identified upon review of the postmarket data of the previously available marketed unapproved formulations. Absence of any major identifiable safety signal within the published literature and the FDA Adverse Event Reporting System (FAERS) database gives reasonable reassurance of the overall safety of cysteine hydrochloride. As cysteine is a naturally-occurring AA that can be endogenously synthesized from methionine, the product is anticipated to be well-tolerated. In general, risks of Nouress appear consistent with the known risks of other AA solutions; however, the risk of metabolic acidosis in preterm infants may be increased specifically with cysteine administration. This risk is likely to be mitigated by the expected usage of this product by providers with expertise in managing TPN, including titration of cysteine (and other small volume parenterals) in the context of individual patients' requirements and tolerance.

Discrepancies and variabilities in the dosing exist between the original approved dose for the LD and the current clinical practice guidelines; however, there are insufficient data to warrant a modification to the proposed dose recommendation of 15 mg cysteine/g of AA to an alternate higher dose (i.e., 20 mg, 30 mg or 40 mg/g) at this time.

In summary, Nouress represents a medically necessary product. Based on the comparability of the proposed product to the LD,

<p>scientific understanding of protein and AA metabolism, which supports the conditional essentiality of cysteine, the benefits of the proposed product outweigh the risks. Cysteine hydrochloride products have been on the national drug shortage list in the past. Approval of an additional cysteine hydrochloride product will ensure quality and availability. Therefore, the overall benefit/risk assessment is favorable and the approval of Nouress for the proposed indication is recommended.</p>		
<b>Dimension</b>	<b>Evidence and Uncertainties</b>	<b>Conclusions and Reasons</b>
<a href="#">Analysis of Condition</a>	<p>Cysteine is used in vivo as a building block in the biosynthesis of various proteins necessary for growth and development.</p> <p>In addition, as a precursor for both glutathione and taurine, cysteine is thought to be necessary for formation of natural antioxidants and soluble biliary salts, respectively.</p> <p>In adults, cysteine is synthesized <i>de novo</i> from ingested methionine via cystathionase enzyme in the trans-sulfuration pathway and is considered non-essential. However, in preterm and term infants, the cystathionase activity does not reach mature levels until about 3 months of age. This pathway is also impaired in adults with liver insufficiency.</p> <p>Cysteine reduces the pH of TPN mixtures and increases the solubility of calcium and phosphate, thereby decreasing precipitation and enhancing availability.</p> <p>Published clinical practice guidelines by both American and European parenteral nutrition societies recommend routine cysteine supplementation for neonates.</p>	<p>There is an unmet need for an intravenous source of cysteine for TPN-dependent patients such as preterm and term neonates, in whom cysteine is a conditionally essential AA due to immature or impaired liver function.</p>
<a href="#">Current Treatment Options</a>	<p>Commercially available AA formulations do not contain an appreciable amount of cysteine hydrochloride. In premixed solutions of crystalline AAs, cysteine is relatively unstable over time, eventually converting to insoluble cystine. To limit precipitation and provide usable cysteine, doses of cysteine hydrochloride products are commonly admixed into parenteral nutrition on the day of administration. There has been a reported drug shortage of L-cysteine from January 9, 2015 to April 16, 2019. There is one approved product, Elcys (NDA 210660; approved 2019).</p>	<p>Cysteine hydrochloride products are critical to public supply and patient needs.</p> <p>Approved injectable cysteine hydrochloride products provide assurance of product quality and availability.</p>
<a href="#">Benefit</a>	<p>Plasma cysteine concentrations have been shown to increase with cysteine supplementation.</p>	<p>Parenterally administered cysteine products are effective sources of this conditionally essential AA, evidenced by the increased</p>

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>Plasma taurine concentrations have been shown to increase or normalize after cysteine supplementation in studies of older pediatric patients.</p> <p>The 2006 Cochrane review meta-analysis of the available data from four randomized controlled trials concluded that cysteine supplementation significantly increased nitrogen retention. Growth was not significantly affected by cysteine supplementation in the meta-analysis; this is likely due to the limitations of the trial design.</p> <p>Clinical uses of cysteine supplementation in TPN also include acidification of the admixture to improve calcium and phosphate solubility.</p>	<p>plasma cysteine and taurine concentration following cysteine supplementation.</p> <p>The impact of the addition of cysteine to affect calcium and phosphate delivery to premature infants who require TPN is beneficial, as calcium and phosphate availability may be limited due to incompatibility with the components of TPN solutions.</p>
<p><a href="#">Risk and Risk Management</a></p>	<p>No new safety data were submitted using the proposed drug product. No new safety signals were identified upon review of the postmarket data with comparable marketed unapproved formulations of cysteine.</p> <p>The major known safety concerns with Nouress are vein damage and thrombosis, increased blood urea nitrogen, acid-base imbalance (e.g., metabolic acidosis), hepatobiliary disorders, hyperammonemia, and aluminum toxicity.</p> <p>Nouress is intended to be prescribed by physicians as a component of the daily TPN prescription, prepared by dedicated TPN pharmacies, and administered intravenously as part of an admixture solution by trained nursing staff.</p> <p>Typical prescribers, i.e., neonatologists, intensivists, etc., are well-versed in the identification and management of the toxicities associated with parenteral nutrition administration.</p>	<p>The overall safety profile of Nouress as a source of intravenous cysteine is acceptable. In general, risks of Nouress appear consistent with the known risks of AA solutions, albeit certain potentially serious risks may be potentiated, including metabolic acidosis. In clinical practice, Nouress will be used by providers experienced with the potential risks of administration in a setting where those risks can be adequately monitored and managed. A Risk Evaluation and Mitigation Strategy (REMS) or Food and Drug Administration Amendments Act of 2007 postmarketing requirements are not needed to ensure the benefits of Nouress outweigh its risks.</p>

## 1.4. Patient Experience Data

**Patient Experience Data Relevant to This Application** (check all that apply)

<input type="checkbox"/>	<b>The patient experience data that were submitted as part of the application include:</b>	Section of review where discussed, if applicable
<input type="checkbox"/>	Clinical outcome assessment data, such as	
<input type="checkbox"/>	Patient reported outcome (PRO)	
<input type="checkbox"/>	Observer reported outcome (ObsRO)	
<input type="checkbox"/>	Clinician reported outcome (ClinRO)	
<input type="checkbox"/>	Performance outcome (PerfO)	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies (e.g., submitted studies or scientific publications)	
<input type="checkbox"/>	Other: (Please specify):	
<input type="checkbox"/>	<b>Patient experience data that were not submitted in the application, but were considered in this review:</b>	
<input type="checkbox"/>	Input informed from participation in meetings with patient stakeholders	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Other: (Please specify):	
<input checked="" type="checkbox"/>	<b>Patient experience data was not submitted as part of this application.</b>	

## 2. Therapeutic Context

### 2.1. Analysis of Condition

The prevailing rationale for the addition of cysteine to standard parenteral nutrition formulations is two-fold. First, cysteine is a conditionally essential AA, as it is produced in

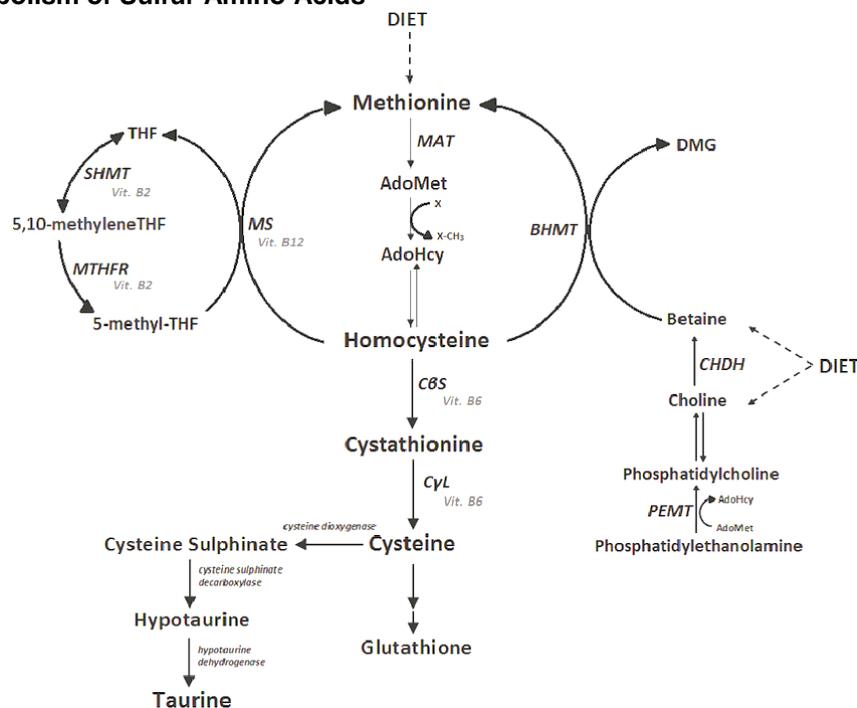
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limited supply by certain populations and may not be synthesized in a sufficient quantity in times of stress or illness. Secondly, cysteine reduces the pH of TPN mixtures and increases the solubility of calcium and phosphate, thereby decreasing precipitation and enhancing availability of these components for patients receiving TPN.

Cysteine is used *in vivo* as a building block in the synthesis of various proteins necessary for growth and development. In addition, as a precursor for both glutathione and taurine, cysteine is thought to be necessary for formation of natural antioxidants and soluble biliary salts, respectively.

While cysteine is non-essential in adults, as it is synthesized *de novo* from methionine and serine, it is essential in preterm and term infants due to enzymatic immaturity of the trans-sulfuration pathway (Figure 1)(1, 2). In adults, about 90% of ingested methionine is converted to cystine or L-cysteine via cystathionase in the trans-sulfuration pathway; however, this is not the case for preterm and term infants, as cystathionase activity does not reach mature levels until about 3 months of age (3, 4).

**Figure 1. Metabolism of Sulfur Amino Acids**



Enzymes are shown in italics, and their cofactors are shown in gray.

Abbreviations: MAT = methionine adenosyltransferase; AdoMet = S-adenosylmethionine; AdoHcy = S-adenosylhomocysteine; X = methyl acceptor; CBS = cystathionine β-synthase; CyL = cystathionine γ-lyase; MS = methionine synthase; THF = tetrahydrofolate; MTHFR = 5,10-methylene-THF reductase; SHMT = serine hydroxymethyltransferase; BHMT = betaine-homocysteine S-methyltransferase; DMG = dimethylglycine; CHDH = choline dehydrogenase; PEMT = phosphatidylethanolamine *N*-methyltransferase.

Source: Poloni S, Blom HJ, Schwartz IVD. Stearoyl-CoA Desaturase-1: Is it the Link between Sulfur Amino Acids and Lipid Metabolism? *Biology* 2015, 4(2), 383-396; doi:[10.3390/biology4020383](https://doi.org/10.3390/biology4020383)

## **2.2. Analysis of Current Treatment Options**

In premixed solutions of crystalline AAs, cysteine is relatively unstable over time, eventually converting to insoluble cystine. Commercially available AA formulations do not contain appreciable amount of cysteine hydrochloride (Table 1). In clinical practice, to limit precipitation and provide usable cysteine, doses of cysteine hydrochloride products are commonly admixed into parenteral nutrition on the day of administration.

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**Table 1. Approved Amino Acid Products**

Products	AA concentration	Nitrogen (g/100mL)	Amino acids (essential) (mg/100 mL)								Amino acids (nonessential) (mg/100mL)										
			Isoleucine	Leucine	Lysine	Methionine	Phenylalanine	Threonine	Tryptophan	Valine	Alanine	Arginine	Histidine	Proline	Serine	Taurine	Tyrosine	Glycine	Glutamic acid	Aspartic acid	Cysteine
Aminosyn 3.5% (Hospira)	3.5%	0.55	252	329	252	140	154	182	56	280	448	343	105	300	147	31	448				
Aminosyn II 3.5% (Hospira)	3.5%	0.54	231	350	368	60	104	140	70	175	348	356	105	253	186	95	175	258	245		
Aminosyn 5% (Abbott)	5%	0.79	360	470	360	200	220	260	80	400	640	490	150	430	210	44	640				
Aminosyn II 5% (Abbott)	5%	0.77	330	500	525	86	149	200	100	250	497	509	150	361	265	135	250	369	350		
TrophAmine 6% (B.Braun)	6%	0.93	490	840	490	200	290	250	120	470	320	730	290	410	230	15	140	220	300	190	<14
Aminosyn 7% (Hospira)	7%	1.10	510	660	510	280	310	370	120	560	900	690	210	610	300	44	900				
Aminosyn-PF7% (Hospira)	7%	1.07	534	831	475	125	300	360	125	452	490	861	220	570	347	50	44	270	576	370	
Aminosyn II 7% (Hospira)	7%	1.07	462	700	735	120	209	280	140	350	695	713	210	505	371	189	350	517	490		
Aminosyn 8.5% (Hospira)	8.5%	1.34	620	810	624	340	380	460	150	680	1100	850	260	750	370	44	1100				
Aminosyn II 8.5% (Hospira)	8.5%	1.30	561	850	893	146	253	340	170	425	844	865	255	614	450	230	425	627	595		
FreAmine III 8.5% (B.Braun)	8.5%	1.30	590	770	620	450	480	340	130	560	600	810	240	950	500		1190				<14
TrophAmine 10% (B.Braun)	10%	1.55	820	1400	820	340	480	420	200	780	540	1200	480	680	380	25	240	360	500	320	<16
Aminosyn 10% (Hospira)	10%	1.57	720	940	720	400	440	520	160	800	1280	980	300	860	420	44	1280				
Aminosyn-PF 10% (Hospira)	10%	1.52	760	1200	677	180	427	512	180	673	698	1227	312	812	495	70	44	385	820	527	
Aminosyn II 10% (Hospira)	10%	1.53	660	1000	1050	172	298	400	200	500	993	1018	300	722	530	270	500	738	700		
Travasol 10% (Baxter)	10%	1.65	600	730	580	400	560	420	180	580	2070	1150	480	680	500	40	1030				
FreAmine III 10% (B.Braun)	10%	1.53	690	910	730	530	560	400	150	660	710	950	280	1120	590		1400				<16
Aminosyn II 15% (Hospira)	15%	2.30	990	1500	1575	258	447	600	300	750	1490	1527	450	1083	795	405	750	1107	1050		
Clinisol 15% (Baxter)	15%	2.37	749	1040	1180	749	1040	749	250	960	2170	1470	894	894	592	39	1040	749	434		
Plenamaine 15% (B.Braun)	15%	2.37	749	1040	1180	749	1040	749	250	960	2170	1470	890	894	592	39	1040	749	434		
Premasol 6% (Baxter)	6%	0.93	490	840	490	200	290	250	120	470	320	730	280	410	230	15	140	220	300	190	<14
Premasol 10% (Baxter)	10%	1.55	820	1400	820	340	480	420	200	780	540	1200	480	680	380	25	240	360	500	320	<16

Source: Amino Acids Injection (General Formulations) Updated March 18, 2019. Facts & Comparisons®  
[http://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/fc\\_dfc/5548357](http://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/fc_dfc/5548357)

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**Table 2. Currently Available Approved Cysteine Products**

<b>Product Name</b>	<b>Manufacturer</b>	<b>Type</b>	<b>Pediatric Indication</b>	<b>Approval Date</b>
Elcys	Exela Pharma	Cysteine Hydrochloride 5% Injection	Birth to <17 years	April 16, 2019

There were multiple unapproved and compounded cysteine products manufactured and distributed prior to the approval of Elcys, as Hospira’s 7.25% Cysteine Hydrochloride Injection was withdrawn effective June 16, 2006 (NDA 019523). However, cysteine product is no longer on the drug shortage list since the approval of Elcys.

### **3. Regulatory Background**

#### **3.1. U.S. Regulatory Actions and Marketing History**

NDA 212535 is a 505(b)(2) application for cysteine hydrochloride that relies on FDA’s findings of safety and effectiveness for the LD 7.25% Cysteine Hydrochloride (NDA 019523, held by Hospira, Inc.). NDA 019523 was initially approved on October 22, 1986. In a letter dated May 26, 2005, Hospira informed FDA that the product was never commercially manufactured or marketed, and requested a withdrawal of the NDA. The drug product was moved to the “Discontinued Drug Product List” section of the Orange Book, and FDA withdrew the approval of NDA 019523 effective June 16, 2006 (71 FR 34940).

On April 30, 2008, Regulus Pharmaceutical Consulting, Inc. submitted a citizen’s petition (Docket No. FDA-2008-P-0278) to request that the FDA determine whether the LD’s withdrawal from the market was secondary to efficacy or safety concerns. Pursuant to 21 Code of Federal Regulations (CFR) 314.161, on December 19, 2008 and followed by two subsequent addenda, FDA determined that 7.25% Cysteine Hydrochloride Injection, United States Pharmacopeia (USP), was not withdrawn for reasons of safety or effectiveness. The Safety and Efficacy Relisting Petition memoranda are summarized as below:

#### December 19, 2008

- FDA determined that prior to market reintroduction, labeling changes were needed, and additional studies were warranted to:
  1. Address a safety concern of metabolic acidosis among preterm neonates during drug administration,
  2. Complete dosage recommendations for drug administration in the pediatric population other than neonates, and
  3. More thoroughly prepare the newly required Physician Labeling Rule (PLR) formatted label.

#### June 22, 2009

- FDA amended the original consult review to address the need for safety studies prior to

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product relisting.

- This amendment erroneously<sup>1</sup> recommended an alternative to conducting safety studies by including the safety language as referenced in a 2004 labeling for cysteine hydrochloride (Hospira).

April 20, 2010

- To clarify the recommended safety and pediatric dosing studies, in a response, FDA stated that an “abbreviated new drug application (ANDA) for a cysteine hydrochloride product referencing NDA 019523 could be approved today with certain changes to the most recently approved (1986) labeling, *without* reference to new studies.”
- FDA further clarified that the addition of the AA class labeling language regarding metabolic acidosis in the Warnings and Precautions and safety labeling language regarding the product’s aluminum content, per the requirements of 21 CFR 201.323, would obviate the need for further studies regarding these safety concerns.
- FDA noted that the 1986 approved labeling omits dosage recommendations for the indicated population of pediatric patients with severe liver disease; however, the lack of dosing recommendations for pediatric patients with severe liver disease would not be considered a reason to initiate withdrawal of the drug product for reasons of safety or efficacy.
- FDA stated that “although we would prefer to see such dosing recommendations in the labeling, we recognize that physicians are able to determine the appropriate dosing for these pediatric patients by relying on their clinical expertise, the medical literature, and standard guidelines for parenteral nutrition.”
- FDA concluded that an “ANDA relying on NDA 019523 would be approvable without the addition of dosage recommendations for pediatric patients with severe liver disease and without reference to studies or data supporting such dosage recommendations.”
- After reviewing the regulations governing revisions to the content and format of labeling (PLR formatted label), notably 21 CFR 201.56(b), it was determined that there was no requirement to update this product’s labeling to the PLR format, because NDA 019523 was approved prior to June 1, 2001, and no efficacy supplements were approved.

Of note, on December 1, 2008, an additional manufacturer, Sandoz, began marketing an unapproved L-Cysteine Hydrochloride product in the US (national drug code (NDC) 66758-004-01).

The initial drug shortage was reported on January 9, 2015 (NDC 66758-004-02). On March 1,

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<sup>1</sup> The referenced 2004 label was associated with a different cysteine hydrochloride product, and this error was corrected in the April 20, 2010 memo.

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2016, temporary importation of Canadian product (NDC 0781-8940-70) was authorized to alleviate the continued US shortage of cysteine hydrochloride.<sup>2</sup>

On April 16, 2019, Elcys™ (cysteine hydrochloride injection) was approved for use to meet the nutritional requirements of newborn infants requiring TPN, and of adult and pediatric patients with severe liver disease who may have impaired enzymatic processes and require TPN. Elcys is currently the only approved cysteine product on the market. Cysteine hydrochloride injection is no longer on the FDA drug shortage list since the approval of Elcys.

### **3.2. Summary of Presubmission/Submission Regulatory Activity**

Four pre-Investigational New Drug (IND) meeting/Written Response Only (WRO) were held with the Division under IND 132382 and are listed below by date. Points of discussion or Division recommendations are provided as a bulleted list for each meeting.

#### November 19, 2016

A WRO was provided regarding the development of L-Cysteine Hydrochloride Injection, USP.

- Confirmed a 505(b)(2) regulatory pathway rather than a 505(j) ANDA
- Accepted Hospira's cysteine injection (NDA 019523) as the LD
- Agreed to not conducting nonclinical studies but relying on prior safety and efficacy findings by Hospira
- Agreed to not conducting any clinical studies
- FDA recommended literature review for updated safety data for newborns
- Disagreed on an in vivo biowaiver, but recommended the Applicant submit a tabular comparison and details of admixture and administration studies
- Clarified that Pediatric Research Equity Act (PREA) does not apply if same dosing regimen used as LD
- Recommended the Applicant conduct a compatibility study with diluents and other PN products

#### April 5, 2017

A WRO was provided to discuss and clarify the 505(b)(2) regulatory pathway.

- Confirmed 505(b)(2) pathway of the proposed product, which is not identical to active ingredients of Aminosyn, another previously approved parenteral AA product containing cysteine
- Clarified the requirements of a compatibility study with other diluents, parenteral nutrition products and components
- Recommended labeling requirements to address Pregnant and Lactating Women

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<sup>2</sup> <https://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM511888.pdf>

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November 21, 2017

Type B meeting was held to discuss the acceptability of nonclinical & clinical information

- Agreed on reliance of nonclinical data in NDA 19523
- Advised on proposed bridging rationale regarding pharmacokinetics of the final solution
- Provided FDA guidance material for clinical pharmacology information
- Advised on dose determination and new safety data based on literature search
- Recommended that the Applicant consider other pediatric populations, in addition to neonates
- Advised on the organization of the NDA: providing a summary review of the available literature would obviate the need for a separate integrated summary of efficacy and integrated summary of safety components in the submission
- Clarified the requirement regarding aluminum content for L-cysteine product
- Clarified that the Applicant may submit information from literature, if available, to support compatibility in lieu of conducting an admixture study

July 25, 2018

A WRO was provided regarding exemption from PREA

- Confirmed that PREA would not be triggered if Avadel's proposed dose regimen is the same as the LD, provided the dose regimen is based a systematic review of updated literature on all pediatric ages.

The Applicant completed the submission of the NDA 212535 on March 15, 2019. Due to ongoing cysteine drug shortages at the time of filing, NDA 212535 was granted priority review designation and the user fee goal date was initially set for September 15, 2019. However, during the review cycle, due to a major amendment submission on July 15, 2019 for leachable and extractable data, the goal date was extended to December 15, 2019.

## **4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety**

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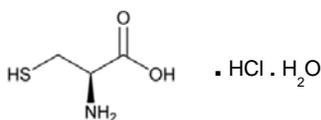
### **4.1. Office of Scientific Investigations (OSI)**

This section is not applicable.

## 4.2. Product Quality

### 4.2.1. Drug Substance

**Drug Substance:** The active ingredient, L-Cysteine Hydrochloride Monohydrate, is a white crystalline powder. It is hygroscopic and highly soluble in water (b) (4). L-Cysteine Hydrochloride Monohydrate is a chiral naturally-occurring AA with a molecular weight of 175.63 g/mol and a molecular formula of  $C_3H_7NO_2S \cdot HCl \cdot H_2O$ .



It is manufactured by (b) (4). The complete chemistry, manufacturing, and controls information regarding raw materials, manufacturing, purification, characterization, stability, storage, and container closure is provided in the drug master file (DMF) (b) (4) 4. The DMF (b) (4) was reviewed and deemed adequate.

The active pharmaceutical ingredient, L-Cysteine Hydrochloride Monohydrate, manufactured by (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 a 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 supplied as 10 mL USP (b) (4) clear glass vials, closed with stopper, and sealed with brown flip-off cap. There are no preservatives or anti-oxidants in the drug product formulation, so it is a single-dose drug product.

Nouress is manufactured by (b) (4). The approximate drug product batch size is (b) (4) for exhibition batches and (b) (4) for proposed commercial batches. The drug product manufacturing process, in-process controls, drug product release tests, and executed batch records were reviewed and deemed satisfactory.

The compatibility of Nouress was studied with commonly used TPNs and diluents. During the compatibility study, the admixture appearance, pH, osmolality, viscosity, assay, related substances, particulate matter, and in-use stability were assessed. The applicant performed two in-use admixture stability studies.

**In-use Admixture Stability Study #1:** In this study Nouress was admixed with 10% Dextrose Injection, TrophAmine 6%, Calcium Gluconate Injection and Potassium Phosphates Injection. The admixture appears to be stable up to 24 hours at room temperature. However, visible

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particulate matter was observed when stored at refrigerated temperature at 6-hour and 24-hour time periods.

**In-use Admixture Stability Study #2:** This study was performed to investigate if electrolytes, Calcium Gluconate Injection and Potassium Phosphates Injection, are the potential cause of visible particulate matter formation in the admixture. In addition, ELCYS was also used for a side by side comparison.

In this study Nouress was admixed with 10% Dextrose Injection and TrophAmine 6%. The admixtures appear to be stable and visible particulate matter was not observed in Nouress and ELCYS admixtures when refrigerated up to 24 hours followed by storage at room temperature up to 24 hours.

Thus, from CMC perspective it is recommended that when Nouress is admixed with electrolytes, it should be administered within 24 hours at room temperature. The unused portion should be discarded.

The drug product strength is the only difference between the reference 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 greater 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, it was determined that a biobridge has been established between the proposed and the listed product per 21 CFR 320.24 (b)(6) to assure similar in vivo disposition of cysteine. Thus, an additional in vivo bioequivalence bridging study is not needed.

The overall quality of Nouress (cysteine hydrochloride injection) 500 mg/10 mL (50 mg/mL) is controlled by its specification. Based on satisfactory stability testing of three registration batches, the proposed 24-month of expiration dating period when stored at 25°C in the proposed container closure system is granted.

#### **4.2.2. Summary and Recommendation**

The Applicant has provided adequate chemistry, manufacturing, and controls 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 has made a final overall "Approval" recommendation for the facilities involved in this application.

The label/labeling is acceptable from the CMC perspective.

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Therefore, this NDA is recommended for approval from the Office of Pharmaceutical Quality (OPQ) perspective.

### **4.3. Clinical Microbiology**

The (b) (4) manufacturing process, hold time study, drug product bulk solution (b) (4) of vials, rubber stoppers and equipment, container integrity by microbial ingress test as well as the microbiology-related attributes of the drug product specification, including bacterial endotoxins and sterility, were reviewed. This NDA is recommended for approval based on drug product sterility assurance from the microbiological perspective.

### **4.4. Devices and Companion Diagnostic Issues**

This section is not applicable.

### **4.5. Biopharmaceutics**

Consistent with 21 CFR 320.24(b)(6), FDA deemed the information supporting the relative bioavailability of the proposed drug product to the LD to be adequate, and a biobridge has been established to the Agency's finding of safety and effectiveness for the LD. Thus, an additional in vivo relative bioavailability/bioequivalence study is not needed.

## **5. Nonclinical Pharmacology/Toxicology**

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### **5.1. Executive Summary**

The Applicant has not conducted new studies to assess the safety of Nouress (cysteine hydrochloride injection) in nonclinical species. In accordance with 21 CFR 314.54(a)(1)(iii) and under Section 505(b)(2), the Applicant has proposed to rely on the Agency's finding of safety for the LD, 7.25% Cysteine Hydrochloride Injection, USP, approved under NDA 019523 (October 22, 1986). Accordingly, the nonclinical assessment of the drug product is limited to the evaluation of impurities, leachables, and elemental impurities based on the long-term stability data provided in the Quality section of the application (see Appendix 15.3 below). There are no safety concerns about impurities, leachables, or elemental impurities from a nonclinical viewpoint.

### **5.2. Referenced NDAs, BLAs, DMFs**

NDA 019523

### **5.3. Pharmacology**

No new data submitted.

### **5.4. ADME/PK**

None.

### **5.5. Toxicology**

#### **5.5.1. General Toxicology**

None.

#### **5.5.2. Genetic Toxicology**

None.

#### **5.5.3. Carcinogenicity**

None.

#### **5.5.4. Reproductive and Developmental Toxicology**

None.

## **6. Clinical Pharmacology**

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### **6.1. Executive Summary**

As indicated in Section 3.1 of this review, the Applicant relies on the Agency's findings of safety and effectiveness for Hospira's 7.25% Cysteine Hydrochloride, the LD (NDA 19523) via the 505(b)(2) pathway. The Applicant has also provided literature data to support the effective and safe use of the proposed product. The LD is approved in adults and pediatric patients of all ages with a specific neonatal dose recommendation for cysteine hydrochloride as 2.2% of total AAs being supplied. The Applicant did not conduct any clinical studies using the proposed product. Thus, no clinical pharmacokinetics or pharmacodynamics data for the proposed product were available.

Given that the proposed product is a solution for intravenous use, in vivo bioavailability is self-evident and an in vivo relative bioavailability study between the proposed product and the LD is not needed for approval under the 505(b)(2) pathway. Refer to Section 4.5 for the summary of the biobridge assessment.

### 6.1.1. Recommendations

From a Clinical Pharmacology standpoint, the NDA is acceptable to support the approval of Nouress (cysteine hydrochloride injection) for use as an additive to AA solutions to meet the nutritional requirements of neonates (preterm and term infants less than one month of age) requiring TPN.

## 6.2. General Dosing and Therapeutic Individualization

### 6.2.1. General Dosing

The recommended dosage and volume of Nouress is based upon the recommended daily protein (AA) requirements, as shown in Table 3. The proposed dose for Nouress is to provide cysteine hydrochloride as 2.2% of the total parenteral AAs being supplied, which is consistent with the approved dose of the LD for neonates. Note that Nouress contains 50 mg of cysteine hydrochloride/mL (5%), which is equivalent to 34.5 mg of cysteine/mL. Therefore, the recommended dose of Nouress, 22 mg cysteine hydrochloride/g of AA provides approximately 15 mg cysteine/g of AAs for neonates.

**Table 3. Recommended Daily Dosage of Nouress in Neonates (Preterm and Term Infants Less Than One Month of Age)**

Dosage	Protein <sup>a</sup> Requirement (g Amino Acids/kg/day)	Dosage (mg Nouress/g Amino Acids)	Volume (mL Nouress/g Amino Acids)
Neonates	3 to 4	22	0.44

<sup>a</sup>Protein is provided as amino acids.

### 6.2.2. Therapeutic Individualization

The body weight-based dose is reasonable. No further dose individualization based on intrinsic factors is recommended.

Refer to Sections 8.1.5 and 11.1 for the basis of these dosing recommendations.

## 6.3. Summary of Clinical Pharmacology Assessment

### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant submitted published articles evaluating plasma concentrations of cysteine as well as information on biomarkers (taurine and glutathione) following administration of cysteine in neonates ranging in postnatal age from 3-53 days. However, given the 1) different dosing regimens of both cysteine and background macronutrients (i.e., dextrose and AAs) for parenteral nutrition, 2) different bioanalytical methods that were used in the literature, and 3) lack of individual patient data, these literature data were considered to be supportive of efficacy, but should not be included in the product label. The more detailed review of these data is provided in Section 8.1.2 Published Literature.

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The only information relevant to clinical pharmacology in the LD's label is the mechanism of action of cysteine (Section 12.1 of the label). The language in Section 12.1 of the proposed label is based upon those in the LD's label, with editorial changes to meet FDA's current labeling standards.

### **6.3.2. Clinical Pharmacology Questions**

#### **Does the clinical pharmacology program provide supportive evidence of effectiveness?**

The Applicant has not conducted clinical pharmacology studies that provide supportive evidence of effectiveness.

#### **Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?**

The proposed dose to provide cysteine hydrochloride as 2.2% of the total parenteral AAs (i.e., cysteine hydrochloride 22 mg/g AAs) being supplied, is consistent with the recommended dose in neonates for the LD and is appropriate.

#### **Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?**

No, an alternative dosing regimen or management strategy is not required for subpopulations based on intrinsic factors. The dosing of Nouress is based upon the recommended daily protein (AA) requirements. See Section 8.1.5 for Clinical Efficacy for detailed discussion.

#### **Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?**

No, there are no clinically relevant food-drug interactions because Nouress is administered by intravenous infusion. There are also no known clinically significant drug-drug interactions based on the current knowledge of cysteine hydrochloride.

## **7. Sources of Clinical Data and Review Strategy**

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### **7.1. Table of Clinical Studies**

No formal clinical trials were conducted by the Applicant in support of NDA 212535.

### **7.2. Review Strategy**

Consistent with the intended 505(b)(2) submission, this NDA is supported by FDA's finding of efficacy and safety from the previous approval of the LD, 7.25% Cysteine Hydrochloride, USP (NDA 019523). As such, the evidence of safety and effectiveness in the original LD NDA

submission (see Section 8.1.1), as well as the subsequent safety and efficacy determinations of the product after its withdrawal (see Section 3.1), were considered. The comparative analysis of the differences between the proposed product and the LD, namely in the concentration and the container closure system, was assessed (see Section 4, 5, and 6). The Applicant was requested to submit available up-to-date clinical information from published literature to support any necessary updates in the label, i.e., pregnancy, lactation, and fertility, dosing and safety information, clinical pharmacology, and TPN admixture guidelines.

From an efficacy perspective, a formulation of intravenous cysteine hydrochloride for clinical use should be expected to supply an adequate amount of this conditionally-essential AA to prevent the development of cysteine deficiency in at-risk patients, such as preterm and term neonates. Considering the known and well-established biochemistry of AAs, a review of the available published literature was conducted to evaluate additional evidence of the effectiveness of supplemental cysteine on nutrition and related measurable parameters (i.e., plasma AA concentrations, growth, and nitrogen balance) as well as to assess updates for available dosing information.

There were no safety data submitted for the LD. Upon Division of Gastroenterology and Inborn Errors Products (DGIEP) request, the Office of Surveillance and Epidemiology (OSE) conducted a search of the spontaneous safety reports for cysteine hydrochloride in the FDA Adverse Event Reporting System (FAERS). The FAERS search period was from the date of original approval to October 29, 2019. The OSE review was reported to the Document Archiving, Reporting, and Regulatory Tracking System on April 5, 2019 and updated on October 29, 2019, and is discussed in Section 8.2 (see Section 8.2.10). In addition, safety information from studies in published literature involving patients who received IV administration of cysteine as an additive to TPN solutions was reviewed.

## **8. Statistical and Clinical and Evaluation**

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### **8.1. Review of Evidence Used to Support Efficacy**

#### **8.1.1. Listed Drug**

The NDA for the proposed product relies upon the Agency's findings of safety and efficacy for 7.25% Cysteine Hydrochloride, approved in 1986. Of note, the approval of NDA 019523 was largely based on the prior approval of NeoPham 6.4% (NDA 018792) in 1984. Prior to approval, no clinical studies were performed with 7.25% Cysteine Hydrochloride Injection, USP. However, clinical studies were performed with NeoPham 6.4% AAs Injection, which contained 100 mg/100 mL of cysteine (Section 2.e.iii., dated May 7, 1982 of NDA 018792). NeoPham 6.4% was withdrawn from the market at the same time as 7.25% Cysteine Hydrochloride. Of note, the LD was determined to not have been withdrawn from the market due to reasons of efficacy or safety (see Section 3.1), and according to the June 6, 2005 Acknowledge Withdrawal letter,

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NeoPham 6.4% was withdrawn at the Applicant's request due to a decision to discontinue marketing the product.

### **8.1.2. Published Literature**

Overall, there is a lack of well-controlled trials investigating the clinical outcomes associated with cysteine supplementation. Available published clinical trials were conducted under widely varying conditions, and datasets and case report forms from these trials are not available for further review. The Applicant identified six small randomized trials related to the use of cysteine parental supplementation in neonates. As the indicated population for Nouress is exclusively neonates, the chosen publication included subjects ranging in postnatal age from 3-53 days. Preterm infants were included as well. The review and analyses of those six studies are included in the discussion below.

Overall, there is a lack of well-controlled trials investigating the clinical outcomes associated with cysteine supplementation. Available published clinical trials were conducted under widely varying conditions, and datasets and case report forms from these trials are not available for further review. The Applicant identified six small randomized trials<sup>3</sup> related to the use of cysteine parental supplementation in neonates. As the indicated population for Nouress is exclusively neonates, the chosen publication included subjects ranging in postnatal age from 3-53 days. Preterm infants were included as well. The review and analyses of those six studies are included in the discussion below.

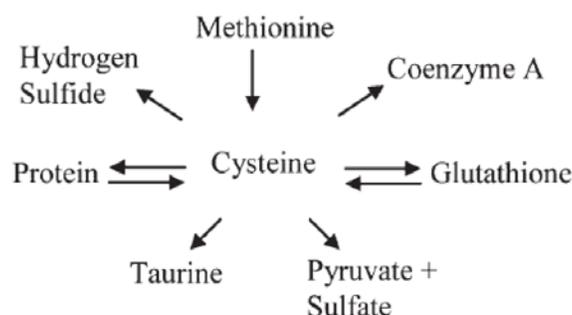
The outcomes assessed in the literature for cysteine supplementation in TPN mixtures include:

- Cysteine plasma concentration
- Plasma taurine concentration (Figure 2)
- Glutathione concentration in red blood cells and plasma (Figure 2)
- Nitrogen retention (with positive nitrogen balance indicative of sufficient AAs available for protein synthesis/growth) (Figure 2)
- Growth

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<sup>3</sup> Malloy MH et al. 1984; Kashyap S et al. 1992; Shew SB et al. 1999; Storm C. et al. 2003; Calkins KL et al. 2016; and Jadhav P et al. 2007;

**Figure 2. Major Pathways of Cysteine Metabolism in Mammals**



Source: NDA 212535 Submission, Module 2.7.2. Figure 2 (modified from:(5) Look MP, Riezler R, Reichel C, Brensing KA, Rockstroh JK, Stabler SP, et al. Is the increase in serum cystathionine levels in patients with liver cirrhosis a consequence of impaired homocysteine transsulfuration at the level of gamma-cystathionase? *Scandinavian journal of gastroenterology*. 2000;35(8):866-72).

### Plasma Cysteine and Taurine Concentrations

There is evidence to indicate that plasma cysteine concentrations increase with cysteine supplementation as demonstrated in studies shown in Table 4 and Table 5. Cysteine is utilized to synthesize taurine, which plays a role in a variety of physiological processes such as formation of bile salts, modulation of intracellular calcium concentration, central nervous system development, and cytoprotection. However, there were conflicting results regarding effect of cysteine supplementation on taurine levels.

The increase in plasma cysteine concentrations following cysteine supplementation provides evidence that parenterally administered cysteine products are effective sources of the conditionally essential AA (6). Although plasma AAs represent approximately 4% of the total free AA pool, they are in dynamic equilibrium within metabolically active cells (7). Stable plasma concentrations of essential AAs and molar ratios with other essential AAs are important for promotion of normal growth.

**Table 4. Effect of Cysteine Supplementation on Plasma Levels of Cysteine and Taurine**

Amino Acid, Sulfate, or Nitrogen	Low Nitrogen Intake		High Nitrogen Intake		Cysteine Effect p value	Nitrogen Effect p value	Cysteine Nitrogen Interaction p value
	Group 1 TPN n=5	Group 2 TPN +CYSE n=5	Group 3 TPN n=5	Group 4 TPN + CYSE n=5			
<b>Plasma Concentration (µmol/dL)</b>							
Methionine	2.38 ± 0.66	2.84 ± 2.31	3.94 ± 2.19	3.0 ± 3.4	0.8221	0.4249	0.5146
Cystathionine	0.12 ± 0.27	0.32 ± 0.44	0.44 ± 0.87	0.0	0.6054	1.0000	0.1790
Free Cyst(e)ine	4.46 ± 1.13	11.34 ± 3.38	4.20 ± 1.34	14.48 ± 3.83	0.0001	0.2509	0.1787
Bound half-Cystine	7.40 ± 3.20	7.90 ± 2.80	4.20 ± 2.10	5.40 ± 2.40	0.2500	0.0251	0.1376
Total Cyst(e)ine	11.9 ± 3.7	19.2 ± 5.9	8.4 ± 3.1	19.9 ± 6.0	0.0005	0.2250	0.1115
Taurine	4.12 ± 1.99	2.36 ± 1.34	5.96 ± 3.98	11.22 ± 7.07	0.3664	0.0118	0.0807

Abbreviations: TPN = total parenteral nutrition

Source: Table 3, Page 6, NDA 212535 Module 2.7.3.

Reference: Malloy MH, Rassins DK, Gauli GE. A method for measurement of free and bound plasma cyst(e)ine. *Anal Biochem.* 1981;113(2):407-15.

**Table 5. Effect of Cysteine Supplementation on Plasma Levels of Taurine and Cystine**

	Cysteine dose (mg/g AA)			
	0	10	20	40
<b>Plasma AA (Mean of Normal)</b>				
Taurine (nmoles/mL) <sup>a</sup>	41.2/5.47	54.8/5.22	64.8/4.27	76.1/9.60
Cystine <sup>a</sup>	38.9/3.71	45.8/4.89	46.7/3.31	54.3/7.90
Methionine <sup>a</sup>	74.1/7.59	59.5/4.08	60.6/3.44	65.3/4.55

<sup>a</sup> results presented as mean/SEM

Abbreviations: AA = amino acid

Source: Table 7, Page 10, NDA 212535 Module 2.7.3

Reference: Storm MC, Helms RA. Cysteine supplementation normalizes plasma taurine concentrations in low birth weight premature infants requiring parenteral nutrition support. *Journal of Parenteral and Enteral Nutrition* 2003; Vol. 27:S4-S5.

### Glutathione Concentrations

Cysteine is utilized by the body to synthesize glutathione (Figure 2), which is known as an antioxidant and important for counteracting oxidative stress. Glutathione also protects S-adenosylmethionine synthase, a key enzyme in the hepatic transmethylation/trans-sulfuration pathway, from oxidative damage. However, the available literature suggests that cysteine supplementation was found to have no effect on glutathione concentrations at doses studied (Table 6).

**Table 6. Effect of Cysteine Supplementation on Glutathione Levels**

Study	Measure	Cysteine		No Cysteine	p-value
Kashyap et al. 1992 (8)	Plasma glutathione (µm/dL)	1.5 ± 0.7 <sup>a</sup>	1.39 ± 0.5 <sup>b</sup>	1.57 ± 0.6	Not Provided
Shew et al. 1999 (9)	RBC-GSH (mmol/L)	0.62 ± 0.05		0.57 ± 0.04	0.47
Calkins et al. 2016 (10)	GSH (mmol/L)	1.4 (0.9, 2.6)		1.6 (1, 1.8)	0.7

<sup>a</sup> Added to total parenteral nutrition

<sup>b</sup> Infused separately

Source: Table 15, Page 16, NDA 212535, Module 2.7.3

## Nitrogen Balance and Growth

The clinical significance of increased levels of specific AAs should, in theory, be measurable as positive nitrogen balance or retention, and resultant overall improvement in neonatal growth. Table 7 and Table 8 summarized four such studies to evaluate the effect of cysteine supplementation on nitrogen retention and growth, respectively. Cysteine supplementation groups showed a trend of increasing nitrogen balance; however, the results did not reach statistical significance. There was no data showing that cysteine supplementation resulted in increased growth in neonates.

A 2006 Cochrane review meta-analysis (11) of the available data from the four randomized controlled trials concluded that cysteine supplementation significantly increased nitrogen retention. As expected, the significance was more pronounced in a subgroup where there were no documented low intakes of other essential nutrients. The weighted mean difference of nitrogen retention reported was 31.8 mg/kg/day (95% CI: 8 mg/kg/day to 55.4 mg/kg/day). However, growth was not significantly affected by cysteine supplementation in the meta-analysis. There were several limitations to the interpretability of the studies included in the Cochrane review including: short duration, heterogeneity in the concomitantly administered parenteral nutrients with variability in AA and dextrose doses, and variable addition of enteral nutrition. More recent studies using consumption of an isotope-labeled essential AA, phenylalanine, as an indicator of protein synthesis in fully enterally fed low birth weight and very low birth weight preterm infants (32 to 35 weeks gestational age) at approximately 1 and 2 months of age showed that the cysteine requirement is <18.7 mg/kg/day, equivalent to <4.5 mg cysteine/g AA, when sufficient levels of methionine are provided (12, 13).

**Table 7. Effect of Cysteine Supplementation on Nitrogen Balance**

Study	Measure	Cysteine		No Cysteine		p-value
Zlotkin et al. 1981 (14)	Nitrogen Retention (%)	55.7%		55.6%		NS
Malloy et al. 1984 (15)	Nitrogen Retention (mg/kg/day)	150.20 ± 61.98 <sup>a</sup>	291.60 ± 35.74 <sup>b</sup>	114.00 ± 20.05 <sup>a</sup>	229.80 ± 34.24 <sup>b</sup>	0.4552
Kashyap et al. 1992 (8)	Nitrogen Balance (mg/kg/day)	228 ± 32 <sup>c</sup>	228 ± 72 <sup>d</sup>	168 ± 81		Not Provided
Shew et al. 1999 (9)	Nitrogen Balance (mg/kg/day)	282 ± 35		207 ± 37		0.17

<sup>a</sup> Low nitrogen intake

<sup>b</sup> High nitrogen intake

<sup>c</sup> Added to TPN

<sup>d</sup> Infused separately

Abbreviations: NS = not significant

Source: Table 14, Page 16, NDA 212535 Module 2.7.3

**Table 8. Effect of Cysteine Supplementation on Growth**

	Weight Change	Difference in Head Circumference	Length Change
Supplemented (n=18)	6.1 ± 2.3 g/kg/24 hours	0.9 ± 0.2 cm/6 days	0.6 ± 0.1 cm/6 days
Control (n=18)	10.2 ± 1.7 g/kg/24 hours	0.6 ± 0.1 cm/6 days	0.6 ± 0.2 cm/6 days

<sup>a</sup> Results are presented as mean ± SEM

Source: Table 11, Page 12, NDA 212535 Module 2.7.3

Reference: Zlotkin et al., Cysteine supplementation to cysteine-free intravenous feeding regimens in newborn infants. The American Journal of Clinical Nutrition. 1981 May: 914-923.

## Other Clinical Uses of Cysteine

An additional clinical use of cysteine supplementation includes acidification of the TPN admixture to improve calcium and phosphorus (i.e., phosphate) solubility (11, 16). This effect of cysteine supplementation is beneficial because the availability of calcium and phosphate ions is typically limited due to incompatibility and solubility factors when admixed with the components of TPN solutions, thus creating challenges in supplying sufficient calcium and phosphate to premature infants who require TPN.

### 8.1.3. Assessment of Efficacy Across Trials

### 8.1.4. Assessment of Efficacy Across Trials

Not Applicable.

### 8.1.5. Integrated Assessment of Effectiveness

In summary, the limited available literature reporting on trials that investigated the clinical impact of the use of cysteine supplementation in neonates did not demonstrate significant effects in terms of measurable clinical outcomes. While some studies have shown a significant increase in serum cysteine levels and taurine levels after supplementation (Table 4 and Table 5), the ultimate clinical benefit of the increased serum cysteine remains unclear, as no study

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has shown that cysteine supplementation has a significant effect on neonatal growth (11).

It is likely that there is a range of effective doses for cysteine supplementation and that this range is dependent on multiple individual factors, which creates challenges to optimal study design. Cysteine supplementation increases the AA substrates for protein synthesis and allows increased provision of critical elements (e.g., calcium and phosphate) to support bone and linear growth; however, cysteine also acidifies the TPN admixture and metabolic acidosis can inhibit neonatal growth. Therefore, the optimal dose for each patient should consider the individual's AA requirement and tolerance and be based on the patient's weight, age, renal function, and concomitant nutrition and medical history. In contrast to a clinical trial setting, in clinical practice, the parenteral cysteine doses are indeed titrated to "effect" over a range of doses (see Section 9), which are prescribed daily within the context of the individual patient's requirements and tolerance.

Despite the lack of definitive clinical outcome-based efficacy, evidence in published literature and the scientific understanding of protein and AA metabolism that supports the conditional essentiality of cysteine (17) have contributed to published clinical practice guidelines by both American and European parenteral nutrition societies that recommend routine cysteine supplementation for neonates (18, 19).

## **8.2. Review of Safety**

No new safety data were submitted using the proposed product.

### **8.2.1. Safety Review Approach**

The safety review for the proposed product relies on the previous findings of safety for the LD as well as on systematic literature review. The Prescribing Information of the LD did not describe any adverse events, and there are no relevant postmarketing adverse events described in literature or FAERS specific to the LD, as it was never manufactured or marketed. Further support of safety for the candidate product, Nouress, was provided by an evaluation of published literature as well as postmarketing FAERS reports (Section 8.2.10) of available "cysteine" products to identify any "class effects."

### **8.2.2. Review of the Safety Database**

#### **Overall Exposure**

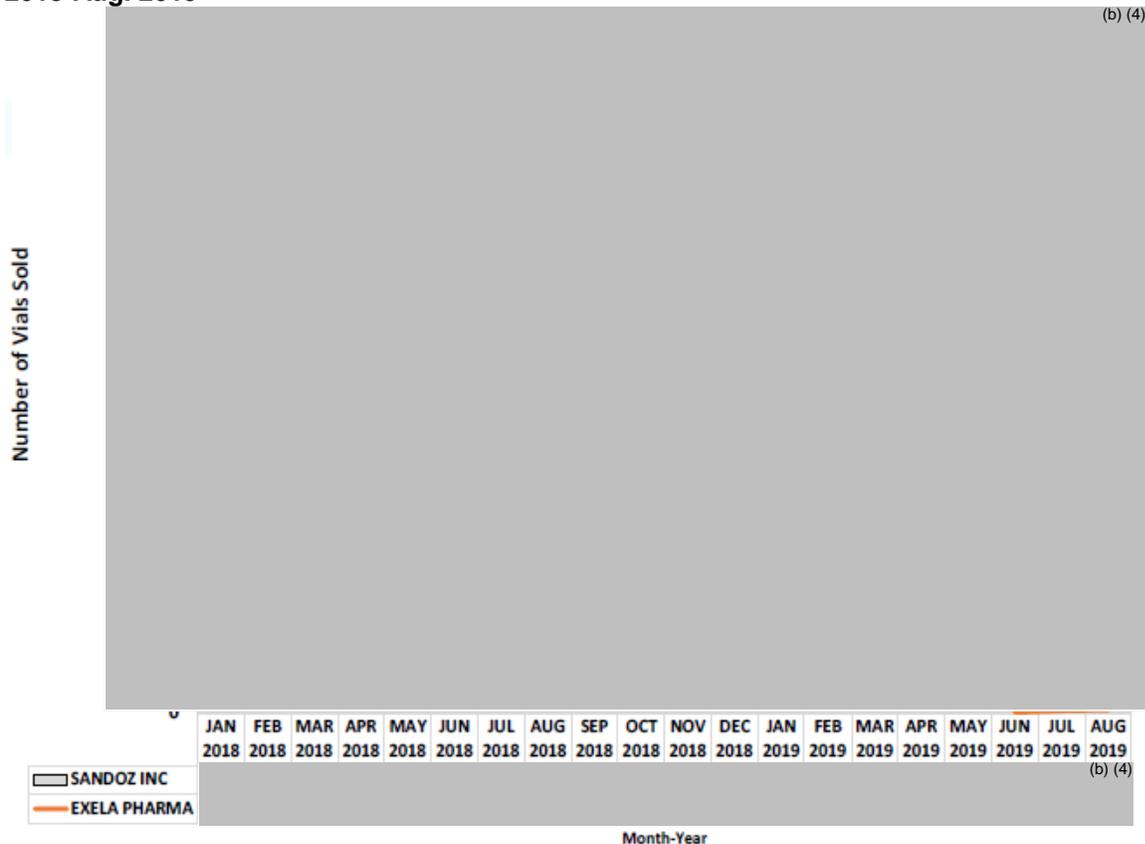
No new safety data were submitted using the proposed drug product. OSE conducted a FAERS search for postmarket safety updates for "cysteine hydrochloride," in which no new safety signals were identified (FAERS search by Jamie Klucken on Oct. 29, 2019).

As shown in Figure 3 below, marketed unapproved drug usage data shows active use of cysteine in the US market. Although the usage data reflects only one of the marketed

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unapproved products, it provides a general estimate of the denominator for the FAERS “post-marketing” safety database search. As of June 2019, Exela Pharmaceutical started distributing their approved cysteine product Elcys in a small quantity.

**Figure 3. Marketed Unapproved (Sandoz Inc) and Approved (Exela Pharma) Usage Data From Jan. 2018-Aug. 2019**



Source: Symphony Health PFAST NonRetail Monthly. Extracted October 2019

Source: Review by Patty Greene, PharmD, Division of Epidemiology II.

**Adequacy of the safety database:**

There were no specific safety data submitted for the LD, which was never marketed or manufactured. However, evidence of the safety of the historical and current clinical use of cysteine is demonstrated by the published literature, including current practice guidelines (19), supported by clinicians’ response to product shortage, and affirmed by the field experts in parenteral nutrition (see section 9).

Regardless of the specific cysteine product used in clinical practice, it is reasonable to conclude, barring quality issues, that any safety signal identified for one injectable cysteine used as a parenteral supplement would be applicable to the entire class of cysteine products that are expected to achieve the same bioavailability after administration of the same dose. Therefore, the available safety database, including the above FAERS database search for safety signals, is reasonably adequate to evaluate the safety of the proposed product.

### **8.2.3. Adequacy of Applicant's Clinical Safety Assessments**

#### **Issues Regarding Data Integrity and Submission Quality**

Not applicable.

#### **Categorization of Adverse Events**

Not applicable.

#### **Routine Clinical Tests**

Not applicable.

### **8.2.4. Safety Results**

#### **Deaths**

Not applicable.

#### **Serious Adverse Events**

Not applicable.

#### **Dropouts and/or Discontinuations Due to Adverse Effects**

Not applicable.

#### **Significant Adverse Events**

Not applicable.

#### **Treatment Emergent Adverse Events and Adverse Reactions**

Not applicable.

#### **Laboratory Findings**

Not applicable.

#### **Vital Signs**

Not applicable.

#### **Electrocardiograms (ECGs)**

Not applicable.

## **QT**

Not applicable.

## **Immunogenicity**

Not applicable.

### **8.2.5. Analysis of Submission-Specific Safety Issues**

#### **Metabolic Acidosis**

There are reports of metabolic acidosis in preterm infants less than 36 weeks gestational age, with cysteine hydrochloride added to parenteral nutrition (20-22). The incidence of these reports is greatest in the first two weeks of treatment. Metabolic acidosis is known to be a risk with TPN infusion and is managed with daily alterations to the TPN solution by providers with training and expertise in such scenarios while the patient is being monitored with both clinical and laboratory assessments (see Section 9). Current class labeling for marketed AA admixtures adequately addresses this safety concern regarding metabolic acidosis in the Warnings and Precautions section. Addition of the class language to the cysteine hydrochloride labeling is recommended.

#### **Aluminum Toxicity**

There have been numerous reports of aluminum toxicity resulting from this impurity found in PN solutions over the past three decades. A landmark study by Bishop et al. (23) compared neurological development in premature infants who received a standard TPN formula with median aluminum content of 45 mcg/kg/day to those who received an aluminum-depleted formula with a median aluminum content of 4 to 5 mcg/kg/day for a period of 5 to 16 days. The authors concluded that for infants receiving the standard TPN solution, the Bayley Mental Development Index score would be reduced by approximately 1 point per day of TPN.

A follow-up study of these former infants evaluated changes in bone mineralization 15 years after the intervention (24). Dual-energy radiograph absorptiometry showed that the now-adolescent patients who had received the aluminum-depleted TPN solutions during prematurity had a higher bone mineral content and bone area than did those who received the standard TPN solution. These findings suggest that the total aluminum exposure from prolonged TPN administration to premature infants is a contributing factor to adverse neurologic sequelae and altered bone development and mineralization.

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21 CFR 201.323 (e) specifies aluminum concentration limits in large<sup>4</sup> and small<sup>5</sup> volume parenteral nutrition products. The aluminum content of the LD and the other available marketed unapproved or compounded products do not meet the regulatory requirements of 21 CFR 201.323 (e). The proposed cysteine product significantly reduces the aluminum content (see Appendix 15.3) and ensures acceptable aluminum exposures in patients receiving this formulation of cysteine hydrochloride.

#### **8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability**

Not applicable.

#### **8.2.7. Safety Analyses by Demographic Subgroups**

Not applicable.

#### **8.2.8. Specific Safety Studies/Clinical Trials**

Not applicable.

#### **8.2.9. Additional Safety Explorations**

##### **Human Carcinogenicity or Tumor Development**

Not applicable.

##### **Human Reproduction and Pregnancy**

Not applicable.

##### **Pediatrics and Assessment of Effects on Growth**

See above (Section 8.1.2)

##### **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

Not applicable.

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<sup>4</sup> According to 21 CFR 201.323, aluminum content of large volume parenteral (LVP) products used in total parenteral nutrition (TPN) therapy must not exceed 25 micrograms per liter ([micro]g/L).

<sup>5</sup> Per 21 CFR 201.323 (e), "Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 [micro]g/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration."

### **8.2.10. Safety in the Postmarket Setting**

#### **Safety Concerns Identified Through Postmarket Experience**

The Applicant conducted a search using the FAERS Public Dashboard to identify adverse events (AEs) due to cysteine product (search terms: cysteine, cysteine hydrochloride) reported between 1968 and September 30, 2018, in all ages. The search identified 59 cases of AEs, of which 53 were categorized as serious AEs. The most common serious AEs associated with cysteine as the “sole suspect medication” were acidosis (n=12) (Table 3, Page 12, Section 7, Module 2.7.4). The most common AE reported among the remaining 47 cases, was parenteral nutrition-associated liver disease (n=27), but no further specifics were provided for causality assessment. All other case are single occurring AEs distributed in various organ systems.

No new safety signals were identified upon review of the postmarket data for available cysteine products (OSE FAERS search by Jamie Klucken on October 29, 2019).

#### **Expectations on Safety in the Postmarket Setting**

Published clinical practice guidelines reflect and suggest a prescribing pattern using higher than the proposed dose of 15 mg cysteine/g of AA. The most recent L-Cysteine Product Shortage Consideration released by the American Society for Parenteral and Enteral Nutrition identified the commonly accepted dosing of L-cysteine in parenteral nutrition formulations to be 30-40 mg cysteine/g of AA and recommended that this be decreased to 20 mg cysteine/g of AA during the shortage (22). The European Society for Clinical Nutrition and Metabolism Guidelines on Pediatric Parenteral Nutrition recommend a minimum advisable cysteine intake between 30-55 mg/kg/day in infants and young children (19). Of note, the current enteral cysteine requirement by the American Society for Nutritional Sciences is 66-95 mg/kg/day, which corresponds to the minimum and maximum amount found in breast milk protein (25).

Consistent with the published clinical management guidelines, literature review, and other field experts in parenteral nutrition (see Section 9), dosing in clinical practice is highly variable and ranges between 20–40 mg of cysteine/g of AA. Although this represents a significant difference from the proposed labelled dose of 15 mg of cysteine/g of AA (equivalent to 22 mg cysteine hydrochloride/g of AA), it does not significantly impact the assessment of safety for the product, as the available data reviewed during the safety assessment reflect actual use scenarios in which variable and likely higher doses were administered.

### **8.2.11. Integrated Assessment of Safety**

Cysteine supplementation via the intravenous route may be associated with risks of metabolic acidosis and aluminum toxicity, particularly in preterm infants; however, the risks can be monitored and mitigated by adequate labeling and quality control of the product. Previously, FDA has determined that the LD was not withdrawn for reasons of safety or effectiveness (see Section 3.1). Absence of any other major identifiable safety signal within the published

literature and FAERS database gives reasonable reassurance of the overall safety of cysteine hydrochloride. As cysteine is a naturally-occurring AA that can be endogenously synthesized from methionine, the product is anticipated to be well-tolerated. However, the optimal dose for cysteine, both for maximizing efficacy and minimizing safety considerations, has yet to be identified. This limitation is mitigated by the anticipated intended use scenario, in which providers with expertise in administering TPN titrate cysteine over a range of doses, which are prescribed daily within the context of the individual patient's requirements and tolerance, while the patient is actively monitored through both clinical and laboratory assessments.

### **8.3. Statistical Issues**

Not applicable.

### **8.4. Conclusions and Recommendations**

In summary, Nouress has a comparable benefit-risk profile to the LD 7.25% Cysteine Hydrochloride. In addition, approval of a product with quality-controlled impurities (i.e., leachables, extractables), especially aluminum exposure, and detailed dosage and administration instruction offers a significant benefit. The optimal dose of cysteine hydrochloride for both efficacy and safety has yet to be identified due to evolution of both clinical practice and management of parenteral nutrition since the time of original NDA approval of the LD. At this time, there are insufficient data to support modification of the proposed dose recommendation from 15 mg cysteine/g of AA to a higher dose (i.e., 20 mg, 30 mg or 40 mg/g of AA). As stated in the previous relisting memo<sup>6</sup> for the LD, FDA has "recognize[d] that physicians are able to determine the appropriate dosing for these pediatric patients by relying on their clinical expertise, the medical literature and standard guidelines for parenteral nutrition." Despite the uncertainty regarding the dosing, the benefits of the proposed product outweigh the potential risks, and the clinical reviewer recommends approval of Nouress for the proposed indication.

## **9. Advisory Committee Meeting and Other External Consultations**

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This application was not referred to an FDA Advisory Committee as no controversial issues that would benefit from advisory committee discussion were identified. To better understand the current best practices, scientific rationale, and the current clinical use of cysteine hydrochloride, the Division obtained expertise/experience of physicians who have provided care, especially in prescribing parenteral nutrition, to neonatal and pediatric patients.

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<sup>6</sup> Addendum re: Consult Review of Cysteine Citizen's Petition, 12/21/2008, Safety and Efficacy Relisting Petition for Cysteine Hydrochloride (7.25%, injectable). April 20, 2010, NDA19523.

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**Table 9. Summary of Discussions With the Experts**

	<b>Expert<sup>1</sup> October 15, 2018</b>	<b>Expert<sup>2</sup> October 15, 2018</b>	<b>Expert<sup>3</sup> October 29, 2018</b>	<b>Expert<sup>4</sup> November 19, 2018</b>
<b>Patient population / clinical criteria</b>	All neonates <1000g	All premature and term newborns in the NICU	All infants and older pediatric patients receiving infant AA formulation	All premature and term newborns in the NICU
<b>Recommended Cysteine Dose</b>	40 mg/g AA; 20 mg/g AA during shortage	30 mg/g AA	30-40 mg/g AA	40 mg/g AA
<b>Typical Duration of Therapy</b>	2-3 weeks or approximately a month, until patient reaches 1000 g. Max 5 months	2-3 weeks	Several weeks;  Max over 1 year in infants with intestinal failure on long-term PN	2-3 weeks; 7-8 days for “older kids”
<b>Risk of Deficiency and Toxicity</b>	None	None	None	None
<b>Safety Concerns</b>	None	None	None	None
<b>Recommended Monitoring</b>	Routine	Routine	Routine	Routine
<b>Management of Adverse Reactions</b>	N/A	Metabolic Acidosis: -Mild: self-resolve -Moderate: Give bicarbonate -Severe: Reduce or stop cysteine dosing	N/A	Metabolic Acidosis: -add acetate buffer -adjust AA content -maintain the cysteine dose at 40 mg/g of AA
<b>Other notes:</b>		Used to solubilize calcium and phosphate in the TPN admixture		Cysteine addition improves calcium and phosphate solubility

<sup>1</sup> Doctor of Pharmacy, parenteral nutrition expertise..

<sup>2</sup> Neonatologist, Director of Newborn Services.

<sup>3</sup> Chief of pediatric, Gastroenterology, Hepatology, and Nutrition.

<sup>4</sup> Neonatologist.

Abbreviations: AA = amino acid; NICU = neonatal intensive care unit; PN = parenteral nutrition; TPN = total parenteral nutrition

## 10. Pediatrics

Under the Pediatric Research Equity Act (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. This 505(b)(2), NDA 212535 does not trigger PREA, as there is no new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. There is no change in the dosing regimen compared with the recently approved labeling for Elcys (cysteine hydrochloride injection) under NDA 210660. L-Cysteine can be fully labeled in pediatric patients with pediatric dosing and dosing instructions supported by published pediatric literature and clinical practice

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guidelines submitted in a pediatric assessment. Together, DGIEP and the Division of Pediatric and Maternal Health (DPMH) determined that the dosage and dosing regimen in neonates (including preterm and term infants) is consistent with Cysteine HCl labeling for alignment with community best practices.

PREA requirements were not applicable to this 505(b)(2) NDA.

The DPMH consult review by Carolyn L. Yancey, MD, primarily focusing on labeling recommendations, is filed separately under NDA 212535.

## **11. Labeling Recommendations**

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### **11.1. Prescription Drug Labeling**

The proposed prescribing information for Nouress relies on the LD (7.25% Cysteine Hydrochloride; NDA 019523) label, and was updated and modified according to the Physician Labeling Rule.<sup>7</sup>

Highlights of final labeling negotiations with the Applicant include the following:

- The established name of the drug product was made consistent with the USP monograph (i.e., cysteine hydrochloride injection). Because of the existing monograph, the product was allowed an exception to the USP Salt Policy, per the FDA guidance.<sup>8</sup> The resulting Product Title is:  

Nouress (cysteine hydrochloride injection), for intravenous use
- The strength is expressed in terms of cysteine hydrochloride (500 mg/10 mL; 50 mg/mL) with an equivalency statement in the Description section that provides the equivalent dose of cysteine:  

Each mL of NOURESS contains 50 mg of cysteine hydrochloride (equivalent to 34.5 mg of cysteine).
- Per the Dosage and Administration section guidance,<sup>9</sup> the section was revised to include specific administration instructions that are important for safe and effective use of the

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<sup>7</sup> 21 CFR 201.56(b),(c),(d), and 201.57. See final rule (PLR) "Requirements on Content and Format of Labeling For Human Prescription Drug and Biological Products" 71 FR 3922 (January 24, 2006)

<sup>8</sup> <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm379753.pdf>

<sup>9</sup> <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075066.pdf>

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drug and pertinent restrictions on intravenous administration (e.g., administer via (b) (4) line only).

- DGIEP recommended a dosing table under Section 2.5 of the label as used in other AA product labels,<sup>10</sup> for clarity. The table includes the recommended daily dosage in terms of mg and mL of cysteine hydrochloride in relation to protein requirements: 22 mg Nouress/g AA and a corresponding volume of 0.44 mL Nouress/g AA.
  - The dosing table shows the Nouress dose only as the salt form, cysteine hydrochloride, to match the current pharmacy practice and reduce potential for prescription error. It is the FDA’s understanding that a prescription order for “cysteine” is consistently interpreted as an order for the salt (cysteine hydrochloride), and the pharmacies use the cysteine hydrochloride concentration of 50 mg/mL to fill the order.
- Information on the compatibility of the product when admixed with TPN solutions, and the procedure for adding Nouress to the TPN admixture was included.
- Storage conditions were updated based on the available stability data of the product, i.e., any storage must be under refrigerated conditions and no longer than 24 hours. In addition, the solution should be inspected for precipitates formation upon removal of the solution from refrigeration and prior to infusion.
- The Warnings and Precautions section was updated to include pertinent PN AA product class safety information, i.e., pulmonary embolism, vein damage and thrombosis, increased blood urea nitrogen, acid-base imbalance, hepatobiliary toxicity including hyperammonemia, and fluid and electrolyte imbalance.
  - A subsection on aluminum toxicity per CFR 201.323e was included and adapted as described below:
    - “(b) (4)” was replaced with the specific drug product (NOURESS).
    - “(b) (4)” was replaced with “renal impairment” to be consistent with other sections of labeling.
    - “(b) (4)” was replaced by “preterm infants” because the affected patient population may extend beyond the first 28 days of life (as defined by the guidance for industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population). (26)
    - Risk mitigation was added to limit total daily exposure to aluminum in the final prepared PN solution.

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<sup>10</sup> See Prosol: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/020849s024lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020849s024lbl.pdf)

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Please see the approved label for Nouress for final agreed upon labeling.

## **12. Risk Evaluation and Mitigation Strategies (REMS)**

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The benefit-risk profile for Nouress is favorable, and the risks can be mitigated through professional labeling (see Section 11). There are no additional risk management strategies required beyond the recommended labeling. Therefore, the subsequent subsections are not applicable for this review and have been omitted.

## **13. Postmarketing Requirements and Commitment**

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Not applicable.

## **14. Division Director Comments**

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I concur with recommendations of the review team for approval of NDA 212535. This 505(b)(2) NDA relies on FDA's findings of safety and efficacy for NDA 019523, which was approved in 1986, but never marketed, and formally withdrawn from marketing in 2006. Relisting petitions addressed by DGIEP in 2008-10 determined that the LD was not withdrawn due to reasons of safety or effectiveness, and that an ANDA referencing NDA 019523 could be approved with some labeling revision, but without new studies.

The current product differs from NDA 019523 in terms of concentration (5% versus 7.25%) and container-closure (glass vial versus prefilled syringe). OPQ reviewers concluded that the bioavailability information submitted was adequate to establish a biobridge between Nouress and the LD, such that a biowaiver of relative BA studies was granted.

Cysteine is a conditionally essential AA, with preterm and term neonates having reduced ability to synthesize cysteine. Clinical practice guidelines recommend routine cysteine supplementation in neonates; however, commercially available AA formulations do not provide appreciable amounts of cysteine. As with the LD, the indication is characterized as "use as an additive....to meet nutritional requirements," reflecting the evidence that parenterally-administered cysteine products are an effective source of this AA. In addition, by reducing the pH of TPN mixtures, the solubility of calcium and phosphate is increased, enhancing their availability. In the absence of adequate and well-controlled trials evaluating clinical outcomes associated with cysteine supplementation, it is appropriate that the indication does not contain a "treatment" or "prevention" claim.

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The labeled weight-based dosage of cysteine hydrochloride 22 mg/g of AA in preterm and term neonates is consistent with the LD. While this is lower than the dosages recommended by clinical practice guidelines or described in consultations with clinicians conducted through the Network of Experts program, it is also clear that clinicians are experienced in titrating the dosage to the individual patient's needs and tolerability.

No new safety data were submitted in this application, and a search of FAERS did not find any reports of adverse events associated with cysteine hydrochloride products.

There is currently a single FDA-approved cysteine product marketed for all ages, which has alleviated the prior drug shortage. Approval of Nouress provides an additional quality-controlled cysteine product that provides acceptable aluminum exposure for neonates.

## 15. Appendices

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### 15.1. References

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## 15.2. Financial Disclosure

Not applicable.

## 15.3. Nonclinical Pharmacology/Toxicology

### Drug Product Specifications

The proposed acceptance criteria for impurities (drug-related compounds) in the drug product specifications are shown in the table below (modified from the Applicant).

**Table 10. Acceptance Criteria for Impurities in Drug Product**

Test	Tested on Release and/or Stability	Acceptance Criteria	Analytical Procedure Reference
Related compounds <sup>1</sup>	R, S	Specified Impurity (b) (4)	HPLC <sup>2</sup>
		Specified Impurity	
		Specified Impurity RRT (b) (4) NMT (b) (4) % <sup>3</sup>	
		Unspecified impurities: NMT (b) (4) % for each individual unspecified impurity. Report result and RRT for all peaks (b) (4) %	
		Total Unspecified Impurities: NMT (b) (4) %	

<sup>1</sup>Test not in the USP monograph.

<sup>2</sup>

<sup>3</sup>Specified impurity at RRT (b) (4) has been preliminarily identified as (b) (4). This identification is in the process of being confirmed.

Abbreviations: HPLC = High Performance Liquid Chromatography; NMT = not more than; R = release; RRT = relative retention time; S = Stability; DL = detection limit; QL = quantitation limit

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The maximum daily dose of this cysteine HCl product (Table 11) is estimated to be (b) (4) mg, based on the maximum recommended dose of AA (4 g/kg/day) for parenteral nutrition, the maximum recommended dose of L-cysteine free base equivalent (15 mg cysteine/g AAs/day), and an assumed bodyweight of 4.3 kg in term infants (95<sup>th</sup> percentile bodyweight reported by the Center for Disease Control and Prevention<sup>11</sup> for term male infants age 0 months). For the estimated maximum daily dose of (b) (4) mg cysteine HCl, the qualification threshold for all degradation products of the drug substance is 0.2%, per the International Council on Harmonization (ICH) Q3B(R2).

**Table 11. Maximum Daily Dose of Cysteine•HCl•H<sub>2</sub>O for Term Infants Less Than 1 Month of Age**

Recommended protein requirement (g AA/kg/day)	Recommended dosage (mg Cys•HCl•H <sub>2</sub> O/g AA)	Cysteine• HCl•H <sub>2</sub> O Concentration (mg/mL)	Total volume (mL)	Total dose (mg)*	Qualification threshold for drug product*
3-4	22 (15 mg Cys/g AA)	50 (34.5 mg/mL Cys)	(b) (4)	(b) (4)	0.2%

\*For assumed bodyweight of 4.3 kg  
+ICH Q3B(R2)  
Abbreviations: AA = amino acid

Cysteine was reported to be positive in the Ames test in the presence of a metabolic activation system, indicating that a cysteine metabolite(s) is mutagenic (27, 28). Therefore, the recommendations in ICH M7(R1) are not appropriate for the evaluation of the acceptance criteria for cysteine degradants, which may be controlled as ordinary impurities in accordance with ICH Q3B(R2).

(b) (4)

The proposed limit for (b) (4) is NMT (not more than) (b) (4) %, which exceeds the qualification threshold (b) (4) mg/day per ICH Q3B(R2)). At the current specification, the maximum possible total daily intake (TDI) of (b) (4) is (b) (4) (b) (4) ). At the maximum amount observed in the stability batches from long-term storage conditions at 25°C and 60% relative humidity (2%, 18 months), the TDI is (b) (4) is formed through oxidation of cysteine and is reversibly interconverted back to cysteine. (b) (4) comprises approximately (b) (4) % of the sum of (b) (4) cysteine in the plasma (29, 30). However, infants receiving parenteral nutrition supplemented with cysteine HCl (85-99 mg/kg/day) were shown to have lower (b) (4) levels than normal breastfed infants, despite a higher sum total of (b) (4) levels (proportion of (b) (4) was (b) (4) cysteine as compared to (b) (4) % in normal breastfed infants) (31). Similar findings were seen in children age 0-7 years receiving parenteral nutrition (TrophAmine plus cysteine•HCl•H<sub>2</sub>O at 40 mg/g of AA), although this effect was smaller in neonates compared to older pediatric patients (6).

<sup>11</sup> [https://www.cdc.gov/growthcharts/html\\_charts/wtageinf.htm](https://www.cdc.gov/growthcharts/html_charts/wtageinf.htm)

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The toxicity of intravenous cystine has not been well studied, compared to the toxicity of orally administered (b) (4). In one acute toxicity study published in 1925, high doses of (b) (4) 104-415 times the maximum possible human dose based on the proposed limit administered intravenously to juvenile dogs resulted in kidney injury (microscopic findings of necrosis, swelling of tubules, casts) (32). In a 93-day repeat dose oral toxicity study in rats, (b) (4) was administered at doses up to 3000 mg/kg (185 times the maximum proposed human dose).<sup>12</sup> At 3000 mg/kg, 3 animals/sex (out of 10/sex) died prematurely. Histological findings at 3000 mg/kg included fibrosis in the Glisson's sheath periphery in the liver, as well as cell vacuolation and focal eosinophilic necrosis. In the animals that died, congestion in the cortex and medulla of the lungs and kidneys was observed. The NOAEL was (b) (4) mg/kg (37 times the maximum possible human dose based on the proposed limit). Given the totality of the data, a TDI of (b) (4) is not expected to pose any toxicological risks. Therefore, the specification of NMT (b) (4)% is acceptable.

(b) (4)

The proposed limit of NMT (b) (4)%, which allows a maximum TDI of (b) (4) mg, exceeds the qualification threshold (0.2%) established by ICH Q3B(R2). The maximum amount of (b) (4) impurity (b) (4)% observed in the stability batches from long-term storage conditions at 25°C and 60% relative humidity (18 months) is equal to but does not exceed the qualification threshold. Given that (b) (4) are expected from the breakdown of proteins and are usually subject to further (b) (4), they are not expected to pose any toxicological risk. Therefore, the specification of NMT (b) (4)% is acceptable.

**Specified Impurity Relative Retention Time (RRT)** (b) (4)

At the proposed acceptance criterion (NMT (b) (4)%), the TDI of the specified impurity RRT (b) (4) is (b) (4) mg. This is equivalent to the identification threshold and the qualification threshold of (b) (4)% (per ICH), and is therefore acceptable. RRT 0 (b) (4) has been preliminarily identified as (b) (4); however, the identification has not yet been confirmed. It was first observed at the 9-month time point in stability batches from long-term storage conditions (25°C and 60% relative humidity) and is therefore considered to be (b) (4). RRT (b) (4) was also observed in the stability batches ((b) (4)% at 18 months) from long-term storage conditions (25°C and 60% relative humidity), with a resulting TDI of (b) (4) mg. It was also observed at the 6-month time point under accelerated conditions (40°C), at (b) (4)%. Additional stability data indicate that this impurity accumulated to levels ((b) (4)% exceeding its acceptance criterion at the 16-month time point under intermediate storage conditions (30°C). Based on the structure of L-cysteine, it is reasonably assumed that there is a limited

(b) (4)

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range of chemical structures among its degradants, which may not present a safety risk substantially different from L-cysteine or its metabolites. Therefore, the potential for accumulation of (b) (4) RRT (b) (4) to levels up to (b) (4) % (TDI = (b) (4) mg) is not a safety concern from a nonclinical perspective.

### Unspecified Impurities

The proposed limit for the individual unspecified impurities (NMT (b) (4) %) does not exceed the impurity qualification threshold (0.2%) recommended in ICH Q3B(R2). Therefore, from a nonclinical safety perspective, this is acceptable. At the proposed limit for total unspecified impurities (NMT (b) (4) %), the TDI is (b) (4) mg. The stability data for the primary registration batches indicate that the levels of total unspecified impurities were not detected or were below the quantitation limit of (b) (4) %. Therefore, there are no safety concerns for the acceptance criterion of NMT (b) (4) % for total unspecified impurities.

### Extractables Assessment

The Applicant submitted a new extractables study report (522-EXR-B) in response to an Information Request dated 04-18-2019.

### Extracts of the primary container closure system

In report 522-EXR-B, components of the primary container closure system were analyzed for extractables. Stoppers (b) (4) and vials (b) (4) from 3 lots/batches each were analyzed (b) (4). The study design is outlined in the Applicant's table below.

**Table 12. Experimental Design for Extractables Study (522-EXR-B)**

(b) (4)

Non-volatile extractables were measured by Liquid Chromatography/Diode Array Detector/Mass Spectrometry (LC/DAD/MS) and semi-volatile extractables were measured by Gas Chromatography/Mass Spectrometry Direct Injection (GC/MS DI). For the LC/DAD/MS and GC/MS DI analyses of the stopper (weight of 1 stopper = (b) (4) g), the analytical evaluation threshold (AET) was calculated by the Applicant as follows:

(b) (4)

The Applicant's calculated AET for the extraction studies may be considered an underestimation of the AET, since (b) (4) doses/system is more likely to be administered rather than (b) (4) doses/system (for total daily dose) as shown in the calculation. This approach is acceptable since it provides a more conservative safety assessment of extractables, thereby allowing for the reporting of exposures above (b) (4) which is less than the threshold of toxicological concern (TTC) of (b) (4)  $\mu\text{g}/\text{day}$ .

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The LC/DAD/MS and GC/MS DI results indicate that no peaks above the AET of <sup>(b) (4)</sup> µg/g were detected <sup>(b) (4)</sup>.

Extractable elements were measured by Inductively Coupled Plasma / Mass Spectrometry (ICP-MS). The ICP-MS results for the <sup>(b) (4)</sup> parts per billion (ppb) <sup>(b) (4)</sup> extracts of the vial and stopper samples are summarized in the tables below.

**Table 13. Summary of Extractable Elements<sup>1</sup> From the Vial and Stopper Samples**

Component	Element	Max level detected (µg/g)	Component (g/day)	Max amount of element (µg/day)	PDE (µg/day)
Vials					<sup>(b) (4)</sup>
Stoppers					

<sup>1</sup> Elements not intentionally added to TPN as nutrients.  
Abbreviations: PDE = permitted daily exposure

Study report 522-EXR-B did not include headspace analysis for volatile extractables. In the original extractables study report (158-EXR), volatile compounds from the stopper were extracted <sup>(b) (4)</sup>. The extracts were then analyzed by GC/MS. Significant peaks were defined as peaks detected in all preparations of a sample at or above signal to noise ratio of <sup>(b) (4)</sup>, that were not detected in a headspace blank. Estimated concentrations were calculated based on the response of significant peaks compared to the response of an external standard peak. The estimated concentrations did not exceed the AET of <sup>(b) (4)</sup> µg/g (see Table 14 from the Applicant below).

**Table 14. GC/MS Results From the Headspace Analysis of the Stopper (Study Report 158-EXR)**

Ret. Time (min)	Compound (m/z)	Confidence	CAS#	Extracted Amount, µg/g	
				Stopper	
				Prep 1	Prep 2
	<sup>(b) (4)</sup>	Confident			<sup>(b) (4)</sup>
		Confident			

**Leachables Assessment**

The Applicant submitted study report 561-SCR in which stability batches (primary registration and confirmatory/optimized-process batches) for the drug product were evaluated for leachables. The samples analyzed are summarized in the Applicant's table below.

**Table 15. Samples Evaluated for Leachables**

(b) (4) Sample ID	Sample Description	Reference in Report (b) (4)
[Redacted Table Content]		

The analytical methods used for detection of specific leachable types in the drug product include LC/DAD/MS, GC/MS DI, and ICP-MS (for detection of non-volatile, semi-volatile, and elemental leachables, respectively). Target analytes included (b) (4)

[Redacted] These targets were identified in (b) (4) extracts of the stopper from the first extractables study report, 158-EXR. Samples for LC/DAD/MS were extracted with (b) (4) while samples for GC/MS DI were extracted with an equal volume of (b) (4). Samples for ICP-MS were prepared in a solution of (b) (4).

The Agency requested that the Applicant use an AET of (b) (4) µg/mL. Therefore, in the LC/DAD/MS and GC/MS DI analyses, significant peaks were defined as peaks detected in all preparations of a sample above (b) (4) µg/mL. The selected AET allows for analysis of leachable compounds for which dose levels of approximately (b) (4) µg/day or higher are predicted, based on the estimated maximum daily dose volume of (b) (4) (see Table 11). The Applicant also calculated their own AET (b) (4) µg/mL but did not use it to guide the evaluation of leachables. Their calculation is shown below:



The Applicant's calculated AET for the leachables study may be considered an underestimation of the AET, since (b) (4) doses/system is more likely to be administered rather than (b) (4) doses/system (for total daily dose) as shown in the calculation. This approach is acceptable since it provides a more conservative safety assessment of leachables, thereby allowing for the reporting of exposures above (b) (4) system/day, based on administration of (b) (4) doses/system), which is less than the TTC of (b) (4) µg/day.

The results of the LC/DAD/MS analysis indicate that there were no non-volatile leachable compounds detected above (b) (4) µg/mL in packaged sample solutions stored for 7 or 14 months. However, the limit of detection of the targeted analyte (b) (4) that was spiked into the matrix blank was estimated to be (b) (4) µg/mL. At the limit of detection for (b) (4), the potential total daily intake of (b) (4) µg/day is less than the TTC of (b) (4) µg/day (based on a maximum daily dose of (b) (4) mL/day for term neonates).

The results of the GC/MS analysis indicate that there were no semi-volatile leachable compounds detected above (b) (4) µg/mL in packaged sample solutions stored for 7 or 14 months. The percent recovery of the targeted analytes that were spiked into the matrix blank and their limit of detection are summarized in the table below (modified from the Applicant). At the limit of detection adjusted for percent recovery for the targeted analytes, the total daily intake of each analyte (b) (4) µg/day) would be less than the TTC of (b) (4) µg/day (based on a maximum daily dose of (b) (4) /day for term neonates).

**Table 16. GC/MS DI Spike Recovery and Estimated Detection Limit of Targeted Analytes**

Compound	% Recovery	Estimated Detection Limit (µg/mL of drug product)	Estimated Detection Limit Adjusted for Recovery (µg/mL of drug product)
(b) (4)			

Abbreviations: GC/MS DI = Gas Chromatography/Mass Spectrometry Direct Injection

In response to an IR, the Applicant submitted study report 601-SCR for leachables evaluation in additional 3- and 4-month stability batches as detailed in the table below (modified from the

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Applicant). The samples were prepared as previously described above for LC/DAD/MS, GC/MS DI, and ICP-MS analysis. The AET was also the same as previously described ( $(b) (4)$   $\mu\text{g}/\text{mL}$ ). Analysis of volatile leachables was conducted using a GC/MS headspace (HS) method, for which an aliquot of each sample listed in Table 17 and Table 19 was transferred to and sealed in a headspace vial. Significant peaks were defined as peaks detected in all preparations of a sample at or above a signal to noise ratio of  $(b) (4)$ , that were not detected in the corresponding unspiked matrix blanks.

**Table 17. Additional Samples Evaluated for Leachables**

$(b) (4)$ Sample ID	Sample Description	Reference in Report
$(b) (4)$		

Standards for targeted analytes were prepared for the GC/MS HS analysis and for ICP-MS analysis. For GC/MS HS analysis, the targeted analytes were  $(b) (4)$

The results of the LC/DAD/MS analysis indicate that there were no non-volatile leachable compounds detected above  $(b) (4)$   $\mu\text{g}/\text{mL}$  in packaged sample solutions stored for 3 or 4 months. Although the previous leachables study showed that the limit of detection for the targeted spiked analyte  $(b) (4)$  was greater than  $(b) (4)$   $\mu\text{g}/\text{mL}$ , the potential total daily intake would be less than the TTC of  $(b) (4)$   $\mu\text{g}/\text{day}$ .

The results of the GC/MS DI analysis indicate that there were no semi-volatile leachable compounds detected above  $(b) (4)$   $\mu\text{g}/\text{mL}$  in packaged sample solutions stored 3 or 4 months. Although the previous leachables study showed that the limit of detection for some of the targeted spiked analytes were greater than  $(b) (4)$   $\mu\text{g}/\text{mL}$ , the calculated total daily intake of each analyte  $(b) (4)$   $\mu\text{g}/\text{day}$ ) would be less than the TTC of  $(b) (4)$   $\mu\text{g}/\text{day}$ .

The results of the GC/MS HS analysis indicate that there were no volatile leachable compounds detected above a signal to noise ratio of  $(b) (4)$  in packaged sample solutions stored for 3, 4, 7, or 14 months. However, the criterion of  $(b) (4)$  % recovery was not met by two of the three spiked preparations of the targeted analytes, as shown in the Applicant's table below. The criterion of no more than  $(b) (4)$  % relative standard deviation (RSD) was also not met. The results of the spike recovery assay indicate that the method used for the GC/MS HS analysis produced highly variable measurements of the targeted analytes. Given that the measurements were generally

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higher than the actual spiked amount, it is reasonable to assume that if the analytes were present in the samples they would be detected by this method.

**Table 18. GC/MS HS Spike Recovery and % RSD of Spiked Matrix Blank Injections**

Ret. Time (min)	Compound	% Recovery			%RSD
		Spiked Matrix Blank Prep 1	Spiked Matrix Blank Prep 2	Spiked Matrix Blank Prep 3	
(b) (4)					

Abbreviations: RSD = relative standard deviation; GC/MS HS = Gas Chromatography/Mass Spectrometry headspace

### Elemental Impurities

#### **Aluminum**

The Code of Federal Regulations provides labeling requirements for aluminum levels in large and small volume parenterals used in TPN (21 CFR 201.323). The Applicant established the aluminum acceptance criterion at NMT 145 ng/mL (145 µg/L). Safety assessment of the aluminum acceptance criterion was based on the dosing of cysteine in preterm and term infants. The maximum dose is 60 mg cysteine/kg/day in preterm and term infants, calculated based on 4 g/kg/day AAs and 15 mg cysteine/g AAs, as recommended (22 mg cysteine•HCl•H<sub>2</sub>O)/g AAs as stated in label). The dose volume needed to deliver this dose is (b) (4) mL/kg cysteine hydrochloride injection (see Table 11). At the maximum cysteine dose in preterm and term infants, the aluminum limit of 145 µg/L will allow a maximum dose of 0.26 µg/kg/day. This amount is a small fraction of the maximum dose range (4 to 5 µg/kg/day) identified as the safe limit for aluminum intake from total parenteral nutrition (21 CFR 201.323). Therefore, the proposed aluminum acceptance criterion is acceptable. The levels of aluminum from three registration batches and two confirmatory batches of the drug product (lots C1800029, C1800030, C1800031, C1800172, and C1800229, respectively) were measured. The levels were (b) (4) in the registration batches and (b) (4) in the confirmatory batches. The levels of aluminum were also measured in stability studies (up to 12 months) of the same batches of drug product and all measurements were within specification.

#### **Screen of elemental impurities in packaged drug product**

In report 522-EXR-A, extracts of drug product samples were analyzed by ICP-MS for elemental impurities. The samples analyzed in 522-EXR-A were from three registration batches and two confirmatory batches of the drug product (lots C1800029, C1800030, C1800031, C1800172, and C1800229, respectively). The sample extracts were prepared by adding (b) (4)

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to a final solution of (b) (4) to a final concentration of (b) (4)%. The limits of quantitation (LOQs) for the elements evaluated ranged from (b) (4). The reporting threshold concentrations for individual elements were 10 times the specific LOQ for each element.

The safety assessment of elemental impurities included the evaluation of: 1) elements not intentionally added in TPN as nutritional supplements and 2) elements that may be intentionally added in TPN as nutritional supplements (b) (4)

For elemental impurities in the first category, safety assessment of each element was based on compliance of the maximum daily dose with the PDE (Permitted Daily Exposure), as provided in ICH Guidance Q3D. For elements that may be intentionally added in TPN as nutritional supplements, the maximum daily dose of each elemental impurity was compared to the dose of element routinely used in TPN for preterm and term neonates.

Levels of (b) (4) were detected above their reporting threshold (10 times their specific LOQ) in one duplicate of one lot. Based on a dose of (b) (4) mL/kg/day of cysteine HCl and an assumed weight of 4.3 kg for a term infant (see Table 11 above), the levels of (b) (4) would be equivalent to approximately (b) (4) µg/day, respectively. Levels of (b) (4) were detected above their reporting threshold in both duplicates from all lots. The maximum levels of (b) (4) detected would be equivalent to approximately (b) (4) µg/day, respectively. The maximum levels of the elemental impurities in the drug product are summarized in the table below. (b) (4) were also detected in the leachables study. Levels of all other elements were below their respective LOQs. At the highest LOQ, the level of elemental impurity would be (b) (4) µg/day, which is far below the parenteral PDE for all elements included in ICH Q3D.

**Table 19. Elements<sup>1</sup> Detected in the Packaged Drug Product**

Component	Element	Max level detected (µg/mL)	Max amount of element (µg/day)	Max dose of element (µg/kg/day)	PDE (µg/day)
Drug Product	(b) (4)	(b) (4)	(b) (4)	(b) (4)	10
					20
					5

<sup>1</sup> Elements not intentionally added to TPN as nutrients.

Abbreviations: PDE = permitted daily exposure; TPN = total parenteral nutrition

**Screen of elemental impurities in packaged drug product stored at different times, temperatures, and/or positions (upright or inverted)**

In study report 601-SCR, several lots of the drug product stored at different times, temperatures, and/or positions (upright or inverted), were analyzed by ICP-MS for potential elemental impurities. (b) (4) were detected in the drug product batches stored for 7 and 14 months, while (b) (4) were detected in the drug batches stored for 3 and 4 months, as shown in the table below (see Table 15 and Table 17 for the list of batches). (b) (4) was also detected in the preparation blank control, suggesting that this element is not a true

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impurity. (b) (4) were also detected in the matrix blank, suggesting that these elements are present in the drug product prior to being stored. (b) (4) was observed in one preparation of the 4-month 25°C/Inverted Batch C1900094 sample, but not in the duplicate preparation of the same sample, the 4-month 40°C/Inverted Batch C1900094 sample, or the 3-month samples. As shown in the table below, assuming the worst-case scenario, the maximum dose of each element (calculated based on a maximum volume of (b) (4) mL/day; see Table 11) is markedly lower than the PDE (as per ICH Q3D). Levels of all other elements were below their respective LOQs. At the highest LOQ, the amount of elemental impurity would be (b) (4) µg/day, which is far below the parenteral PDE for any element included in ICH Q3D. Therefore, there is no safety concern for the potential exposure to these elements from administration of the drug product.

**Table 20. Summary of Elemental Impurities<sup>1</sup> Detected in Drug Product Stored at Different Times, Temperatures, and/or Positions (Upright or Inverted)**

Batch	Element	Prep blank (ng/mL)	Max level in matrix blank (ng/mL)	Max level detected (ng/mL)	Total volume (mL/day)	Max amount of element (µg/day)	PDE (µg/day)
7 months	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	10
							20
14 months	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	5
							10
3 months	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	20
							5
4 months	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	90
							20
							5
							90
							10

<sup>1</sup> Elements not intentionally added to TPN as nutrients.  
Abbreviations: PDE = permitted daily exposure; LOQ = limits of quantitation

For elemental impurities that may be intentionally added in TPN as nutritional supplements (with the exception of (b) (4)), safety assessment was performed by comparing the maximum daily dose of each elemental impurity to the dose of element routinely used in TPN for preterm and term neonates. The dose comparison was based on µg/kg/day, which is the dosing unit routinely used for neonates and infants. Calculations for this analysis were based on the maximum recommended dose of L-cysteine (15 mg/g AAs) administered in 4 g/kg/day AAs in preterm and term infants less than 1 month of age. This dosing regimen requires administration of (b) (4) mL/kg/day of drug product.

The Applicant's analysis of (b) (4) in cysteine hydrochloride injection assures that each of these elements are present only at very low levels, such that the maximum potential exposure levels will only be a fraction of the dose levels routinely used in TPN for neonates and infants (i.e., (b) (4) % of dose levels for individual elements).

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For the ICP-MS spike recovery assay, the targeted analytes were (b) (4). With %recovery ranging from (b) (4)%, the criterion of (b) (4)% recovery was met by all three spike preparations of the targeted analytes. With the %RSD ranging from (b) (4)%, the criterion of no more than (b) (4)% RSD was also met. Therefore, the results of the spike recovery assay indicate that the method used for the ICP-MS analysis was appropriate for the targeted analytes.

(b) (4)

There is no available information on the (b) (4) dose level routinely used in TPN. However, the potential exposure to (b) (4) as an impurity in TPN warrants special consideration for neonates/infants age 0-6 months, given that (b) (4) supplementation is not recommended for this age group due to safety concerns related to skeletal development. (b) (4) levels were measured in the cysteine hydrochloride drug product (5 lots) using a (b) (4). In samples from the stability/leachables study, the highest concentration of (b) (4) detected was (b) (4) (ng/mL), which would result in a maximum dose of (b) (4) µg/kg/day in preterm and term infants less than 1 month of age. This extremely low dose is approximately (b) (4)% of the estimated (b) (4) intake in breastfed neonates/infants (based on the consumption of 200 mL/kg/day of breastmilk with a (b) (4) concentration of (b) (4) mg/L). Therefore, the detected levels of (b) (4) in cysteine hydrochloride injection do not present a safety concern for neonates or infants age 0-6 months.

**Table 21. Levels of (b) (4) From Five Lots of Drug Product**

Lot #	Max level detected (ppb)	Max amount of element (µg/day)	Max dose of (b) (4) (µg/kg/day)	% of average dose of (b) (4) in breastmilk* (1.2 µg/kg/day)
C1800029	(b) (4)	(b) (4)	(b) (4)	(b) (4)
C1800172	(b) (4)	(b) (4)	(b) (4)	(b) (4)
C1800031	(b) (4)	(b) (4)	(b) (4)	(b) (4)
C1800030	(b) (4)	(b) (4)	(b) (4)	(b) (4)
C1800229	(b) (4)	(b) (4)	(b) (4)	(b) (4)

\*Based on the consumption of 200 mL/kg/day of breastmilk with a (b) (4) concentration of (b) (4) mg/L (b) (4)

Abbreviation: ppb = parts per billion

The results of the spike recovery assay from the method validation report indicate that % recovery and % RSD at (b) (4) met the acceptance criteria. Therefore, the method for measurement of (b) (4) levels is acceptable.

In summary, based on the worst-case exposure as calculated from the maximum detected level of each elemental impurity or leachable, there are no safety concerns from a nonclinical viewpoint. The low concentrations of leachables and elemental impurities do not warrant the addition of acceptance criteria in the drug product specifications.

**15.4. OCP Appendices (Technical documents supporting OCP recommendations)**

N/A

**15.5. Additional Clinical Outcome Assessment Analyses**

N/A

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Clinical Team Leader	Suna Seo	OND/ODEIII/DGIEP	Section Authored: 1, 2, 3, 7, 8,9, 10, 11, 12, 13, 15 Reviewed/Edited/Cleared: ALL	Select up to two: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Cleared
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Clinical Reviewer	Yao-Yao Zhu	OND/ODEIII/DGIEP	Sections Authored: 1, 2, 3, 7, 8,9, 10, 11, 12, 13, 15 Reviewed/Edited/Cleared: ALL	Select up to two: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Cleared
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