CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210660Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 5, 2019

To: Thao Vu, Regulatory Project Manager, (DGIEP)

Joette Meyer, Associate Director for Labeling, (DGIEP)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for ELCYS (cysteine hydrochloride injection), for intravenous use

NDA: 210660

In response to DGIEP's consult request dated June 22, 2017, OPDP has reviewed the proposed product labeling (PI), and carton and container labeling for the original NDA submission for ELCYS.

PI: OPDP has no comments on the proposed labeling are based on the draft PI received by electronic mail from DGIEP on April 5, 2019.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling, received by email on April 5, 2019 from DGIEP, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MEETA N PATEL
04/05/2019 10:56:45 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 27, 2018
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 210660
Product Name and Strength:	Elcys (cysteine hydrochloride injection)[a], USP 50 mg/mL
Total Product Strength:	500 mg/10 mL (50 mg/mL)
Applicant/Sponsor Name:	Exela Pharma Sciences, LLC
FDA Received Date:	March 19, 2019
OSE RCM #:	2017-1073-2
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Sarah K. Vee, Pharm.D.

1 PURPOSE OF MEMORANDUM

Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the revised carton labeling and container label for Elcys (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to a previous review.[b] In addition, the proprietary name was changed to Elcys, which was found acceptable on March 14, 2019.[c]

2 CONCLUSION

The proposed labeling is acceptable from a medication error perspective. We have no further recommendations at this time.

[a] The established name was revised as per Office of Pharmaceutical Quality (OPQ) recommendation.

[b] Abraham, S. Label and Labeling Review for (b) (4) (NDA 210660). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Dec 13. RCM No.:2017-1073-1.

[c] Abraham, S. Proprietary Name Review for Elcys (NDA 210660). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Mar 11. Panorama. 2018-28050621.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MARCH 19, 2019

Container label

Carton labeling

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/s/

SHERLY ABRAHAM
03/27/2019 02:59:08 PM

SARAH K VEE
03/27/2019 04:20:31 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 13, 2018
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 210660
Product Name and Strength:	(b) (4) (cysteine hydrochloride injection)[a], USP, 50 mg/mL
Total Product Strength:	500 mg/10 mL
Applicant/Sponsor Name:	Exela Pharma Sciences, LLC
FDA Received Date:	December 11, 2018
OSE RCM #:	2017-1073-1
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Sarah K. Vee, Pharm.D.

1 PURPOSE OF MEMORANDUM

Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the revised carton labeling and container label for (b) (4) (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

The revised carton labeling and container label are unacceptable from a medication error perspective. We requested the applicant to revise the strength presentation statement (b) (4) to 500 mg/10 mL to be consistent with the prescribing information. The applicant has incorrectly stated (b) (4) instead of "500 mg".

[a] The established name was revised as per Office of Pharmaceutical Quality (OPQ) recommendation.
[b] Abraham, S. Label and Labeling Review for (b) (4) (NDA 210660). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Nov 29. RCM No.:2017-1073.

3 RECOMMENDATIONS FOR EXELA PHARMA SCIENCES, LLC

We recommend the following be implemented prior to approval of this NDA:

A. Both Carton Labeling and container label:

1. Revise the strength presentation statement (b) (4) to 500 mg/10 mL to be consistent with the prescribing information. Currently, you have it incorrectly stated as (b) (4) instead of "500 mg".

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON DECEMBER 11, 2018

Container label

Carton labeling

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/s/

SHERLY ABRAHAM
12/13/2018

SARAH K VEE
12/13/2018

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 29, 2018
Requesting Office or Division:	Division of Gastrointestinal and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 210660
Product Name and Strength:	(b) (4) (L-cysteine hydrochloride) injection, 50 mg/mL
Total Product Strength:	500 mg/10 mL
Product Type:	Single-ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Exela Pharma Sciences, LLC
Submission Dates:	July 27, 2018 October 9, 2018
OSE RCM #:	2017-1073
DMEPA Primary Reviewer:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Sarah K. Vee, Pharm.D.

1 REASON FOR REVIEW

This review evaluates the labels and labeling for (b) (4) (NDA 210660), 505 (b)(2) NDA, submitted on July 27, 2018. The Division of Gastroenterology and Inborn Error Products (DGIEP) requested that DMEPA review the proposed prescribing information (PI), container label, and carton labeling for any areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Exela Pharma Sciences, LLC submitted a 505 (b) (2) NDA for (b) (4) on July 27, 2018. The reference listed drug (RLD) for this product is Cysteine Hydrochloride Injection, USP, 7.25% (NDA 19523), which was withdrawn from the market on June 16, 2006. RLD was not withdrawn for reasons of safety and effectiveness and currently there is no approved L-Cysteine Hydrochloride Injection formulation on the market.

We identified areas in the Prescribing Information (PI), container label, and carton labeling that can be improved to increase the clarity of information to promote the safe use of the product. We communicated recommendations on the PI directly to DGIEP and the recommendations for the Applicant are listed below in Section 4.1.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI, container label, and carton labeling can be improved to increase the clarity of information to promote the safe use of the product. We provide our recommendations in Section 4.1 below.

4.1 RECOMMENDATIONS FOR EXELA PHARMA SCIENCES LLC

We recommend the following be implemented prior to approval of this NDA:

A. Both Carton Labeling and container label:

1. The established name is not at least half the size of the proprietary name. Revise the established name to be in accordance with 21 CFR 201.10(g)(2).

2. Revise the strength presentation statement [redacted] (b) (4) to 500 mg/10 mL to be consistent with the prescribing information.

3. Consider revising and combining the statements [redacted] (b) (4) to "Must be diluted. For intravenous infusion only". We recommend this to minimize the risk of administering the drug as an intravenous bolus.[a]

4. Consider combining the statements "Single-Dose Vial", "Discard unused portion" to read "Single-Dose Vial – Discard Unused Portion" to minimize risk of the entire contents of the vial being given as a single dose.[a]

5. As per 21 CFR 201.55, add the usual dosage statement "Usual dose: see prescribing information" to the side panel.

6. If space permits, information on post-admixing storage should also be included on the labels. These instructions will inform persons responsible for preparing the product and minimize the risk of administering expired products.
7. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as:

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[a] Draft Guidance for Industry: Safety Consideration for container labels and carton labeling design to minimize medication errors. 2013.
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for (b) (4) received on July 27, 2018, from Exela Pharma Sciences, LLC.

Relevant Product	Information for (b) (4)
Initial Approval Date	N/A
Active Ingredient	L-cysteine hydrochloride
Indication	(b) (4) is indicated for: Meeting the intravenous amino acid nutritional requirements of infants and adults Adult and pediatric patients with severe liver disease who may have impaired enzymatic processes and require TPN As an additive to amino acid solutions providing a more complete profile of amino acids for protein synthesis
Route of Administration	Intravenous infusion
Dosage Form	injection
Strength	500 mg/10 mL (50 mg/mL)
Dose and Frequency	(b) (4)
How Supplied	500 mg/10 mL (50 mg/mL) in 10 mL single-dose vials, packaged as 10 per carton

Storage	Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature]. Avoid excessive heat. Protect from freezing.
Reference Listed Drug (RLD)	Cysteine Hydrochloride Injection, USP, 7.25% (NDA 19523)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following (b) (4) labels and labeling submitted by (b) (4) on October 9, 2018.

- Container label received on October 9, 2018
- Carton labeling received on October 9, 2018
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

Container label:

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SHERLY ABRAHAM
11/29/2018

SARAH K VEE
11/29/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: November 15, 2018 **Date Consulted:** June 21, 2017

From: Jane Liedtka M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Thao Vu, Regulatory Project Manager (RPM)
Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: (b) (4) Cysteine HCl injection, (b) (4)

NDA: 210660

Indication: (b) (4) Cysteine Hydrochloride Injection, USP is an amino acid indicated (b) (4)

- to meet the nutritional requirements of newborn infants requiring total parenteral nutrition (TPN)
- for adult and pediatric patients with severe liver disease who may have impaired enzymatic processes and require TPN
- to provide a more complete profile of amino acids for protein synthesis.

Applicant: Exela Pharma Sciences, LLC

Subject: Pregnancy and Lactation labeling [New non-NME 505(b) (2) NDA, Fast Track, Rolling Review]

Materials Reviewed:

- Applicant's submitted background package for NDA 210660 submitted on May 23, 2017.
- Agency request (IR) for review of published clinical literature with regards to L-cysteine use in pregnancy and lactation on June 22, 2017.
- Applicant's a review of published clinical literature with regards to L-cysteine use in pregnancy and lactation, submitted on July 3, 2017.

Consult Question: New NDA labeling review and PLLR conversion

INTRODUCTION AND BACKGROUND

On June 21, 2017, DGIEP consulted DPMH to provide input for appropriate format and content of the pregnancy and lactation sections of (b) (4) Cysteine HCl injection, (b) (4) labeling to be in compliance with the Pregnancy and Lactation Labeling (PLLR) format.

- The listed drug relied upon for this 505(B)(2) submission is NDA 19523, Cysteine hydrochloride (HCl) 7.5% for injection, which was originally approved in the U.S. on October 22, 1986 for 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. Cysteine HCl can also be added to amino acids solutions to provide a more complete profile of amino acids tor protein synthesis. The product was never marketed. NDA 19523 was withdrawn/ discontinued (not for reasons of safety or efficacy) in 2010. Currently there are no approved cysteine HCl for intravenous (IV) injection products marketed in the United States.
- On May 23, 2017, Exela Pharma Sciences, LLC submitted a new non-NME NDA 210660.
- On June 22, 2017, the Agency requested a review of published clinical literature with regards to L-cysteine use in pregnancy and lactation.
- On July 3, 2017, the Applicant submitted the requested information.
- On July 21, 2017, the submission was given Fast Track designation with Rolling Review status.
- On July 27, 2018, the submission was completed, and the NDA was acknowledged. The PDUFA date for the priority review is January 27, 2019.

<u>Current State of the Labeling</u>

- L-Cysteine HCl has no currently approved labeling since the listed drug (LD) relied upon was withdrawn in 1986. The 1986 labeling for the LD is in the old format.
- L-Cysteine HCl has a contraindication to "direct injection into a peripheral vein" due to "the acidity of the solution" and potential for phlebitis.
- L-Cysteine HCl has a Warning and Precaution that the product is "to be administered only as a component of an admixture of parenteral nutrients" since it is a hypertonic solution.
- L-Cysteine HCl is categorized as "Pregnancy Category C", "animal studies have not been conducted" and "It is also not known whether 7.25% Cysteine Hydrochloride Injection, USP can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity…should be given to a pregnant woman only if clearly needed".

- L-Cysteine HC 1986 label states "In the adult, cysteine is synthesized from methionine via the transsulfuration pathway. However, in newborn infants' maturation of the enzyme system needed to convert methionine to cysteine is not complete; therefore, cysteine is generally considered an essential amino acid in infants. In addition, adult and pediatric patients with severe liver disease may have an impairment of the enzymatic conversion of methionine to cysteine.
- There is no mention of nursing, lactation or breastfeeding in the 1986 label for the LD.

REVIEW

Pregnancy

Nonclinical Experience

According to the pharmacology/toxicology reviewer, none of the published data regarding nonclinical studies for L-cysteine meets FDA standards so no nonclinical studies will be included in labeling.

Applicant's Review of Literature

A review of the published literature was conducted by the Applicant using the following databases: Google, Google Scholar, Science Direct, PubMed, FDA Pregnancy Registries, CDC.gov, Cochrane Library, Medline, LactMed (TOXNET), DART (TOXNET), Motherisk, OTIS/MotherToBaby, UpToDate, MedWatch, the European Drug Consumption Database and ADR Database, with regards to L-Cysteine use in pregnancy. The applicant cites the following publications regarding L-cysteine (none of which have exposure during pregnancy as subject matter):

- The Authors' conclusions from a Cochrane review[1] of cysteine chloride use in parenterally fed neonates (mostly preterm infants) - six trials [five small, of which three were randomized and two used blind allocation and one large randomized controlled trial (RCT)] are summarized below:

  > Available evidence from randomized clinical trials shows that routine short-term cysteine chloride supplementation of cysteine-free parenteral nutrition in preterm infants improves nitrogen balance. However, there is insufficient evidence to assess the risks of cysteine supplementation, especially regarding metabolic acidosis, which has been reported during the first two weeks of cysteine chloride administration. Available evidence from a large RCT does not support routine N-acetylcysteine (NAC) supplementation of cysteine-containing PN in extremely low birth weight infants (NAC is a precursor of cysteine that undergoes de-acetylation in the small intestine and in the liver and serves as a source of sulfhydryl groups and as a stimulus to the production of glutathione)…We conclude that present data are insufficient to justify routine addition of cysteine to the intravenous nutrition of newborn infants that does not contain cysteine. Available evidence does not support routine

[1] Soghier, LM and Brion, LP. Cysteine, cystine or N-acetylcysteine supplementation in parenterally fed neonates. Cochrane Database Syst Rev. 2006; 18(4): CD004869.

addition of NAC to intravenous nutrition of newborn infants not containing cysteine.

- A single case study[2] concluded that excess sulfite and cysteine toxicity may be involved in causing amyotrophic lateral sclerosis (ALS). Elevated plasma cysteine has been reported in patients with ALS prior to the case study reported. In the reported case, the patient (53-year old female) exhibited elevated levels of sulfur, cysteine, sulfite, glutamate and low whole blood glutathione. Strict dietary and supplement measures normalized the patient's whole blood glutathione, blood cysteine, and urine sulfite. The authors' concluded that patients suffering from ALS need to be monitored for excess amounts of sulfur and cysteine received through diet and supplements.

DPMH's Review of Literature

DPMH conducted a search of published literature in Embase using the search terms "L-cysteine and pregnancy," "L-cysteine and pregnant women," "L-cysteine and pregnancy and birth defects," "L-cysteine and pregnancy and congenital malformations," "L-cysteine and pregnancy and stillbirth," "L-cysteine and spontaneous abortion" and "L-cysteine and pregnancy and miscarriage." No reports of adequate and well-controlled studies of L-cysteine use in pregnant women were found. No published case reports involving use of L-cysteine in pregnant patients were identified.

A notation regarding L-cysteine in Micromedex[3] states that it is a pregnancy category C drug.

In the Reprotox[4] database the authors' stated

> Cysteine is a naturally-occurring amino acid. Excessively high dose levels of cysteine produced toxicity in neonatal rodents. The dose of cysteine that might be harmful in humans, if any, is unknown… Cysteine is transferred across the placenta, and the placenta appears to concentrate this amino acid, perhaps by using it in the production of glutathione[5]… A possible role of cysteine deprivation in very low birth weight pregnancies has been proposed by French clinicians[6].

L-cysteine is not referenced in Briggs,[7] but NAC[2] is, and the authors' Pregnancy Recommendation is "Compatible—Maternal Benefits >> Embryo-Fetal Risk".
The authors provide nonclinical study results and state that the product crosses the placenta. The authors also cite several reports of NAC use to treat acetaminophen overdose in pregnancy which are summarized below:

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[2] Woolsey, PB. Cysteine, sulfite, and glutamate toxicity: a cause of ALS? J Altern Complement Med, 14(9): 1159-64, 2008.
[3] Truven Health Analytics information, http://www micromedexsolutions.com/. Accessed 7/1/16.
[4] Reprotox® Website: www.Reprotox.org. Accessed on October 31, 2018.
[5] Malloy MH, Rassin DK, McGanity WJ. Maternal-fetal cyst(e)ine transfer. Biol Neonate. 1983; 44:1-9.
[6] Kuster A et al. Cord blood glutathione depletion in preterm infants: correlation with maternal cysteine depletion. PLoS One. 2011; 6(11):e27626. doi:10.1371/journal.pone.0027626.
[7] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2015). Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.

In a study of three pregnant women[8] who delivered viable infants while undergoing treatment for acetaminophen toxicity, the mean acetylcysteine cord blood concentrations was 9.4 mcg/mL (range 8.6-10.9 mcg/mL). The corresponding maternal serum concentrations (trough levels, 4 hours after a dose) ranged from 7.2-11.8 mcg/mL. In a fourth nonviable infant delivered at 22 weeks' gestation, the acetylcysteine level in a postmortem cardiac blood sample obtained 48 hours after death was 55.8 mcg/mL. The mean cord blood level was within the range associated with therapeutic acetylcysteine doses in adults. No adverse effects attributable to acetylcysteine or acetaminophen were observed in the three viable infants, nor was there evidence of acetaminophen toxicity in the fourth infant.

In a 1989 study from the Rocky Mountain Poison and Drug Center, covering 1976-1985, pregnancy outcomes were available for 60 of the 110 women who had an acute acetaminophen overdose during gestation[9]. Of the 60 women, 24 were treated with IV acetylcysteine (4 in the 1st trimester) for toxic acetaminophen serum levels. The outcomes of the 24 cases were 14 viable infants (2 premature), 3 spontaneous abortions (SABs), 5 elective abortions (TABs), 1 stillbirth, and 1 maternal death. In the stillbirth case, the mother overdosed at 33 weeks' gestation with fetal death occurring 2 days later. An autopsy of the fetus revealed massive centri-lobular hepatic necrosis that was consistent with acetaminophen-induced hepatotoxicity. Of the five potential independent variables evaluated, only two were significantly predictive of pregnancy outcome: time to start of acetylcysteine and gestational age. The probability of fetal death increased the longer it took to receive the antidote and the lower the gestational age. One infant was reported to have a mild positional deformity of the feet. No other congenital defects were reported[10].

A 1997 study from a teratology information service in England reported the pregnancy outcomes of 300 cases of acute acetaminophen overdose.[11] A total of 33 mothers were treated with IV acetylcysteine. The outcomes of these cases were 24 normal infants, 3 SABs or fetal deaths, 5 elective terminations, and 1 infant with hypospadias. There was no relationship between the defect and either acetaminophen or acetylcysteine due to the timing of exposure. None of the other adverse outcomes were related to acetylcysteine[10].

Pharmacovigilance Database Summary

The Applicant did not conduct any clinical studies for this submission so there is no PVDB.

[8] Horowitz RS et al. Placental transfer of N-acetylcysteine following human maternal acetaminophen toxicity. Clin Toxicol. 1997; 35:447-51.

[9] Riggs BS et al. Acute acetaminophen overdose during pregnancy. Obstet Gynecol. 1989; 74:247-53.

[10] McElhatton PR, Sullivan FM, Volans GN. Paracetamol overdose in pregnancy: analysis of the outcomes of 300 cases referred to the teratology information service. Reprod Toxicol 1997; 11:85-94.

Lactation

Applicant's Review of Literature

A review of the published literature was conducted by the Applicant using the following databases: Google, Google Scholar, Science Direct, PubMed, FDA Pregnancy Registries, CDC.gov, Cochrane Library, Medline, LactMed (TOXNET), DART (TOXNET), Motherisk, OTIS/MotherToBaby, UpToDate, MedWatch, the European Drug Consumption Database and ADR Database, with regards to L-Cysteine use in lactation. No relevant literature was identified.

DPMH Review of Literature

DPMH conducted a search of *Medications and Mother's Milk*[11], the Drugs and Lactation Database (LactMed),[12] Micromedex[3], and of published literature in Embase using the search terms "L-cysteine and lactation" and "L-cysteine and breastfeeding." No reports of adequate and well-controlled studies of L-cysteine use in lactating women were found. No published case reports involving lactation in L-cysteine patients were identified.

No mention of L-cysteine was found in *Medications and Mother's Milk*[14].

L-cysteine is not referenced in LactMed, but NAC is and the "Summary of Use during Lactation" states

> No information is available on the use of NAC during breastfeeding. If oral or intravenous NAC is required by the mother, it is not a reason to discontinue breastfeeding. To avoid infant exposure, nursing mothers may consider pumping and discarding their milk for 30 hours after administration.

L-cysteine is not referenced in Briggs, [7] but NAC is and the authors' breastfeeding recommendation is "No Human Data—Probably Compatible". In the breastfeeding summary, the authors; state

> No reports have described the use of acetylcysteine during lactation. Although the molecular weight of the drug (≈163) is low enough for excretion into breast milk, the various conditions in which acetylcysteine is used suggest that the drug will rarely be prescribed during breastfeeding. Moreover, IV acetylcysteine has been administered directly to preterm neonates for

[11] Hale, Thomas (2012) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing, pg. 422-423.

[12] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

therapeutic indications, at doses far above those that would be obtained from milk, without causing toxicity[13, 14].

Literature on the use of L-cysteine in neonates

As previously discussed in this review under "Applicant's Review of Literature" for pregnancy, there is a body of literature on the use of L-cysteine supplementation of TPN given directly to neonates (including premature and very low birth weight neonates). The Cochrane Review by Soghier[1] (2006) describes 6 publications.

- The largest, by Ahola[15] (2003) involved 391extremely low birth weight infants (500-999gms), half of whom received N acetylcysteine supplementation to their TPN. The authors note that "No differences were found between the treatment groups in blood pressure or in laboratory tests during the first 2 weeks of life. No adverse effects were observed that could be ascribed to NAC."
- One of the small studies, reported by Zlotkin[16](1981), involved 28 infants (17 of whom were premature with a mean gestational age of 31 weeks). They were divided equally into either TPN + cysteine or TPN alone. The authors reported "None of the following biochemical and hematological parameters were affected by the parenteral cysteine supplementation: hemoglobin, hematocrit, platelet count, Na, K, Cl, BUN, Ca, P, and acid-base status".
- The other four studies (all small) did not address adverse effects in the publication.

Reviewer's Comments

Limited published literature on cysteine supplementation of TPN in neonates does not report an increase in adverse events.

Use in Females and Males of Reproductive Potential

Applicant's Review of Literature

A review of the literature regarding L-cysteine and its effects on fertility was not recieved by the Agency.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMED and Embase regarding L-cysteine and its effects on fertility and found no relevant articles regarding the topic.

DISCUSSION AND CONCLUSIONS

Pregnancy

[13]Ahola TM et al. Pharmacokinetics of intravenous N-acetylcysteine in preterm neonates (abstract). Pediatr Res 1998; 43(Suppl 2):163.

[14] Isbister GK et al. Paracetamol overdose in a preterm neonate. Arch Dis Child Fetal Neonat Ed. 2001;85:F702.

[15] Ahola T et al. N-acetylcysteine does not prevent bronchopulmonary dysplasia in immature infants: a randomized controlled trial. J Pediatr. 2003; 143: 713-9.

[16] Zlotkin SH et al. Cysteine supplementation to cysteine-free intravenous feeding regimens in newborn infants. American Journal of Clinical Nutrition.1981; 34: 914-23.

Human pregnancy outcome data for L-cysteine was not found in the published literature. The findings in animal studies found in published literature did not meet FDA standards; therefore, the animal reproduction studies will not be discussed further. Cysteine is a nonessential amino acid that is typically found in high protein foods (meat, eggs, dairy, garlic, onions, broccoli, lentils, etc) and is part of a normal human diet. Published literature suggests that, in neonates, maturation of the enzyme system needed to convert methionine to cysteine is not complete; therefore, cysteine is generally considered an essential amino acid in infants. Appropriate administration of L-cysteine is not expected to be harmful during pregnancy. See DPMH proposed labeling below for further details.

Lactation

There are no data available on the presence of L-cysteine in human or animal milk, its effects on the breastfed infant or on milk production. Some pharmacokinetic parameters such as a molecular weight of ≈ 121 Daltons suggest it could be present in milk. Available information from studies of L-cysteine given to neonates as part of TPN do not suggest an increase in adverse events. The dose of L-cysteine that could potentially get into breastmilk is expected to be lower than the dose that neonates receive as part of TPN. In addition, L-cysteine is an essential amino acid that newborns need as part of their diet and administration of L-cysteine to a lactating woman and is not expected to be harmful during lactation. Therefore, DPMH recommends that the breastfeeding risk/benefit statement that allows for breastfeeding be included in subsection 8.2 of labeling. See DPMH proposed labeling below for further details.

Females and Males of Reproductive Potential

There are no human data available on the effect of L-cysteine on fertility. There are no animal studies of the effects on fertility. Therefore, DPMH recommends that subsection 8.3 be omitted from labeling.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1 and 8.2 of L-cysteine labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with DGIEP on November 27, 2018. DPMH refers to the final NDA action for final labeling.

DPMH Proposed L-Cysteine Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Appropriate administration of (b) (4) is not expected to cause major birth defects, miscarriage or adverse maternal or fetal outcomes.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major

birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

Data available on the effects of (b) (4) on infants, either directly or through breastmilk, do not suggest a significant risk of adverse events from exposure. Although there are no data on the presence of (b) (4) in human or animal milk or the effects on milk production, appropriate administration of (b) (4) is not expected to cause harm to a breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for (b) (4) and any potential adverse effects on the breastfed infant from (b) (4) or from the underlying maternal condition.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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11/15/2018

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11/16/2018