CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210660Orig1s000

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

Application Type	NDA
Application Number(s)	210660
Priority or Standard	Priority
Submit Date(s)	5/22/2017 (Rolling Review)
Received Date(s)	7/27/2018
PDUFA Goal Date	4/27/2019 (3-month clock extension)
Division/Office	DGIEP
Review Completion Date	4/15/19
Established/Proper Name	L-cysteine hydrochloride
(Proposed) Trade Name	ELCYS
Pharmacologic Class	Small Volume Parenteral
Code name	
Applicant	Exela Pharma Sciences, LLC.
Dosage form	Injection
Applicant proposed Dosing Regimen	50 mg/ml
Applicant Proposed Indication(s)/Population(s)	Use as an additive to amino acids (AA) solutions to meet the nutritional requirements of newborns requiring total parental nutrition (TPN) and of adults and pediatric patients with severe liver disease who have impaired enzymatic processes and require TPN
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Use as an additive to amino acids (AA) solutions to meet the nutritional requirements of newborns requiring total parental nutrition (TPN) and of adults and pediatric patients with severe liver disease who have impaired enzymatic processes and require TPN
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	
Recommended Dosing Regimen	50 mg/ml

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
SRPM= Safety Regulatory Project Manager
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DPV=Division of Pharmacovigilance
DPMH-Division of Pediatric and Maternal Health
RPM-Regulatory Project Manager
ATL: Application Technical Lead
DP: Drug Product
DS: Drug Substance
OGD: Office of Generic Drugs
DSS: Drug Shortage Staff

Glossary

AA	amino acid
AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AET	analytical evaluation threshold
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDC	Center for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
cys	cysteine
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
DMF	drug master file
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat

MCP	methylcyclopentane
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NMT	not more than
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PDE	permitted daily exposure
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
RH	relative humidity
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TPN	total parenteral nutrition
TTC	threshold for toxicological concern
USP	United States Phamacopeia

1 Executive Summary

1.1. Product Introduction

Cysteine hydrochloride is a sulfur-containing amino acid (AA) supplement administered through parenteral nutrition. Currently, although there are no FDA-approved products on the market in the US, cysteine hydrochloride injection, USP is routinely used as an additive to amino acid injections in individuals requiring total parenteral nutrition (TPN), through the use of marketed unapproved products.

The Applicant's proposed indication at the time of NDA submission and the recommended indication is use as an additive to amino acid solutions 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. It can also be added to amino acid solutions to provide a more complete profile of amino acids for protein synthesis.

The recommended dose for cysteine is 15 mg cysteine/gram AA for pediatric patients from preterm infants to 11 years of age, inclusive, 5 mg cysteine/gram AA for patients 12 -17 years of age inclusive, and 5 mg cysteine/gram AA for adults.

1.2. Conclusions on the Substantial Evidence of Effectiveness

As a 505(b)2 application, the efficacy of Elcys 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 [redacted] (b) (4) " is inadequate to support a complete assessment of Elcys' 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., "amino acids are building blocks of protein synthesis," "supply of amino acids promotes growth," and "parenteral nutrition that provides a full profile of AA 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 Elcys for the recommended indication as source of cysteine.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The proposed product is relying upon the Agency's findings of safety and efficacy for 7.25% Cysteine Hydrochloride, initially approved in 1986. Of note, although the listed drug has been withdrawn, it was determined not to have been withdrawn from the market 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 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 in growth in neonates was reported with the administration of parenteral cysteine products. In clinical practice, addition of cysteine to 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 post-market data of the currently available marketed unapproved formulations. Absence of any 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 amino acid that can be endogenously synthesized from methionine, the product is anticipated to be well-tolerated. In general, risks of Elcys appear consistent with the known risks of other amino acid 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 listed drug and the current clinical practice guidelines; however, there are insufficient data to warrant a modification to the proposed dose recommendation of 15 mg cysteine/gram of amino acid to an alternate higher dose (i.e., 20 mg, 30 mg or 40 mg/g) at this time.

Elcys is a candidate product with a potentially positive impact on the current cysteine drug shortage. Based on the comparability of the proposed product to the listed drug, scientific understanding of protein and amino acid metabolism, which supports the conditional essentiality

of cysteine, and given the lack of approved cysteine products in the current US market, the benefits of the proposed product outweigh the risks. Approval of Elcys for the proposed indication is recommended.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Cysteine is used *in vivo* as a building block in the biosynthesis 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. • In adults, cysteine is synthesized *de novo* 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. • Cysteine reduces the pH of TPN mixtures and increases the solubility of calcium and phosphate, thereby decreasing precipitation and enhancing availability. • Published clinical practice guidelines by both American and European parenteral nutrition societies recommend routine cysteine supplementation for neonates.	• There is an unmet need for an intravenous source of cysteine for TPN-dependent patients in whom cysteine is a conditionally essential amino acid, such as preterm and term infants and/or patients with impaired liver function.
Current Treatment Options	• Commercially available amino acid formulations do not contain an appreciable amount of cysteine hydrochloride. In premixed solutions of crystalline amino acids, cysteine is relatively unstable over time, eventually converting to insoluble cystine. To limit precipitation and provide usable cysteine, doses of cysteine	• Since the withdrawal of the listed drug product, there is an unmet need for an approved intravenous cysteine product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	hydrochloride products are commonly admixed into parenteral nutrition on the day of administration. • Currently, since the withdrawal of Hospira's 7.25% Cysteine Hydrochloride injection effective June 16, 2006 (NDA 19523), there are no approved intravenous L-cysteine hydrochloride formulations on the market. Multiple unapproved and compounded products are currently being used in clinical practice. • There has been a reported drug shortage of L-cysteine since January 9, 2015.	
Benefit	• Plasma cysteine concentrations have been shown to increase with cysteine supplementation. • Plasma taurine concentrations have been shown to increase or normalize after cysteine supplementation in studies of older pediatric patients. • 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. • Clinical uses of cysteine supplementation in TPN also include acidification of the admixture to improve calcium and phosphate solubility.	• Parenterally administered cysteine products are effective sources of this conditionally essential amino acid, evidenced by the increased plasma cysteine and taurine concentration following cysteine supplementation. • 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.
Risk and Risk Management	• No new safety data were submitted using the proposed drug product. • No new safety signals were identified upon review of the post-market data with comparable marketed unapproved formulations of cysteine. • The major known safety concerns with Elcys are vein damage and thrombosis, increased blood urea nitrogen (BUN), acid-base imbalance (e.g., metabolic acidosis), hepatobiliary disorders,	• The overall safety profile of Elcys as a source of intravenous cysteine is acceptable. • In general, risks of Elcys appear consistent with the known risks of amino acid solutions, albeit certain potentially serious

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	hyperammonemia, and aluminum toxicity. • Elcys 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. • Typical prescribers, i.e., neonatologists, intensivists, etc., are well versed in the identification and management of the toxicities associated with parenteral nutrition administration.	risks may be potentiated, including metabolic acidosis. • In clinical practice, Elcys 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) is not needed to ensure the benefits of Elcys outweigh its risks.

1.4. Patient Experience Data

Patient experience data that was not submitted in the application, but were considered in this review:

- On April 30, 2008, Regulus Pharmaceutical Consulting, Inc., submitted a citizen's petition (Docket No. FDA-2008-P-0278) to request FDA determine whether the LD's withdrawal from sale was secondary to efficacy and safety concerns (see Section 3.1).

2 Therapeutic Context

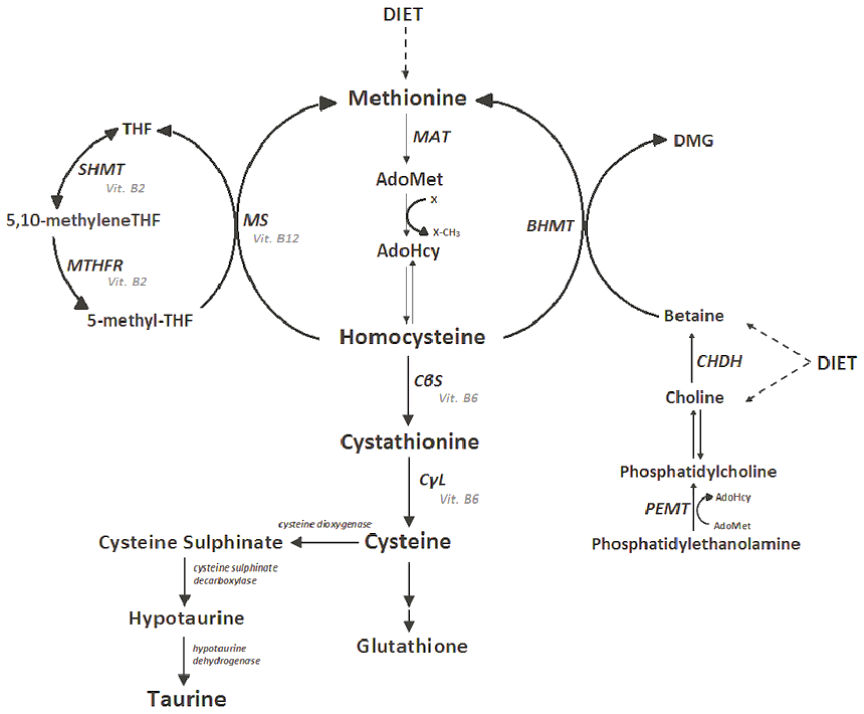
2.1. Analysis of Condition

The prevailing rationale for the addition of cysteine to standard parenteral nutrition formulations is two-fold. First, cysteine is a conditionally essential amino acid, as it is produced in 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). This pathway is also impaired in older children and adults with liver insufficiency (5, 6).

Figure 1. Metabolism of Sulfur Amino Acids



Enzymes are shown in italics, and their cofactors are shown in gray.
MAT, methionine adenosyltransferase; AdoMet, S-adenosylmethionine; AdoHcy, S-adenosylhomocysteine; X, methyl acceptor; CβS, cystathionine β-synthase; CγL, 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

2.2. Analysis of Current Treatment Options

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

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	Histadine	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	
Plenamine 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 3/18/2019. Facts & Comparisons®
http://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/fc_dfc/5548357

Currently, since the withdrawal of Hospira's 7.25% Cysteine Hydrochloride injection effective June 16, 2006 (NDA 19523), there are no approved intravenous L-cysteine hydrochloride

formulations on the market. There are multiple unapproved and compounded products manufactured and distributed by companies including the Applicant. Despite this, there has been a reported drug shortage of L-cysteine since January 9, 2015,[1] and temporary importation of Canadian product by Sandoz, Inc., has been authorized since July 2016 to alleviate the continued US shortage of Cysteine Hydrochloride (see Section 3.1).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

NDA 210660 is a 505(b)2 application for cysteine hydrochloride, which 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 CFR 314.161, on December 19, 2008 and followed by two subsequent addenda, FDA determined that 7.25% Cysteine Hydrochloride Injection, USP was not withdrawn for reasons of safety or effectiveness. The Safety and Efficacy Relisting Petition memoranda are summarized as below:

<u>December 19, 2008</u>

- 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 PLR formatted label.

<u>June 22, 2009</u>

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

[1] source: https://www.accessdata.fda.gov/scripts/drugshortages/

- This amendment erroneously[2] 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

- In a response to clarify the recommended safety and pediatric dosing studies, 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 amino acid 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 (NDC 66758-004-01).

The initial drug shortage was reported on January 9, 2015 (NDA 66758-004-02). On March 1, 2016, temporary importation of Canadian product (NDC 0781-8940-70) was authorized to

[2] The referenced 2004 label was associated with a different cysteine hydrochloride product, and this error was corrected in the April 20, 2010 memo.

alleviate the continued US shortage of Cysteine Hydrochloride.[3] To date, cysteine hydrochloride remains on the FDA drug shortage list.

3.2. Summary of Presubmission/Submission Regulatory Activity

Two pre-IND meetings were held with the Division under IND 128489 and are listed below by date. Points of discussion or Division recommendations are provided as a bulleted list for each meeting.

December 23, 2015:

- Clarified the proposed regulatory pathway as 505(b)2
- Discussed the appropriateness of cysteine hydrochloride product by Hospira (NDA 019523) as the LD
- Clarified the bio-waiver request and recommended the Applicant submit the justification for the request
- Recommended 9 months of long-term and 6 months of accelerated stability be submitted at the time of NDA submission with additional stability data during the NDA review process
- Clarified that the "expedited review" in consideration of the product shortage status would be determined at the time of NDA filing

September 8, 2016:

- Discussed the stability data requirement for NDA submission; FDA agreed to the Applicant's proposal to submit 6 month accelerated and long-term stability data at the time of NDA submission, with plans for additional stability data submissions during the NDA review cycle
- Clarified the requirements for "expedited review"

On May 23, 2017, the Applicant initiated the submission of the current NDA. Due to significant nonclinical/quality deficiencies noted regarding aluminum specification and product impurities requiring substantial changes in the container-closure system, the Applicant was advised to submit a fast track designation and rolling review request.

On June 21, 2017, the NDA was granted fast track designation; and subsequently, under rolling review status, the Applicant completed the submission of the NDA on July 27, 2018.

Due to ongoing cysteine drug shortages, NDA 210660 was granted priority review designation.

[3] https://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM511888.pdf

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

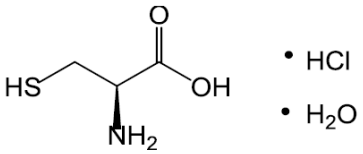
4.1. Office of Scientific Investigations (OSI)

This section is not applicable.

4.2. Product Quality

4.2.1. Drug Substance

Elcys (cysteine hydrochloride injection), 500 mg/10 mL (50 mg/mL) contains the hydrochloride salt of a natural amino acid, cysteine. Cysteine hydrochloride is a compendial active pharmaceutical ingredient with a published USP monograph. Cysteine hydrochloride drug substance for this NDA is manufactured by (b) (4). in accordance to current Good Manufacturing Practices (cGMP). This active ingredient is also referred to as L-cysteine hydrochloride and is produced as a monohydrate crystal form. It is white crystals freely soluble in water with a relative density of 1.50 (20°C). It has a molecular weight of 175.3 g/mol, a molecular formula of $C_3H_7NO_2S.HCl.H_2O.$, and the molecular structure below:



Cysteine Hydrochloride Monohydrate

Cysteine hydrochloride manufactured by (b) (4) is tested and released according to a drug substance specification that includes testing and acceptance criteria for all physical and chemical attributes essential for the determination of identity, strength, purity, and quality of the drug substance at release and throughout its proposed retest date. Information regarding the manufacture of cysteine hydrochloride drug substance is provided in Drug Master File (DMF) (b) (4). This DMF has been reviewed and found to be adequate to support this new drug application.

4.2.2. Drug Product

Elcys (cysteine hydrochloride injection) is a clear, colorless, sterile, nonpyrogenic solution containing 500 mg cysteine hydrochloride, equivalent to 345 mg of cysteine, in 10 mL (34.5 mg/mL cysteine). Cysteine Hydrochloride Injection, 7.25% (72.5 mg/mL) was originally manufactured by Hospira and was approved for the US market on October 22, 1986 (NDA 19523). Although Hospira discontinued marketing of this drug product, Hospira's drug product has been used as the LD in this application. Cysteine hydrochloride injection is a compendial drug product with a published USP monograph.

The composition of Elcys is simple and contains L-cysteine hydrochloride as the active ingredient and Water for Injection with pH (1.0-2.5) adjusted by either hydrochloric acid and/or sodium hydroxide as needed. The manufacturing process for cysteine hydrochloride injection in this application (b) (4)

Elcys is a small volume parenteral (SVP) and is intended for use as a component of TPN, a large volume parenteral for intravenous infusion for the treatment of pre-term neonates, pediatric, and adult patients requiring parenteral nutrition. The prescribed amount of cysteine hydrochloride is added to TPN admixtures containing other nutritional components such as amino acids, dextrose, and other SVP additives (trace elements and electrolytes) per the Prescribing Information, which are combined together to supply appropriate amounts of calories to patients through intravenous infusion. Elcys is not to be administered alone.

Elcys is packaged in a 10-mL (b) (4) single-dose glass vial supplied from (b) (4) closed with (b) (4) 20 mm Gray (b) (4) stopper supplied from (b) (4) as the primary container closure, capped with 20 mm white, matte finish, flip-off button, (b) (4), which is also supplied from (b) (4). The use of the proposed primary container closure system is supported by extractables/leachables and stability studies. The drug product vials are packaged in cartons, each containing 10 vials. This drug product is manufactured in accordance cGMP. The specification for Elcys complies to the USP monograph for cysteine hydrochloride injection and includes testing and acceptance criteria for the assurance of the identity, strength, purity, and quality of the drug product at release and throughout the shelf-life of 24 months. Since Elcys will be used as a component of TPN, the aluminum content of the drug product is controlled to 120 µg/L (equivalent to 0.0035 µg of aluminum per mg of cysteine) by the drug product specification per recommendation by the Pharm/Tox review team to ensure that infants and pediatric patient exposure to aluminum from the final TPN admixture remains at or below 5 mcg/kg/day per 21 CFR 201.323(e).

There are some differences between the current drug product and the referenced drug product. The strength of the current product is 50 mg/mL, while the strength of the LD product was 72.5 mg/mL. The pH of the formulation of the current product is adjusted by hydrochloric acid and/or sodium hydroxide. This drug product is packaged in glass vials, while the LD product was packaged in prefilled syringes. These differences were reviewed, and it was concluded that the supporting bioavailability information provided in the application has adequately established the biobridge between this drug product and the LD product and no additional BE studies are needed. Therefore, biowaiver was granted to this application.

4.2.3. Summary and Recommendation

- The applicant of this 505(b)(2) new drug application has provided sufficient CMC information to assure the identity, purity, strength, and quality of the drug substance and drug product.
- All labels/labeling issues have been resolved.
- The Office of Process and Facility has made an overall "Acceptable" recommendation regarding the facilities involved in this NDA.
- The claim for categorical exclusion of the environmental assessment is granted.

Therefore, from the OPQ perspective, this NDA is recommended for approval with the drug product expiration dating period of 24 months.

4.3. Clinical Microbiology

The drug product is (b) (4). The validation of (b) (4) of related components were reviewed, with the following conclusions:

- The Applicant has provided clear descriptions of all container-closure components and demonstrated that the proposed container-closure configurations form an effective sterile barrier.
- The manufacturing and sterilization processes and process controls were sufficiently described for the reviewer to assess the termina (b) (4)
- Sterilization validation/requalification studies and results were consistent with those delineated in the FDA Guidance for Industry.
- The drug product specification (sterility and bacterial endotoxins testing) and validations comply with USP <1> Injections, <71> Sterility Test, and <85> Bacterial Endotoxins Test, as well as FDA Guidance for Industry: *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*.
- The Applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life. In addition, the stability data submitted to date support the microbiological quality of the subject drug product.

4.4. Devices and Companion Diagnostic Issues

This section is not applicable.

4.5. Biopharmaceutics

Consistence 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

5.1. Executive Summary

The Applicant has not conducted new studies to assess the safety of Elcys (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 the reference drug, 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).

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

6.1. Executive Summary

As indicated in Section 3.1 of this review, the sponsor relies on the Agency's findings of safety and effectiveness for Hospira's 7.25% Cysteine Hydrochloride, the Listed Drug (LD). The sponsor did not conduct any clinical studies using the proposed product. Thus, no clinical pharmacokinetics and 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.

6.2. General Dosing and Therapeutic Individualization

The recommended dosing regimens for adults and infants are as follow:

Table 2. Recommended Dosing Regimens for Cysteine and ELCYS (Cycsteine Hydrochloride)

Age	Protein[a] Requirement (g AA/kg/day)	Cysteine Dosage (mg Cys/ g AA)	Cysteine Dosage (mg Cys /kg/day)	ELCYS Dosage		
				mg Cys HCl /g AA	mL ELCYS[c]/ g AA	mL/kg/day
Preterm and term infants less than 1 month of age	3 to 4	15	45 to 60	22	0.44	1.34-1.76
Patients 1 month to less than 1 year of age	2 to 3	15	30 to 45	22	0.44	0.88-1.34
Patients 1 year to 11 years of age	1 to 2	15	15 to 30	22	0.44	0.44-0.88
Patients 12 years to 17 years of age	0.8 to 1.5	5	4 to 7.5	7	0.14	0.112-0.21
Adults: Stable Patients	0.8 to 1	5	4 to 5	7	0.14	0.112-0.14
Adults: Critically Ill Patients[b]	1.5 to 2	5	7.5 to 10	7	0.14	0.21-0.28

AA = Amino Acid
Cys=cysteine
[a] Protein is provided as amino acids. When infused intravenously, amino acids are metabolized and utilized as the building blocks of protein.
[b] Includes patients requiring more than 2 to 3 days in the intensive care unit with organ failure, sepsis or postoperative major surgery.
Source: Prescription Drug Labeling Section 2.5 and Information Request received March 20, 2019 (NDA210660)
[c] 50 mg cysteine HCl/mL Elcys

Refer to Section 11.1 for the basis of these dosing recommendations.

6.3. Summary of Clininical Pharmacology Assessment

The sponsor submitted published articles evaluating blood concentrations of cysteine as well as information on biomarkers (taurine and glutathione) following administration of cysteine in neonates, infants, and pediatric patients. Given the 1) different dosing regimens of both cysteine and background macronutrients (i.e., dextrose and amino acids) 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 exploratory to support the efficacy but cannot be included in the product label. The more detailed review of these data is provided in Section 8.1.2 Published Literature.

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.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

No formal clinical trials were conducted by the Applicant in support of NDA 210660.

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[4] 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 the conditionally-essential amino acid

[4] NDA 210660 Information Requests sent June 23, 2017 and December 1, 2017

to prevent the development of cysteine deficiency in at-risk patients, such as premature infants and those patients with severe liver disease requiring TPN. Considering the known and well-established biochemistry of amino acids, 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 amino acid 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 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 September 26, 2018. The OSE review was reported to DARRTS on July 24, 2017 and updated on October 1, 2018, 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

8.1. Review of Evidence Used to Support Efficacy

8.1.1. Listed Drug

The proposed product is relying 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 18792) in 1984. Prior to approval, no clinical studies were performed with 7.25% Cysteine Hydrochloride Injection, USP. However, clinical studies were done with NeoPham 6.4% Amino Acids Injection, which contained 100 mg/100 mL of cysteine (Section 2.e.iii., dated 5/7/1982 of NDA 18-792). NeoPham 6.4% was withdrawn from the market at the same time as 7.25% Cysteine Hydrochloride. Of note, the listed drug 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, 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 of cysteine supplementation. Available published clinical trials were conducted under widely varying conditions, and datasets and case report forms (CRFs) from these trials are not available for further review.

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

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

Plasma Cysteine Concentrations

There is evidence to indicate that plasma cysteine concentrations increase with cysteine supplementation (Table 3). Different dosing regimens of both cysteine and background macronutrient (i.e., dextrose and amino acids) parenteral nutrition were evaluated in preterm neonates across several trials. In all of the studies in Table 3, cysteine supplementation consistently increased the free cysteine plasma concentrations, even at doses significantly lower than the proposed dose (i.e., 3 mg cysteine/g AA vs. 15 mg cysteine/g AA); however, the data failed to establish a direct relationship between cysteine dose and the plasma

concentrations, i.e., increased doses do not necessarily correlate directly with increased plasma concentrations. These studies were limited by small sample sizes and the presence of multiple confounders.

Regardless of the dose, the increase in plasma cysteine concentrations following cysteine supplementation provides evidence that parenterally administered cysteine products are effective sources of the conditionally essential AAs (7). Plasma AAs, although they represent approximately 4% of the total free AA pool, are in dynamic equilibrium within metabolically active cells (8). Stable plasma concentrations of essential AAs and molar ratios with other essential AAs is important for promotion of normal growth.

Table 3. Summary of Studies that Evaluated Cysteine Plasma Concentrations

Outcome: Cysteine plasma concentrations					
Reference	Design	Population	Dose(s)	Outcomes	Comments
Storm et al. 2003* [19]	RCT, double blind 18 infants	Gestational age (wk): 30-37 Postnatal age (wk): < 4	All initially received PN with no cysteine supplementation for 3 days followed by PN with 0, 10, 20, or 40 mg cysteine-HCl/g AA for the next 3 days Target PN dosage was 2.5 g of AA/kg/d with a caloric goal of 125 kcal/kg/d	Plasma Cysteine concentrations increased with Cysteine-HCl dose Plasma cysteine concentration was 38.9±3.71 (mean±SEM), 45.8±4.89, 46.7±3.31, and 54.3±7.90 in infants receiving no Cysteine supplementation, 10 mg/g AA, 20 mg/g AA, and 40 mg/g AA supplements of cysteine	Based on abstract. No experimental details were available. Although the mean cysteine levels appear to increase with cysteine dose the differences in cysteine levels between the various cysteine treatment groups do not seem to be statistically significant.
Malloy et al. 1984* [20]	RCT, unblinded 20 infants	Group 1 Birthweight: 1.46 kg (900-2300 g) Age (days): 4 (3-5) Group 2 Birthweight: 1.37 kg (910-2500 g) Age (days): 7 (4-11) Group 3 Birthweight: 1.25 kg (970-1510 g) Age (days): 20 (3-53) Group 4: Birthweight: 1.01 kg (890-1150 g) Age (days): 5 (4-5)	Treatment duration: 6 days Group 1 240 mg/kg/day of nitrogen (Aminosyn) Group 2 240 mg/kg/day of nitrogen (Aminosyn) plus 72 mg/kg/day cysteine-HCl Group 3 400 mg/kg/day of nitrogen (Aminosyn) Group 4 400 mg/kg/day of nitrogen (Aminosyn) plus 72 mg/kg/day cysteine-HCl All groups received TPN and 150 ml/kg/day of fluid and 60 kcal/kg/day of glucose	Cysteine supplementation had a significant effect on free cysteine plasma concentration (Group 1 vs Group 2: 4.46±1.13 vs 11.34±3.38; Group 3 vs Group 4: 4.20±1.34 vs 14.48±3.83 µmol/dL)	No IV fat emulsions used during the study because most infants were still in the acute phase of respiratory disease and on ventilators 72 mg/kg/d of cysteine in this study is roughly equivalent to 300 mg cysteine per gram of Amino Acids or 180 mg per gram of Amino Acids The dose of total amino acids appears to be much lower than the generally recommended dose of 2.5 g/kg/day. It is possible that the significant difference plasma cysteine concentrations between treatment groups and placebo is due to inefficient protein synthesis due to limited availability of other AA.
Courtney-Martin et al. 2010[16]	Other, single-arm crossover study 5 neonates	Gestational age (wk): 36.5 (±2.3) Postnatal age wk): 1.8 (±0.69) Gender (F:M): 2:3 Birth weight (kg): 2.35 ±0.65)	Parenteral AA solution devoid of cysteine during the first 3 days followed by AA solution supplemented by 10 mg/kg/d cysteine on days 4-6 All treatment co-administered with dextrose plus 20% lipid solution. Vitamins and minerals were supplemented and met dietary reference intakes	Plasma cysteine concentration was higher with cysteine supplementation (152.5±43.5 compared to 173.7±53.0 µmol//L) but this difference is not statistically significant	10 mg/kg/d of cysteine in this study is roughly equivalent to 3.34 mg cysteine per gram of Amino Acids

Source: NDA 210660 Module 2.7, SDN24, submission date April 19, 2018.

Plasma Taurine Concentrations

Cysteine doses ranging between 19 mg to 48 mg cysteine/ g AA were studied in the publications that evaluated the plasma concentration of taurine[5] after cysteine supplementation (Table 4). Two small randomized controlled studies by Storm et al. (in abstract form) and te Braake et al. in infants showed conflicting results regarding plasma taurine concentration following supplementation (9, 10). A trial in older pediatric patients (Helms et al.) and a single-arm prospective trial (Heird et al.) in low birth weight infants demonstrated evidence of increased or normalized mean taurine concentration, respectively, following supplementation with cysteine (11, 12).

[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.

Table 4. Summary of Studies that Evaluated Plasma Taurine and Other Plasma Amino Acid Concentrations

Outcome: Plasma Taurine and other plasma amino acid concentrations					
Reference	Design	Population	Dose(s)	Outcomes	Comments
Storm et al. 2003* [19]	RCT, double blind 18 infants	Gestational age (wk): 30-37 Postnatal age (wk): < 4	All initially received PN with no cysteine supplementation for 3 days followed by PN with 0, 10, 20, or 40 mg cysteine-HCl/g AA for the next 3 days Target PN dosage was 2.5 g AA/kg/d with a caloric goal of 125 kcal/kg/d	Plasma Taurine and Cysteine concentrations increased with Cysteine-HCl dose Plasma taurine concentration was 41.2±5.47 (mean±SEM), 54.8±5.22, 64.8±4.27, and 76.1±9.60 in infants receiving no Cysteine supplementation, 10 mg/g AA, 20 mg/g AA, and 40 mg/g AA supplements of cysteine	Based on abstract
te Braake et al. 2009[21]	Prospective RCT 20 infants	All mean ± SE Standard Dose Cysteine (n = 10) Number of Male: 6 Birth weight (g): 978±274 Gestational age (wk): 28±1.71 High Dose Cysteine (n = 10) Number of Male: 8 Birth weight (g): 1006±120 Gestational age (wk): 27.43±1.29	Standard Dose Cysteine Glucose + AAs (2.4 g/kg/day) containing a cysteine dose of 45 mg/kg High Dose Cysteine Glucose + AAs (2.4 g/kg/day) + additional cysteine for a total cysteine dose of 81 mg/kg Treatment was assigned directly after birth with a duration of 2 days	No significant difference in plasma concentration of amino acids between the two groups	45 mg/kg/d of cysteine in this study is roughly equivalent to 19 mg cysteine per gram of Amino Acids 81 mg/kg/d of cysteine in this study is roughly equivalent to 34 mg cysteine per gram of Amino Acids
Helms et al. 1999[22]	Other, one arm crossover 6 children with shot gun syndrome on home parenteral nutrition	Age (mo): 45±30 Weight (kg): 16.8±6 Number of Male: 2	Duration: 5 months Baseline to month 1: Aminosyn without cysteine HCl Month 1 to month 2: Equivalent TrophAmine supplemented with no cysteine HCl Month 2 to month 3: Equivalent TrophAmine supplemented with 20 mg cysteine HCl/g AA Month 3 to month 4: Equivalent TrophAmine supplemented with 30 mg cysteine HCl/g AA Month 4 to month 5: Equivalent TrophAmine supplemented with 40 mg cysteine HCl/g AA	Mean taurine concentrations were below the normal reference range (28 to 98 nmol/mL) without cysteine HCl supplementation. Mean taurine concentrations were within the lower half of the normal reference range at all cysteine HCl dosages (20 through 40 mg/g AA). Only with 30 or 40 mg cysteine HCl/1 g amino acid in parenteral nutrition were mean taurine concentrations significantly increased above baseline.	Neither total or free cysteine/cystine nor methionine plasma concentrations changed with cysteine HCl dosing
Heird et al. 1988[23]	Other 28 low birth weight infants	Gestational Age (wk): 24-36 Birth weight (g): 750-1750 g Number of Male: 18	Infants receiving TPN through peripheral vein (n = 10) or central vein (n = 16) received TPN providing a total amino acid intake of 2.5 g/kg/d plus 1 mmol/kg/d L-cysteine HCl (121 mg/kg/d) plus 60-120 kcal/kg/d of non protein energy including up to 3 g/kg/d of fat (Intralipid or Liposyn). Vitamins and minerals varied based on infant needs 12 infants received some enteral nitrogen intake (12.0%-36.4% of total nitrogen intake for at least part of the study period)	Mean plasma concentration of all amino acids except phenylalanine were within 95% confidence limits of goals for low birth weight infants	Separation of the population into a peripheral vein subgroup and central vein subgroup was not part of the study design and occurred consequentially Cysteine dose in this study was roughly equivalent to 48 mg L-Cysteine HCl/g AA

Source: Applicant submitted NDA 210660 Module 2.7.3

Glutathione Concentrations

In contrast, the available literature suggests that cysteine supplementation was found to have no effect on glutathione[6] concentrations at doses ranging between 3 mg to 40 mg cysteine/g AA (Table 5).

Table 5. Summary of Studies that Evaluated Cysteine Effect on Glutathione Levels

Outcome: Glutathione related results					
Reference	Design	Population	Dose(s)	Outcomes	Comments
Calkins et al. 2016[24]	RCT 46 critically ill neonates	Cysteine group (n = 21) Gestational age (wk): 34±6 Birth weight (kg): 2.4±1 Male (%): 71% Day of life: 5±7 Control group (n = 17) Gestational age (wk): 34±6 Birth weight (kg): 2.3±1 Male (%): 82% Day of life: 3±4	Treatment duration: 7 days PN comprised of dextrose, amino acids, and lipids plus 121 mg/kg/day of supplement as either cysteine-HCl (about 40 mg/g AA/day) and sodium acetate (cysteine group) or additional amino acids (control group)	No significant difference (p = 0.1) in erythrocyte total glutathione concentration (median [IQR]) for the cysteine group (1.4 [1, 2.7]) compared to the control group (1.7 [1.1, 1.9]) There was a significant difference in the mean individual change in total glutathione and GSH for the cysteine group compared to the control group (0.5±0.2 vs. −0.2±0.2, and 0.4±0.2 vs. −0.2±0.2 mmol/L, p=0.02 each)	121 mg/kg/d of cysteine in this study is roughly equivalent to 40 mg cysteine per gram of Amino Acids
Shew et al. 1999* [25]	RCT, single blind 19 neonates	Treatment group (n=9) Birth weight (kg): 1.47±0.25 (SEM) Gestational age (wk): 30.8±1.0 Control group (n=10) Birth weight (kg): 1.54±0.16 (SEM) Gestational age (wk): 29.9±1.4	Treatment (n = 9): PN plus 0.78±0.03 mmol/kg/d of cysteine-HCl for a duration of 5.9±0.5 days Control (n = 10): PN only for a duration of 6.8±0.5 days	No difference in RBC-GSH between the treatment and control groups (0.62 ± 0.05 vs. 0.57 ± 0.04 mmol/L, p = 0.47)	Based on abstract 0.78 mmol/kg/d of cysteine-HCl is equivalent to 94.5 mg/kg/d of cysteine-HCl. Assuming, 2.5 g/kg/day of Amino Acids in the PN, Cysteine dose is equivalent to 37.8 mg per gram of Amino Acids.
te Braake et al. 2009[21]	Prospective RCT 20 infants	All mean ± SE Standard Dose Cysteine (n = 10) Number of Male: 6 Birth weight (g): 978±274 Gestational age (wk): 28±1.71 High Dose Cysteine (n = 10) Number of Male: 8 Birth weight (g): 1006±120 Gestational age (wk): 27.43±1.29	Standard Dose Cysteine Glucose + AAs (2.4 g/kg/day) containing a cysteine dose of 45 mg/kg High Dose Cysteine Glucose + AAs (2.4 g/kg/day) + additional cysteine for a total cysteine dose of 81 mg/kg Treatment was assigned directly after birth with a duration of 2 days	Glutathione fractional synthesis rates were identical (48±11% per day and 48±8% per day in the standard-dose and high-dose cysteine groups, respectively No significant difference in glutathione concentrations (1.83±0.28 mmol/L vs 2.02±0.18 mmol/L in standard and high dose groups respectively [p = 0.10])	45 mg/kg/d of cysteine in this study is roughly equivalent to 19 mg cysteine per gram of Amino Acids 81 mg/kg/d of cysteine in this study is roughly equivalent to 34 mg cysteine per gram of Amino Acids
Courtney-Martin et al. 2010[16]	Other, single-arm crossover study 5 neonates	Gestational age (wk): 36.5 (±2.3) Postnatal age wk): 1.8 (±0.69) Gender (F:M): 2:3 Birth weight (kg): 2.35 ±0.65)	Parenteral AA solution devoid of cysteine during the first 3 days followed by AA solution supplemented by 10 mg/kg/d cysteine on days 4-6 All treatment co-administered with dextrose plus 20% lipid solution. Vitamins and minerals were supplemented and met dietary reference intakes	Cysteine supplementation had no effect on GSH concentration, fractional, or absolute synthesis rates.	10 mg/kg/d of cysteine in this study is roughly equivalent to 3.34 mg cysteine per gram of Amino Acids

Source: Applicant submitted NDA 210660 Module 2.7.3

[6] Cysteine is utilized by the body to synthesize glutathione (GSH), which is known as an antioxidant and important for counteracting oxidative stress. Glutathione also protects S-adenosylmethionine (SAM) synthase, a key enzyme in the hepatic transmethylation/trans-sulfuration pathway, from oxidative damage.

Nitrogen Balance and Growth

The clinical significance of increased levels of specific amino acids should, in theory, be measurable as positive nitrogen balance or retention, and resultant overall improvement in neonatal growth (Table 6).

While the individual small (mean n = 22) randomized controlled trial results showed no significant effect of cysteine supplementation on nitrogen retention, a 2006 Cochrane review meta-analysis (13) 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 amino acid, 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 (14, 15).

Table 6. Summary of Studies Evaluating Growth and Nitrogen Balance Related Endpoints

Outcome: Growth and Nitrogen Balance Related Endpoints (Meta-Analysis)					
Reference	Design	Population	Dose(s)	Outcomes	Comments
Shew et al. 1999* [25]	RCT, single blind 19 neonates	Treatment group (n=9) Birth weight (kg): 1.47±0.25 (SEM) Gestational age (wk): 30.8±1.0 Control group (n=10) Birth weight (kg): 1.54±0.16 (SEM) Gestational age (wk): 29.9±1.4	Treatment (n = 9): PN plus 0.78±0.03 mmol/kg/d of cysteine-HCl for a duration of 5.9±0.5 days Control (n = 10): PN only for a duration of 6.8±0.5 days	No statistically significant difference in endpoints Treatment group had a lower rate of phenylalanine flux (protein turnover): 116 ± 16 vs. 155 ± 16 µmol/kg/hr, p = 0.10) and a lower rate of endogenous phenylalanine flux (protein breakdown): 81 ± 16 vs. 122 ± 15 µmol/kg/hr, p = 0.08) Nitrogen balance was greater in the treatment group (282 ± 35 vs 207 ± 37 mg/kg/d, P = 0.17)	Based on abstract 0.78 mmol/kg/d of cysteine-HCl is equivalent to 94.5 mg/kg/d of cysteine-HCl. Assuming, 2.5 g/kg/day of Amino Acids in the PN, Cysteine dose is equivalent to 37.8 mg per gram of Amino Acids.
Kashyap et al. 1992*.[26]	3-arm trial (single site), unblinded 20 very low birth weight infants	Mean birth weight: 1010 g Mean gestational age: 27.8 weeks	Intravenous cysteine supplementation 1 mmol/kg/day (either in the parenteral solution [n=7] or separately [n=6]) versus no supplementation (n=7). Duration not provided	Type of cysteine supplementation had no effect on nitrogen retention and plasma free cysteine concentration	Patients in the treatment arm required twice as much base to maintain normal acid base status compared to those in the treatment arm. Abstract unable to be found, based on data reported from the Cochrane Review
Heird et al. 1988[23]	Other 28 low birth weight infants	Gestational Age (wk): 24-36 Birth weight (g): 750-1750 g Number of Male: 18	Infants receiving TPN through peripheral vein (n = 10) or central vein (n = 16) received TPN providing a total amino acid intake of 2.5 g/kg/d plus 1 mmol/kg/d L-cysteine HCl (121 mg/kg/d) plus 60-120 kcal/kg/d of non protein energy including up to 3 g/kg/d of fat (Intralipid or Liposyn). Vitamins and minerals varied based on infant needs 12 infants received some enteral nitrogen intake (12.0%-36.4% of total nitrogen intake for at least part of the study period)	Mean weight gain: 14.8±10 g/kg/d Mean nitrogen balance: 273±111 mg/kg/d	Separation of the population into a peripheral vein subgroup and central vein subgroup was not part of the study design and occurred consequentially Cysteine dose in this study was roughly equivalent to 48 mg L-Cysteine HCl/g AA
Zlotkin et al. 1981.* [27]	Other 28 infants	All mean ± SE Cysteine supplemented (n=18) Birth weight (g): 2231±391 Gestational age (wk): 34.4±2.2 Postnatal age (days): 13.7±5.5 Control (n=18) Birth weight (g): 2141±357 Gestational age (wk): 34.2±2.0 Postnatal age (days): 15.0±5.6	Both groups received similar cysteine free control formulation consisting of crystalline L-amino acid mixture in 10% dextrose and water, maintenance fluid and electrolytes in addition to vitamins, minerals, and trace elements. This provided an average fluid intake of 150 mL/kg/24h which included 480 mg of nitrogen and 15 g of carbohydrate per kg/24 h with a planned total energy intake of 90 kcal/kg/24 h Cysteine supplemented group also received 77 mg cysteine-HCl/kg/24h Duration of treatment was 6 days	No significant difference in weight change between two groups (control = 10.2±1.7 g/kg/24h, supplemented = 6.1±2.3) No significant difference in head circumference (control = 0.6±0.1 cm/6 days, supplemented = 0.9±2 cm/6 days) or length change (control = 0.6±0.2 cm/6 days, supplemented = 0.6±0.1 cm/6 days) No significant difference in nitrogen or energy intakes Both groups showed similar positive nitrogen retention (about 56% of infused nitrogen)	Assignment to groups was not randomized For each group n is based on the number of 6 day study periods completed
Outcome: Growth and Nitrogen Balance Related Endpoints (Meta-Analysis)					
Reference	Design	Population	Dose(s)	Outcomes	Comments
Soghier et al 2006.[26]	Meta-analysis of RCTs and quasi-randomized trials 4 trials	N=95 infants including 73 preterm infants	Cysteine doses ranged from 72 mg/kg/day to 157.62 mg/kg/day (1 mmol/kg/day)	Nitrogen retention was significantly increased by cysteine supplementation (weighted mean difference 31.8 mg/kg/day, 95% CI [8.2, 55.4]	Cysteine doses in this meta analysis was roughly equivalent to 30 mg to 63 mg/g AA

Source: NDA210660 Module 2.7.3
* indicates that the study was included in the Cochrane Review meta-analysis

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 (16, 17). This effect of cysteine supplementation is beneficial because the availability of calcium and phosphate ions is

typically limited due to incompatibility 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

Not Applicable.

8.1.4. 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 3 and Table 4), the ultimate clinical benefit of the increased serum cysteine remains unclear, as no study has shown that cysteine supplementation has a significant effect on neonatal growth (13).

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 amino acid 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 amino acid 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 amino acid metabolism that supports the conditional essentiality of cysteine (18) have contributed to published clinical practice guidelines by both American and European parenteral nutrition societies that recommend routine cysteine supplementation for neonates (19, 20). Additionally, older patients with severe liver disease have been shown to have evidence of impaired cystathionase function, and may require cysteine supplementation while on TPN support.

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 of the LD.

As the LD was never manufactured or marketed, there is no relevant literature on postmarketing adverse events. Additionally, there are no postmarketing adverse event reports in FAERS for the LD. Further support of safety for the candidate product, Elcys, was provided by post-marketing FAERS search for available "cysteine" products to identify any "class effects" in conjunction with the safety information updates from the cysteine product currently compounded and distributed by the Applicant.

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 (Section 8.2.10; DARRTS, September 26, 2018).

Marketed unapproved drug usage data (Figure 2) shows active use of cysteine in the US market. Although the usage data reflects only one of the marketed unapproved products, it provides a general estimate of the denominator for the FAERS "post-marketing" safety database search.

Figure 2. Marketed Unapproved Drug Usage Data from 2017-2018

Source: H. Son. Division of Drug Shortage
NSP = National Sales Perspectives

In a previous communication under PIND 128489, dated July 21, 2016, the Applicant had indicated that Exela is a FDA-registered outsourcing facility under Section 503B, and has been manufacturing the product as a compounding pharmacy to supply the unapproved drug product to alleviate the drug shortage. Upon FDA request, the Applicant provided their manufacturing and distribution history, which included two batches of L-Cysteine

Hydrochloride Injection, USP: (b) (4) The list of pharmacies and hospitals where the product was distributed is provided in Appendix 15.6, Table 13.

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 (16), 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. The Applicant also submitted the safety update on the specific cysteine products compounded and distributed from their facility. 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 (13, 21, 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 amino acid 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 the contaminant of PN solutions over the past 3 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.

21 CFR 201.323 (e) specifies aluminum concentration limits in large[7] and small[8] volume parenteral nutrition products. The aluminum content of the listed drug 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 (COA) Analyses Informing Safety/Tolerability

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

Not applicable.

[7] 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).

[8] 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."

8.2.8. 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.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

No new safety signals were identified upon review of the post market data for available cysteine products (see OSE FAERS search consult by Dr. Ivone Kim dated Oct 1, 2018).

Specifically related to the compounded batches of cysteine hydrochloride manufactured and distributed by the Applicant in the past (see Section 8.2.2), the Applicant reports that they have not received any safety complaints.

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 per gram 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 per gram of AA and recommended that this be decreased to 20 mg cysteine per gram of AA during the shortage (19). The European Society for Clinical Nutrition and Metabolism (ESPEN) Guidelines on Pediatric Parenteral Nutrition recommend a minimum advisable cysteine intake between 30-55 mg/kg/day in infants and young children (20). Of note, the current enteral cysteine requirement by The American Society for Nutritional Sciences is 66-95 mg/kg/d, which corresponds to the minimum and maximum amount found in breast milk protein (25).

Consistent with the published clinical management guidelines, in this reviewer's experience as well as according to other field experts in parenteral nutrition (see Section 9), the dosing in clinical practice is highly variable and ranges between 20 – 40 mg of cysteine / gram AA. Although, this represents a significant divergence from the proposed labelled dose of 15 mg of cysteine / gram 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

Overall, there have been no new safety signals identified with the proposed use or suggested dose of cysteine. Previously, FDA has determined that the listed drug was not withdrawn for reasons of safety or effectiveness (see Section 3.1). Absence of any 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 amino acid that can be endogenously synthesized from methionine, the product is anticipated to be well-tolerated. However, the optimal dose for cysteine has yet to be identified, both for maximizing efficacy and minimizing safety considerations. 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, Elcys has a comparable benefit-risk profile to the LD 7.25% Cysteine Hydrochloride. Currently, without any approved products available on the market, marketing approval of a product with quality controlled impurities (i.e., leachables, extractables), especially aluminum exposure, offers a significant benefit. Elcys is a candidate with potentially positive impact on the cysteine drug shortage and was granted priority review. 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/gram of amino acid to a higher

dose (i.e., 20 mg, 30 mg or 40 mg/g AA). As stated in the previous relisting memo[9] for the listed drug, 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 Elcys for the proposed indication.

9 Advisory Committee Meeting and Other External Consultations

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 Network of Experts[10] approach was utilized to obtain expertise/experience of physicians who have provided care, especially in prescribing parenteral nutrition, to neonatal, pediatric, and severe liver disease patients.

[9] 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.
[10] http://inside.fda.gov:9003/CDER/OfficeoftheCenterDirector/ucm524126.htm

Table 7. Summary of Discussions with the Network of Experts

	Expert 1[1] October 15, 2018	Expert 2[2] October 15, 2018	Expert 3[3] October 29, 2018	Expert 4[4] November 19, 2018
Patient population / clinical criteria	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
Recommended Cysteine Dose	40 mg/g AA; 20 mg/g AA during shortage	30 mg/g AA	30-40 mg/g AA	40 mg/g AA
Typical Duration of Therapy	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"
Risk of Deficiency and Toxicity	None	None	None	None
Safety Concerns	None	None	None	None
Recommended Monitoring	Routine	Routine	Routine	Routine
Management of Adverse Reactions	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
Other notes:		Used to solubilize calcium and phosphate in the TPN admixture		Cysteine addition improves calcium and phosphate solubility

[1] Doctor of Pharmacy, parenteral nutrition expertise.

[2] Neonatologist, Director of Newborn Services.

[3] Chief of Pediatrics, Gastroenterology, Hepatology, and Nutrition.

[4] Neonatologist.

10 Pediatrics

Under the Pediatric Research Equity Act (PREA) (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 section is not applicable to NDA 210660 because the application was submitted by way of the 505(b)(2)

regulatory pathway given that there is no change in dosing regimen. L-Cysteine can be fully labeled in pediatric patients with pediatric dosing and dosing instructions supported by published pediatric literature and clinical practice guidelines submitted in a pediatric assessment. Together, DGIEP and the Division of Pediatric and Maternal Health (DPMH) determined that the pediatric dosage and dosing regimen from birth (including preterm infants) to less than 18 years of age needs to be updated in 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 Dr. Carolyn Yancey, primarily focusing on labeling recommendations, is filed separately under NDA 210660.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The proposed PI for Elcys relies on the LD (7.25% Cysteine Hydrochloride; NDA 019523) label, and was updated and modified according to Physician Labeling Rule (PLR).[11]

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.[12] The resulting Product Title is:

  ELCYS (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 10 mL (b) (4) contains 500 mg of cysteine hydrochloride (equivalent to 345 mg of cysteine) in (b) (4) water for injection.

[11] 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)

[12] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm379753.pdf

- Per the Dosage and Administration section guidance,[13] the section was revised to include specific administration instructions that are important to safe and effective use of the drug and pertinent restrictions on intravenous administration (e.g., administer via central line only).
- To clarify the dosage instruction, (b) (4) and the dosing table in Section 2.2 provides the dose of cysteine as mg cysteine/g AA.
- DGIEP recommended a dosing table based on age in pediatric patients and severity of illness in adults,[14] as used in other AA product labels,[15] for clarity.
    - While the LD is approved in pediatric patients of all ages, the PI does not give specific dosing recommendations for all of the pediatric age subgroups beyond newborn infants. Dosing information for older pediatric patients, 1 – 11 years of age, was based on published reports on short gut syndrome patients aged >1 to 8 years who received dose ranges (20 to 40 mg cysteine/g AA), consistent with the published dose ranges in infants (7,11) (See Table 2. Recommend Dosing Regimens for Elcys in Section 6.1).
    - There are no published reports of cysteine use in adolescent patients; however, according to clinical experts, its rare use in this subpopulation is not prohibited. Therefore, given that the weight-based protein requirement for older pediatric patients, 12 – 17 years of age, closely align with adult protein requirements during TPN, the dosing recommendation of 5 mg cysteine/g AA was given to maintain consistency with the adult amino acid profile.
    - The dosing table shows the Elcys dose only as the salt form, cysteine hydrochloride, to match the current pharmacy practice and reduce potential for prescription error. The results of a survey conducted by the Sponsor (see Appendix 15.7) showed 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 oder.
- Information on the compatibility of the product when admixed with TPN solutions, and the procedure for adding Elcys to the TPN admixture was included.

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[13] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075066.pdf

[14] Ayers P. et al. A.S.P.E.N. Parenteral Nutrition Handbook, 2nd ed. 2014 pg. 123 and 124.

[15] See Prosol: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020849s024lbl.pdf

- (b) (4) The Applicant has committed to conducting additional admixture study(s) to support stability and compatibility of lipids with the other components, (b) (4)
- Storage conditions were updated based on the available stability data of the product.
- The Warnings and Precautions section was updated to include pertinent PN AA product class safety information, i.e., vein damage and thrombosis, increased blood urea nitrogen (BUN), fluid and electrolyte imbalance, hyperammonemia, aluminum toxicity, etc.

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

12 Risk Evaluation and Mitigation Strategies (REMS)

The benefit-risk profile for Elcys 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

The Applicant's previous admixture study (Protocol # 2017-RD-042 and SMRY-000052 and SMRY-000170), evaluated a mixture of amino acids (Travasol 10%) and dextrose with ELCYS. While in clinical practice for neonatal TPN, lipids may be administered separately and not combined with amino acid and glucose admixtures to which cysteine is added, in non-pediatric and outpatient TPN settings, cysteine may be administered together with the amino acid, glucose, and lipids. Consistent with the currently available data, ELCYS is labeled for admixing with amino acids and dextrose (2-in-1 solution), but not with all 3 components of a TPN solution, i.e., dextrose, amino acids, and lipids (3-in-1 solution).

Given that in some settings, 3-in-1 admixture may be routine, the Division recommended that the Applicant conduct an additional *in vitro* admixture study (similar in conduct to the study previously conducted) (b) (4)

In an Information Request response dated April 5, 2019, Exela commited to performing the 3-in-1 admixture study(s) (b) (4)

(b) (4)

14 Division Director Comments

I concur with recommendations of the review team for approval of NDA 210-660. This 505(b)(2) NDA relies on FDA's findings of safety and efficacy for NDA 19-523, 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 19-523 could be approved with some labeling revision, but without new studies.

The current product differs from NDA 19-523 in terms of concentration (5% vs. 7.25%) and container-closure (glass vial vs. prefilled syringe). OPQ reviewers concluded that the bioavailability information submitted was adequate to establish a biobridge between Elcys and the LD, such that a biowaiver of relative BA studies was granted.

Cysteine is a conditionally essential amino acid, with preterm and term infants, as well as older children and adults with liver impairment, having reduced ability to synthesize cysteine. Clinical practice guidelines recommend routine cysteine supplementation in neonates; however, commercially available amino acid 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 amino acid. 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.

The labeled range of dosages, from 5 mg/g AA in pediatric patients ≥ 12 years through adults to 15 mg/g AA in pediatric patients < 12 years, is consistent with the LD. While these are 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. The Applicant has been manufacturing a compounded cysteine hydrochloride product, and has not received any safety reports.

There are currently no FDA-approved cysteine products marketed; thus, this SVP product has been in drug shortage since 2015, with FDA permitting importation of a Canadian product to alleviate the shortage. There are also marketed unapproved and compounded cysteine products, with unknown quality control of leachable and extractable impurities; in particular, these products may not meet regulatory requirements under 21 CFR 201.323(3) regarding

aluminum concentration limits in parenteral nutrition products. Approval of Elcys is anticipated to help alleviate the shortage, as well as to provide a quality-controlled cysteine product that provides acceptable aluminum exposure.

15 Appendices

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 Applicant's table below.

Table 8. Acceptance Criteria for Impurities in Drug Product

Product Specifications

TEST	SPECIFICATIONS	METHOD REFERENCE
Related Compounds: R,S a. (b) (4) b. Specified RRT (b) (4) c. Specified RRT d. Specified RRT e. Individual Unspecified Impurity f. Total Impurities	a. NMT (b) (4) b. NMT c. NMT d. NMT e. NMT f. NMT	QCTM-000035

Source: Drug Product Specifications (SPEC-FP-000025)

The maximum daily dose of the drug substance (cysteine•HCl•H_2O) is estimated to be 3.305 g, based on the maximum recommended dose of amino acids (2 g/kg/day) for parenteral nutrition, the maximum recommended dose of L-cysteine free base equivalent (15 mg cysteine/g amino acids/day), and an assumed bodyweight of 76 kg in pediatric patients age 11 years (95th percentile bodyweight reported by the CDC for children age 11) (see Section 6.2). For the estimated maximum daily dose of 3.305 g cysteine•HCl•H_2O, the qualification threshold for degradation products of the drug substance is 0.15%, per ICH Q3B(R2).

The first step in the evaluation of impurity acceptance criteria usually involves the assessment of genotoxic potential of the impurities, based on the recommendations in ICH M7(R1). In the absence of structural information on the impurities, the genotoxic potential cannot be assessed. However, 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[16,17]. 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).

The proposed limit for (b) (4) is not more than (NMT) (b) (4)%. Since (b) (4) is a potential metabolite of L-cysteine and is known to be endogenous, there is no safety concern for the proposed limit of NMT (b) (4)%. With the exception of (b) (4), none of

[16] Glatt H et al., Science 220, pg. 961-963, 1983

[17] Glatt H, Mutagenesis 4(3), pg. 221-227, 1989

the specified or unspecified impurities were identified. However, it is noteworthy that none of the specified or unspecified impurities were detected in the product batches analyzed at the initiation of stability testing. Also, the batch data showed a trend of time-dependent accumulation for the specified impurities. In contrast, the concentration of individual unspecified impurities during stability testing was not time-dependent, which may be indicative of instability. Given the absence of detectable levels of the specified and unspecified impurities at the initial time-point of stability testing, it is reasonable to assume that these are all degradants of L-cysteine. Based on the structure of L-cysteine, it is reasonably assumed that there is a limited range of chemical structures among the degradants, which may not present a safety risk substantially different from L-cysteine or its metabolites. Furthermore, the proposed limits for the specified impurities (NMT (b) (4)%) and individual unspecified impurities (NMT (b) (4)%) do not markedly exceed the impurity qualification threshold (0.15%) recommended in ICH Q3B(R2). Therefore, from a nonclinical safety perspective, the proposed acceptance criteria for drug-related compounds, both for specified impurities and individual unspecified impurities, are acceptable.

Leachables Assessment

The Applicant submitted amendments to the NDA dated October 1, 2018 and January 3, 2019 that included data from analytical testing of leachables in five drug product lots (Module 3.2.P.2. Leachable Impurities in L-Cysteine HCl Injection, USP, (50 mg/mL), 10 mL Vial Drug Product, report # SMRY-000022). For evaluation of leachables and stability, the drug product was stored in its container for up to 12 months, with sampling for analysis at multiple time points. The drug product was stored under the normal recommended conditions (25°C/60% relative humidity (RH)) or under stressed conditions (40°C/75% RH). Drug product was stored in the upright, inverted, and horizontal positions under normal storage conditions, whereas only the upright position was used for storage under stressed conditions. The container closure system is a USP (b) (4) glass vial with rubber stopper. Prior to the leachables study, extractables studies were conducted with all components of the manufacturing system that have contact with the drug product, and with the container closure components with direct contact with the drug product (10-mL (b) (4) single-dose glass vial and (b) (4) 20 mm Gray (b) (4) stopper). The analytical methods used in the extractables studies included HS-GC (for volatile compounds), DI-GC (for semi-volatile compounds), UPLC (for non-volatile compounds), and ICP-MS (for elements). The extrables studies are described in report # SMRY-000053.

The analytical methods used for detection of specific leachable types in the drug product are shown in the Applicant's table below (report # SMRY-000022).

Table 9. Analytical Methods for Detection and Measurement of Leachables

Leachable Type	Technique$^{\Delta}$	Method #	References
Volatile	HSGC	2017-RDTM-117	25, 26
Semi-volatile	DIGC	RDTM-000005	27, 28
Non-volatile	UPLC	2017-RDTM-119	29, 30
Elemental	ICP-MS	2017-RDTM-121	31, 32
Aluminum Content	ICP-MS	QCTM-000032	33, 34
Inorganic Anions	ISE	Fluoride – RDTM-000006	10,11
	ICP-MS	Iodide – RDTM-0000078	12, 13

Δ - Where: HSGC = Headspace Gas Chromatography, DIGC = Direct Injection Gas Chromatography, UPLC = Ultra High Performance Liquid Chromatography, ICP-MS = Inductively Couple Plasma Mass Spectrometry, ISE = Ion Selective Electrode

Source: Study Report # SMRY-000022, NDA 210660

The Sponsor used an analytical evaluation threshold (AET) of (b) (4) ppb ((b) (4) mcg/L) for each method in the table above. Therefore, all peaks that exceeded (b) (4) ppb were identified, quantitated, and reported. The selected AET allows for detection of exposures above (b) (4) mcg/day, which can be delivered in the estimated maximum daily dose volume of 66.1 mL (see table below). The dose of (b) (4) mcg/day is lower than the Threshold of Toxicological Concern (TTC) for genotoxic carcinogens (1.5 mcg/day) stated in ICH M7(R1); therefore, the AET is acceptable for use in safety assessment of leachables. Compliance with the TTC is considered acceptable for assurance that any unstudied chemical will present only a negligible risk of carcinogenicity or other toxic effects.

In the report, the Applicant provided the concentrations of elemental impurities and volatile organic leachable compounds in the drug product solution (semi-volatile and non-volatile leachables were not detected above (b) (4) ppb at any time-point).

Safety assessment of organic leachables was conducted by calculating the maximum daily dose (mcg/day) based on the highest concentration detected among all drug product lots, time-points, and storage conditions, and an assumed maximum dose volume of 66.1 mL/day (volume calculated for 11 year-old pediatric patients in the 95th bodyweight percentile [76 kg]). The selected age and bodyweight for calculation of the the maximum daily dose volume provides a reasonable estimate of the maximum volume (mL/day) that may be administered among all age groups, based on the recommended dosing of cysteine hydrochloride. Relevant information for this aspect of the leachables safety assessment is shown in the following table.

Table 10. Maximum Dose Volume Given to a Pediatric Patient Age 11 Years (76 kg based on 95th bodyweight percentile)

	Mol. Wt.	**Concentation in Drug Product (mg/mL)**	**Maximum Dose (mg/day)**	**Dose Volume for 11-year Old Patient (95th bodyweight percentile) (mL/day)**
L-Cysteine	121.20	34.5	2280	66.1
L-Cysteine• HCl•H_2O	175.60	50	3305	66.1

Source: Reviewer-generated, based on the maximum recommended dose of L-cysteine free base equivalent (30 mg cysteine/kg/day) or L-cysteine•HCl•H_2O (43.49 mg cysteine•HCl•H_2O/kg/day), and an assumed bodyweight of 76 kg in pediatric patients age 11 years (95th percentile bodyweight reported by the CDC for children age 11).

For most leachables, the maximum daily dose (worst-case exposure) was compared to the PDE values in ICH guidance Q3C(R6). For the leachables that are not included in ICH Q3C(R6), PDE values were calculated from available toxicology studies.

Volatile Leachables

The Applicant quantified volatile leachables in five drug product lots using Headspace Gas Chromatography. The maximum dose (mcg/day) of volatile compounds was calculated based on the maximum level (ppm) detected. Safety assessment of each leachable is based on compliance of the maximum daily dose with the Permitted Daily Exposure (PDE), as provided in ICH Guidance Q3C(R6) or calculated from available toxicology studies (shown below in Table 11).

Table 11. Safety Assessment of Maximum Doses of Volatile Leachables Based on Compliance with PDE

Volatile Compounds	Solvent Class[a]	PDE for Parenteral Exposure (mcg/day)	Highest Level Among All Drug Product Lots	
			Maximum Concentration (ppm or mcg/mL)	Maximum Dose (mcg/day)
(b) (4)				

Maximum dose (mcg/day) = Maximum concentration (mcg/mL) x 66.1 mL/day (maximum dose volume).
Calculation of maximum dose volume was based on 95th percentile bodyweight (76 kg) in pediatric patients age 11 years.
a: Class and PDE stated in ICH Guidance Q3C(R6)
b: Calculated from NOAEL (see below for details of calculations)
ND = Not determined
Source: Reviewer-generated based on the Study Report # SMRY-000022, NDA 210660

The maximum dose of every leachable (volatile organic compounds only) is markedly lower than the PDE; therefore, there is no safety concern for the potential exposure to the leachables from administration of the drug product.

PDE values for (b) (4) were calculated from the most relevant published nonclinical toxicity reports. Details of the safety assessment and PDE calculation for these leachables are provided below.

(b) (4)

(b) (4) The worst case exposure to (b) (4) at the maximum dose of volume of 66.1 mL/day is calculated to be (b) (4) mcg/day (Table 11 above).

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0.425 kg

Elemental Impurities

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 120 mcg/L. Safety assessment of the aluminum acceptance criterion should be based on the dosing of cysteine in preterm and term infants, given that the highest cysteine dose (mg/kg/day) will be used in this age group, and because preterm neonates are considered as being at risk for aluminum toxicity (CNS and bone) (21 CFR 201.323). The maximum dose is 60 mg cysteine/kg/day in preterm and term infants, calculated based on 4 g/kg/day amino acids and 15 mg cysteine/g amino acids, as recommended (22 mg cysteine•HCl•H_2O/g amino acids as stated in the label). The dose volume needed to deliver this dose is 1.76 mL/kg cysteine hydrochloride injection. At the maximum cysteine dose in preterm and infants, the aluminum limit of 120 mcg/L will allow a maximum dose of 0.21 mcg/kg/day. This amount is a small fraction of the maximum dose range (4 to 5 mcg/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.

Safety assessment of other elemental impurities is divided into two categories: 1) elements not intentionally added in TPN as nutritional supplements; 2) elements that may be intentionally added in TPN as nutritional supplements. For elemental impurities in the first category, safety assessment of each element is based on compliance of the maximum daily dose with the PDE (Permitted Daily Exposure), as provided in ICH Guidance Q3D. The maximum dose (mcg/day) of

each element was calculated based on the maximum level (ppm) detected, as shown below in Table 12.

Table 12. Maximum Dose of Elemental Impurities in Drug Product Lots

Trace Elements	*PDE for Parenteral Exposure (mcg/day)	Drug Product Lots	
		Maximum Concentration (ppm or mcg/mL)	Maximum Dose (mcg/day)
(b) (4)			

*As per ICH Q3D Step 4 (Guideline for Elemental Impurities)
Maximum dose (mcg/day) = Maximum concentration (mcg/mL) x 66.1 mL/day (maximum dose volume).
Calculation of maximum dose volume was based on 95th percentile bodyweight (76 kg) in pediatric patients age 11 years.
Source: Reviewer-generated based on the Study Report # SMRY-000022, NDA 210660

The maximum dose of each element is markedly lower than the PDE, therefore the there is no safety concern for the potential exposure to these elements from administration of the drug product.

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 most vulnerable population. The dose comparison was based on mcg/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 amino acids) administered in 4 g/kg/day amino acids in preterm and term infants less than 1 month of age (see Section 6.2, Table 2). This dosing regimen requires administration of 1.76 mL/kg/day of drug product, which is the highest dose volume (per kg bodyweight) needed to achieve the maximum recommended dose among all age groups. Therefore, preterm and term infants less than 1 month of age will receive the highest dose (mcg/kg/day) of the elemental impurities that may be intentionally added in TPN.

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., <15% of dose levels for individual elements).

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. In the stability/leachables study, the highest concentration of (b) (4) detected was (b) (4) ppm (mcg/mL), which would result in a maximum dose of (b) (4) mcg/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. 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.

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 concentration of elemental impurities and leachables 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

15.6. L-Cysteine Hydrochloride Compounding History by the Applicant

Table 13. Applicant's Compounded Drug Distribution Information for L-Cysteine Hydrochloride Injection, USP

Lot #	BUD	Customer	Address	UOM	QTY	Date Shipped
(b) (4)						

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Source: Applicant Response to 74 Day Letter, October 9, 2018.

15.7. Current Pharmacy Practice Survey

The Sponsor conducted a survey of various health systems pharmacies to evaluate the pharmacy practice of determining the volume of the currently marketed unapproved cysteine product (i.e., Sandoz) for PN.

Survey (Submitted March 20, 2019, NDA 210660):

For the past several years FDA has permitted the importation by Sandoz of unapproved L-Cysteine Hydrochloride injection from Canada as a means to alleviate the drug shortage problem that existed in the US. For at least the past three years, Sandoz product appears to be the only product available from GMP manufacturers. As per the label, that product contains L-Cysteine Hydrochloride Monohydrate 50 mg/mL, in 10 mL vials. However, the Sandoz Prescriber Information or the label does not provide the equivalency information between the salt/hydrate and the active moiety, i.e., Cysteine base.

We have three questions:
a) In your practice, if the prescription calls for a certain dose (e.g., 5 mg/kg for a 50 kg patient, or 250 mg) of Cysteine for use in a TPN, do you understand this calling for 250 mg of Cysteine base or 250 mg of Cysteine Hydrochloride?

b) In the above example, can you please provide how much volume of the Sandoz Cysteine solution you syringe-out for this patient?

c) Do you use any other presentation of Cysteine solution to compound your TPNs? If so, what is the drug substance in that presentation (Cysteine HCl, Cysteine HCl Monohydrate, or some other); what is the exact concentration stated on the label? And how much volume you syringe-out for the example in a) using this presentation?

We are trying to determine if there is any potential for confusion in the way the Sandoz label describes the Cysteine presentation (i.e., 50 mg/mL Cysteine Hydrochloride Monohydrate), and if this should be clarified by stating the equivalency information between the salt/hydrate and the base.

The responses received are summarized in the Table below:

Table 14. Summary of Pharmacy Responses to Prescription Practice Survey by Exela

Responder	Question 1	Question 2	Question 3	Comment
1	Dosing of L-cysteine HCL injection USP is for the salt. Normal dosing is 40mg L-cysteine HCL / gm of protein from the amino acids injection.	250 mg of L-cysteine HCL injection USP would be 5ml of the commercially available product	No	In my experience 20+ years as (b) (4) Formulary manager, and working with our numerous customers throughout the US. we have not encountered a customer who desired to order by the base.
2	We would likely consider that 250 mg of cysteine base	Would pull 5 mL of the 50 mg/mL solution		We use cysteine HCl in the exact concentration as above, 50 mg/mL, would pull 5 mL of drug
3	We consider this 250mg of cysteine HCL	We outsource our PN orders to (b) (4) so this process would be done at the outside compounder. However, if we consider this 250mg of cysteine HCL I would think using a concentration of 50mg/mL would be 5mL	Not sure what the compounder uses currently	
4		Based on the product we have I would assume if the dose was 250mg that we would "syringe-out" or draw up 5mL of drug	The only one we have is the Sandoz brand. It is *L-Cysteine Hydrochloride Injection, USP (50mg/mL) (0.5gram/10 mL vials)*	We utilize the L-Cysteine Hydrochloride Monohydrate 50mg/mL, in 10mL vials, and use 5 to make a 50mL syringe. Not sure how it is ordered exactly by the Dieticians as that would go through a RPh first. We do not have these on the Compounder but treat this as a *manual* ingredient that is drawn into a syringe and pushed into the TPN after a RPh verifies dose/volume.
5	Understand it to be 250mg of Cysteine Hydrochloride.	Provide 40 mg to every 1 gram of protein in the PN. Would depend on the grams of protein in the PN. L-Cysteine is added to the PN.	Do not use any other presentations of Cysteine in the PN	
6	We view the product concentration as to what's on the label, so 50mg/ml of Cysteine Hydrochloride	Would be 5mL	Not applicable	
7	We understand this to be 250mg of Cysteine Hydrochloride	5ml	We don't and haven't used any other presentation of L-Cysteine	
8	Due to the labeling of the package insert we interpret this to be 50mg of Cysteine Hydrochloride Monohydrate	This would be 5mL	No we do not	

Source: NDA210660, IR Response submitted March 20, 2019

Based on the survey, it appears that the pharmacies consistently use (have used) only one Cysteine product, which is presented as Cysteine Hydrochloride Injection, 50 mg/mL. The vast majority of those surveyed (7 out of 8) interpret a prescription order for Cysteine as calling for an order of Cysteine Hydrochloride, exactly corresponding to the description on the Sandoz label. Accordingly, pharmacies use the Cysteine Hydrochloride concentration of 50 mg/mL in filling the order. For

example, if the prescription calls for 5 mg/kg for a 50 kg patient or 250 mg cysteine dose, 5 mL of the Cysteine Hydrochloride Injection 50 mg/mL will be used.

As noted above, because a prescription order calling for Cysteine (without further qualification as to whether it is the base or the Hydrochloride salt), is interpreted as an order calling for Cysteine Hydrochloride, conversion from the salt to the base is not required. One outsourcing facility, (b) (4) which is a subsidiary of (b) (4), is the majority user of Cysteine Hydrochloride Injection (about (b) (4) of the entire usage in the US) which prepares PN orders for a number of health systems. As stated in the Table above, (b) (4) indicated that in his experience for over 20 years and working with numerous health systems in the US, he has not encountered orders calling for Cysteine in the form of Cysteine base.

Appendices 15.8: Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Pharmacology Reviewer	Vinay Patil	OND/ODEIII/DGIEP	**Sections: 5** **Appendices: 15.3**	**Select up to two:** _X_Authored ___Acknowledged ___Cleared
	Signature: Vinay A. Patil -S Digitally signed by Vinay A. Patil -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Vinay A. Patil -S, 0.9.2342.19200300.100.1.1=2001232169 Date: 2019.04.09 16:44:34 -04'00'			
Lead Pharmacologist	David Joseph	OND/ODEIII/DGIEP	**Sections: 5** **Appendices: 15.3**	**Select up to two:** _X_Authored ___Acknowledged _X_Cleared
	Signature: David B. Joseph -S Digitally signed by David B. Joseph -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300134835, cn=David B. Joseph -S Date: 2019.04.10 10:12:33 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED / APPROVED
Clinical Pharmacology Reviewer	Elizabeth Shang	OTS/OCP/DCPIII	**Sections Authored:** 6 **Reviewed/Edited:** 8, 11	**Select up to two:** _X_ Authored _X_ Acknowledged ___ Cleared
	Signature: Elizabeth Shang -S Digitally signed by Elizabeth Shang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000383853, cn=Elizabeth Shang -S Date: 2019.04.15 16:27:45 -04'00'			
Clinical Pharmacology Team Leader	Insook Kim	OTS/OCP/DCPIII	**Sections:** 6, and 11 **Reviewed/Edited:** 8	**Select up to two:** ___ Authored __Acknowledged _X_ Cleared
	Signature: Insook Kim -S Digitally signed by Insook Kim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Insook Kim -S, 0.9.2342.19200300.100.1.1=1300416436 Date: 2019.04.15 17:08:07 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Regulatory Affairs/ Project Management	Thao Vu	OND/ODEIII/DGIEP	Sections: All	**Select up to two:** ___ Authored _X_ Acknowledged ___ Cleared
	Signature: Thao M. Vu -S Digitally signed by Thao M. Vu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Thao M. Vu -S, 0.9.2342.19200300.100.1.1=2001699412 Date: 2019.04.16 09:36:01 -04'00'			
Associate Director Signatory	Lisa Soule	OND/ODEIII/DGIEP	Sections Authored: 14 Cleared: All	**Select up to two:** _X_ Authored _X_ Cleared
	Signature: Lisa M. Soule -S Digitally signed by Lisa M. Soule -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lisa M. Soule -S, 0.9.2342.19200300.100.1.1=1300219575 Date: 2019.04.16 09:31:00 -04'00'			
Clinical Team Leader	Erica Lyons	OND/ODEIII/DGIEP	Sections Reviewed/Edited/Cleared: 1,2,3,7,8,9,10	**Select up to two:** ___ Authored _X__ Cleared
	Signature: Erica M. Lyons -S Digitally signed by Erica M. Lyons -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Erica M. Lyons -S, 0.9.2342.19200300.100.1.1=2002205132 Date: 2019.04.15 19:00:25 -04'00'			
Clinical Reviewer	Suna Seo	OND/ODEIII/DGIEP	Sections Authored: 1,2,3,4.1,4.3,4.4,4.5,7, 8,9,10,11,12,13,15 Reviewed/Edited/Cleared: 4.2,5,6,15.3	**Select up to two:** _X__ Authored _X__ Cleared
	Signature: Suna Seo -S Digitally signed by Suna Seo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Suna Seo -S, 0.9.2342.19200300.100.1.1=0011249481 Date: 2019.04.15 12:27:57 -04'00'			

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