CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215040Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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:	February 1, 2024
Requesting Office or Division:	Division of Hepatology and Nutrition (DHN)
Application Type and Number:	NDA 215040
Product Name, Dosage Form, and Strength:	Legubeti (acetylcysteine) for oral solution, 500 mg and 2.5 grams
Applicant/Sponsor Name:	Galephar Pharmaceutical R
TTT ID #:	2022-635-3
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container (packet) labels and carton labeling received on January 31, 2024 for Legubeti. The Division of Hepatology and Nutrition (DHN) requested that we review the revised container labels and carton labeling for Legubeti (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[abc]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional

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

[a] Getahun, S. Memorandum Review of Revised Label and Labeling for Legubeti (NDA 215040). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JAN 30. TTT ID No.: 2022-635-2.

[b] Getahun. L. Memorandum Label and Labeling Review for Legubeti (NDA 215040). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 NOV. TTT ID No.: 2022-635-1

[c] Getahun. L. Label and Labeling Review for Legubeti (NDA 215040). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JAN 24. TTT ID No.: 2022-635.

Reference ID: 5321277

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/s/

SOFANIT N GETAHUN
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VALERIE S VAUGHAN
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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:	January 30, 2024
Requesting Office or Division:	Division of Hepatology and Nutrition (DHN)
Application Type and Number:	NDA 215040
Product Name, Dosage Form, and Strength:	Legubeti (acetylcysteine) for oral solution, 500 mg and 2.5 grams
Applicant/Sponsor Name:	Galephar Pharmaceutical Research Inc.
TTT ID #:	2022-635-2
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container (packet) labels and carton labeling received on January 24, 2024, and January 25, 2024 for Legubeti. The Division of Hepatology and Nutrition (DHN) requested that we review the revised container labels and carton labeling for Legubeti (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a,b]

2 DISCUSSION

The Applicant adequately addressed most of our recommendations except for our recommendation to ensure sufficient differentiation between the 500 mg 10-count *versus* 20-count and 2.5 grams 10-count *versus* 20-count carton labeling. We note that the Applicant's proposed mitigation to utilize the equivalency statement to address differentiation between the net quantities of each carton increases the risk of confusion. As such, we communicated to the review team that from a med error perspective, the equivalency statement should describe

[a] Getahun. L. Label and Labeling Review for Legubeti (NDA 215040). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JAN 24. TTT ID No.: 2022-635.

[b] Getahun. L. Memorandum Label and Labeling Review for Legubeti (NDA 215040). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 NOV. TTT ID No.: 2022-635-1.

Reference ID: 5319080

the amount of drug per packet rather than per carton (e.g., "Each packet of Legubeti 500 mg is equivalent to 948 mg acetylcysteine lysine" *instead of* [redacted (b) (4)]), which was communicated to the Applicant. On January 25, 2024, the Applicant responded[c] to our recommendation with an updated carton labeling. We considered that because Legubeti is intended for use in a healthcare setting only, the net quantity statements "Contains 10 packets…" and "Contains 20 packets…" are acceptable.

Additionally, we note the inclusion of the statement [redacted (b) (4)] on the principal display panel of the packet labels and side panel of the carton labeling. References to specific sections of the Prescribing Information may change over time. Thus, we recommend revising the statement to refer to the Prescribing Information instead.

We also reviewed the revised Patient Packet Insert (PPI) received on January 24, 2024, taking into consideration that Legubeti is for use in a healthcare setting only. We note the [redacted (b) (4)] section could be misinterpreted as providing instruction for patient or caregiver administration. Therefore, we recommend the [redacted (b) (4)] section be revised to better communicate how this product is intended to be administered.

3 CONCLUSION

From a medication error perspective, the revised labels and labeling are not acceptable. Thus, we include additional recommendations for the Division in Section 4 and for the Applicant in Section 5.

4 RECOMMENDATIONS FOR DIVISION OF HEPATOLOGY AND NUTRITION (DHN)

A. Revise the Patient Packet Insert (PPI) to better communicate how Legubeti is intended to be used. For example, revise the heading [redacted (b) (4)] to *How should I receive Legubeti?* We defer to the Division of Medical Policy Programs (DMPP) Patient Labeling Team to determine additional edits to the patient labeling, as appropriate.

5 RECOMMENDATIONS FOR GALEPHAR PHARMACEUTICAL RESEARCH INC.

From a medication error perspective, we recommend the following be implemented prior to approval of this NDA:

A. We note the inclusion of the statement [redacted (b) (4)] on the principal display panel (PDP) of the packet labels and side panel of the carton labeling. Given that specific subsections within the Prescribing Information may change over time, we recommend removing specific reference to [redacted (b) (4)] of the Prescribing Information. We recommend revising the statement to "See Prescribing Information."

[c] Jan 25, 2024, FDA Correspondence (NDA 215040 Legubeti). Humacao (Puerto Rico): Galephar Pharmaceutical Research Inc; 2024 JAN 25. Available from: \\CDSESUB1\EVSPROD\nda215040\0019\m1\us\112-other-correspondence\jan-25-2024-fda-correspondance.pdf

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Prescribing Information and Patient Packet Insert (Image not included) received January 24, 2024, available from: \\CDSESUB1\EVSPROD\nda215040\0018\m1\us\114-labeling\draft\labeling\draft-labeling-text-pdf.pdf

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

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

Memorandum

Date: January 10, 2024

To: Chinedu Ebonine, Pharm.D., Project Manager, DHN

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

CC: Adewale Adeleye, Pharm.D., Team Leader, OPDP

Subject: OPDP Labeling Comments for **LEGUBETI (acetylcysteine) for oral solution**

NDA: 215040

In response to DG's consult request dated September 7, 2023, OPDP has reviewed the proposed product labeling (PI), Patient Prescribing Information (PPI), and carton/container labeling for Legubeti.

Labeling: OPDP has some comments on the proposed labeling based on the draft labeling received by electronic mail from DG on December 18, 2023.

OPDP comments on the proposed Patient Labeling was sent under separate cover, as a combined OPDP and Division of Medical Policy Programs (DMPP) review.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room, and we do not have any comments.

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

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MEETA N PATEL
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 4, 2024
To:	Chinedu Ebonine Regulatory Project Manager **Division of Hepatology and Nutrition (DHN)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	LEGUBETI (acetylcysteine)
Dosage Form and Route:	for oral solution
Application Type/Number:	NDA 215040
Applicant:	Galephar Pharmaceutical Research Inc.

1 INTRODUCTION

On August 9, 2023, Galephar Pharmaceutical Research Inc. submitted for the Agency's review a resubmission to their original New Drug Application (NDA) 215040. Reference is made to the original NDA 215040, submitted on July 7, 2022, for LEGUBETI (acetylcysteine) for oral solution, indicated as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen. Reference is also made to the Complete Response (CR) letter from FDA dated May 05, 2023. The purpose of this resubmission is to provide a compete response to the deficiencies outlined in the CR.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hepatology and Nutrition (DHN) on September 8, 2023 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for LEGUBETI (acetylcysteine) for oral solution.

2 MATERIAL REVIEWED

- Draft LEGUBETI (acetylcysteine) PPI received on August 9, 2023, and received by DMPP and OPDP on December 18, 2023.
- Draft LEGUBETI (acetylcysteine) Prescribing Information (PI) received on August 9, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 18, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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MARCIA B WILLIAMS
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LASHAWN M GRIFFITHS
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

M E M O R A N D U M

From: Ndidi Nwokorie, MD Medical Officer
Division of Pediatrics and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
DPMH, ORPURM, OND

John J. Alexander, MD, MPH, Deputy Director
DPMH, ORPURM, OND

To: Division of Hepatology and Nutrition (DHN)
Office of Immunology and Inflammation

Subject: Pediatric Labeling Review

Applicant: Galephar Pharmaceutical Research Inc.

Application number: NDA 215040

Drug: Legubeti™ (acetylcysteine-lysine)

Drug Class: Acetaminophen Toxicity Antidote

Proposed Indication: As an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen.

Proposed Dosage: Loading dose: 140 mg/kg.

Maintenance doses: 70 mg/kg repeated every 4 hours for a total of 17 doses

Route of administration: Oral

Dosage Form: Powder for oral solution

Dosage Strengths: 500 mg and 2.5 gm sachets

Materials Reviewed:

Documents entered in DARRTS under NDA 215040

- Complete Response Letter May 5, 2023
- DPMH Memorandum NDA-215040 Legubeti™ (acetylcysteine lysine) April 14, 2023
- DPMH Addendum NDA-215040 Legubeti™ (acetylcysteine lysine) May 15, 2023

Reference ID: 5291198

Documents submitted to DocuBridge

- Agreed iPSP under IND 130190 on April 15, 2020
- Response to FDA Complete Response Letter under NDA 215040 on August 9, 2023

Consult Request:

DHN consulted DPMH to assist in the review of this resubmission of this new drug application (NDA) 215040, containing the Applicant's response to a Complete Response Letter (CRL) dated May 5, 2023.

I. Purpose

The Applicant is seeking approval for Legubeti (acetylcysteine lysine) as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen.[1] The Applicant originally submitted a new drug application, (NDA) on July 7, 2022, under the 505(b)(2) pathway, relying on Mucomyst, NDA 013601, as the listed drug (LD). The Division issued the Complete Response (CR) due to the following deficiencies:

- Lack of data demonstrating "the tolerability of Legubeti, the lysine salt of acetylcysteine, for the full range of loading and maintenance doses for patients with all body weights proposed in labeling."[2]
- Lack of "adequate information to support the safety of L-lysine administration to pediatric patients weighing down to 1 kg."[2]

To resolve these deficiencies, the Division asked the Applicant to conduct a palatability and tolerability study in adults at clinically relevant doses and to submit "additional information (e.g., published literature or a study) to justify the safety of the L-lysine exposure" anticipated at the proposed dosage in pediatric patients down to 1 kg for the proposed indication. FDA received the Applicant's resubmission addressing these deficiencies on August 14, 2023.

This addendum provides DPMH's assessment of the Applicant's resubmission. For additional background, please refer to DPMH reviews dated April 14, 2023, and May 15, 2023, entered into DARRTS under NDA 215040.

II. DPMH Discussion of NDA 215040 Resubmission

Palatability and Tolerability

The Applicant conducted a phase 1, double-blind, randomized, cross-over study to evaluate the palatability of Legubeti for oral solution versus acetylcysteine solution in healthy adults to

[1] Cover Letter dated July 7, 2022

[2] Complete Response Letter May 5, 2023_NDA 215040

Reference ID: 5291198

demonstrate equivalence in terms of palatability, tolerability, and safety between the products. The Applicant reported difficulty accessing the comparator (LD) and the corresponding generic drug due to shortages but was able to obtain a generic formulation (acetylcysteine 20% solution, USP; Fresenius Kabi LLC, USA) approved by the FDA for the same use. The Applicant was unable to procure adequate amounts of comparator needed for multiple dosing, thus performing tolerability and palatability comparison on the loading dose (140 mg/kg) alone.

The study included 24 healthy, non-smoking, male and female volunteers, 18 years of age or older, with a body mass index (BMI) ≥19 and ≤35 kg/m^2. Subjects fasted 10 hours prior to and 4 hours post-drug administration. All subjects received a single loading dose of assigned drug product according to dosing instructions with a 7-day wash-out period between administration of the two drugs. Safety monitoring included daily temperature assessment, vital signs (pre-dose and 0.5,2,4,8,12, and 23 hours post-dose), ECG (pre-dose and 2-, 6-, and 23-hours post-dose), clinical laboratory tests and health monitoring and adverse events throughout the study. Subjects completed a palatability questionnaire within 10 minutes of receiving each dose of the study drug. The questionnaire assessed the following:

- Palatability
- Mouth feel
- Initial taste
- Overall likeability
- Color of the product
- Appearance of the drug product

Results showed an overall equivalence between Legubeti and the reference product (acetylcysteine 20% solution, USP; Fresenius Kabi USA, LLC, USA). In terms of overall likeability, trial subjects disliked both products (test drug- 66.7% and RLD -54.2%). (b) (4)

Pediatric patients are currently typically treated with intravenous preparations of acetylcysteine because of the tolerability and palatability challenges with approved oral acetylcysteine products. (b) (4) As discussed elsewhere,[4] the use of NGTs in pediatric patients is associated with complications such as misplacement, the need to assess placement prior to use, and poor patient compliance with tube placement and retention. Patients often pull-out the tubing, requiring staff to replace the tube. In addition, NGT placement often

[3] Agreed iPSP submitted to DocuBridge under IND 130190 on April 15, 2020

[4] DPMH Memorandum NDA-215040 LegubetiTM (acetylcysteine lysine) April 14, 2023

requires skilled personnel at institutions with dedicated pediatric staff who may not be available at all institutions where overdose-pediatric patients initially present. All these challenges to oral use potentially lead to delay or failure of administration of the full dosage required to adequately treat an acetaminophen overdose.

(b) (4)

These study results alone are not sufficient to justify not approving the product in the target pediatric population if the Applicant is otherwise able to demonstrate bioequivalence of this product to the LD and there are no unique product-specific safety issues relevant to pediatric patients. DPMH notes that two previously approved oral NAC products were discontinued from marketing for reasons unrelated to safety or efficacy.

Lysine Safety in Pediatric Patients

The NDA resubmission contained additional publications to support the safety of the lysine content of this product at the proposed dosage in term and pre-term infants weighing down to 1 kg. The Applicant noted that publications and information regarding daily requirement and safety of lysine in preterm infants were rare to non-existent but submitted one relevant publication[5] that described that, diets consisting of enterically administered formula delivered 170 mg/kg/d to 256 mg/kg/d of lysine to infants. In addition, DPMH reviewed a publication evaluating the nutritional impact of protein hydrolysate formulas in healthy term infants,[6] which provided the amino acid composition of breast milk and select infant formulas; 2 casein-hydrolysate (CH) formulas (CH-1-Nutramigen and an experimental formula), one whey protein formula (WH) and a powdered whey- predominant, regular milk-based formula (RF). Based on the lysine content of these formulas, this reviewer calculated that the daily intake of lysine a 3-kg infant would be expected to receive per day ranges from 212 mg/kg/d to 392 mg/kg/d.

Table 1 lists the lysine content of breastmilk and common infant formulas. Based on this information, this reviewer calculated the expected daily intake of lysine in a 3 kg newborn who is exclusively breastfed or exclusively fed with a regular milk-based formula or an elemental formula.

[5] Lisha Huang, Jacomine E Hogewind-Schoonenboom, Femke de Groof, Jos WR Twisk, Gardi J Voortman, Kristien Dorst, Henk Schierbeek, Günther Boehm, Ying Huang, Chao Chen, Johannes B van Goudoever, Lysine requirement of the enterally fed term infant in the first month of life, The American Journal of Clinical Nutrition, Volume 94, Issue 6, December 2011, Pages 1496–1503, https://doi.org/10.3945/ajcn.111.024166

[6] Hernell O, Lonnerdal B. Nutritional evaluation of protein hydrolysate formulas in healthy term infants: plasma amino acids, hematology, and trace elements. Am J Clin Nutr 2003;78:296–301

Reference ID: 5291198

Lysine content of BM: 6050 µmol/L = 88.445 mg/100 mL = 0.8844 mg/mL[7]

- 3 kg newborn ingesting and average of 2 -3 ounces of breast milk every 2-3 hours will ingest about 24 ounces/day (720 mL)
- Lysine intake will be about **212.25 mg/kg/day** roughly. [(720 x 0.8844) / 3]

Lysine content of RF:7877 µmol/L = 115.15 mg/100 mL = 1.1515 mg/mL

- 3 kg newborn ingesting and average of 2 -3 ounces of RF every 2-3 hours will ingest about 24 ounces/day (720 mL)
- Lysine intake will be about **276.36 mg/kg/day** roughly

Lysine content of CH-1(Neutramigen): 11,164 µmol/L = 163.21 mg/100 mL = 1.632 mg/mL

- 3 kg newborn ingesting and average of 2 -3 ounces of CH-1 every 2-3 hours will ingest about 720 mL/day
- Lysine intake will be about **391.68 mg/kg/day** roughly

Table 1.

Amino acid composition of breast milk and of the study formulas[1]

	Breast milk	CH-1	CH-2	WH	RF
			µmol/L		
Arginine	2700	4368	4448	2644	2184
Histidine	1920	3677	3503	2129	2000
Isoleucine	4670	8702	8420	6031	6031
Leucine	9500	14 809	13 916	11 145	9924
Lysine	6050	11 164	11 137	9315	7877
Methionine	1090	3960	3523	1812	1946
Cysteine	1780	2479	1901	2727	1653
Phenylalanine	2990	5515	5127	2727	3091
Tyrosine	2970	2320	2215	2376	2707
Threonine	4850	7815	6697	8908	6303
Tryptophan	994	1471	1716	980	931
Valine	6020	12 222	11 222	7436	7179
Alanine	5770	7640	7382	8427	6067
Aspartic acid	9320	11 429	9835	12 932	9248
Glutamic acid	15 650	29 932	21 816	20 816	17 891
Glycine	4360	6133	4760	3733	3200
Proline	8850	18 261	18 461	5217	8783
Serine	5590	11 238	8790	7143	6762
Taurine	574	320	240	400	360

Source: Hernell O, et al.

CH-1 and CH-2, casein-hydrolysate formula; WH, whey-hydrolysate formula; RF, regular milk formula

[7] Conversion Calculator

Reference ID: 5291198

Despite the paucity of data regarding toxicity of lysine in the pediatric population, the knowledge that breastfed and formula-fed infants routinely receive lysine levels above 200 mg/kg/day as part of their diet is reassuring. The amount of daily lysine intake expected with use of this product at the proposed dosage is 502.6 mg/kg/day, Day 1, and 313 mg/kg/day, Days 2 and 3.

The safety of the lysine content of this product is further supported by nonclinical data from at least one publication[8] which summarized a chronic toxicity study in which rats were fed high supplemental levels of lysine for a 2-year period at levels 170% more than the lysine content of un-supplemented feeds. In the study, there were no adverse clinical, hematological, or pathological effects of the lysine supplementation. Based on these findings, the pharmacology/toxicology team concluded that a juvenile animal study was not needed to further inform the risk in the pediatric population.

III. Conclusion

This NDA resubmission did not contain substantive new safety data to inform the pediatric risk assessment for the lysine content of this product. However, DPMH's analyses of the lysine content of infant formulas and breastmilk coupled with available nonclinical data support conclusion that the lysine content of Legubeti appears to be reasonably safe at the proposed dosage for administration to pediatric patients down to 1 kg body weight. (b) (4) , findings from the completed palatability study in adults alone should not preclude pediatric approval of this product, particularly if other oral NAC products approved for the same indication were not removed from marketing for safety reasons and this product otherwise meets the bioequivalence standard for approval. FDA approved NDA 013601 for Mucomyst in 1963 for the treatment of acetaminophen toxicity, but this drug has been discontinued from marketing due to lack of patient preference and use and not for reasons associated with safety and effectiveness.[9] FDA approved NDA 207916 for Cetylev in 2016, but this drug was also subsequently discontinued from marketing due to poor patient preference and compliance and not for reasons associated with safety or effectiveness.[9]

IV. Recommendation

- DPMH recommends extending approval to the pediatric population consistent with the approved LD labeling.
- The Applicant should be considered to have fulfilled its PREA obligations by bridging this product to the LD, Mucomyst.

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[8] N W Flodin (1997) The metabolic roles, pharmacology, and toxicology of lysine., Journal of the American College of Nutrition, 16:1, 7-21, DOI: 10.1080/07315724.1997.10718644

[9] Email conversation with Dr. George Makar on March 28, 2023

Reference ID: 5291198

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JOHN J ALEXANDER
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MEMORANDUM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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 14, 2023
Requesting Office or Division:	Division of Hepatology and Nutrition (DHN)
Application Type and Number:	NDA 215040
Product Name, Dosage Form, and Strength:	Legubeti (acetylcysteine) for oral solution, 500 mg and 2.5 grams
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Galephar Pharmaceutical Research Inc.
FDA Received Date:	August 14, 2023
TTT ID #:	2022-635-1
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

Reference ID: 5276788

1 REASON FOR REVIEW

As part of the approval process for Legubeti (acetylcysteine) for oral solution, the Division of Hepatology and Nutrition (DHN) requested that we review the proposed Legubeti prescribing information (PI), sachet labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

NDA 215040 is a 505(b)(2) NDA and the listed drug product is Mucomyst, NDA 013601.

On January 24, 2023, we completed review of the proposed PI, sachet labels, and carton labeling for Legubeti submitted to NDA 215040 and provided recommendations to minimize the risk for medication errors.[a] However, on May 5, 2023, NDA 215040 was issued a Complete Response (CR) due to clinical and regulatory deficiencies.[b] As such, our label and labeling recommendations were not communicated to Galephar.

On August 14, 2023, Galephar submitted a Class 2 Resubmission to NDA 215040 to address the deficiencies outline in the Agency's May 5, 2023, CR letter, which is the subject of this review.

2 MATERIALS 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
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

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

[a] Getahun, S. Label and labeling Review for Legubeti (NDA215040). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JAN 24. TTT ID No.: 2022-635.

[b] Ebonine, C. Complete Response for Legubeti. Silver Spring (MD): FDA, CDER, OND, DHN (US); 2023 MAY 05. NDA 215040.

Reference ID: 5276788

3 DISCUSSION

On January 24, 2023, we completed our review of the proposed PI, sachet labels, and carton labeling received on July 7, 2022, August 16, 2022, September 22, 2022, and October 7, 2022.[c] We compared the resubmitted PI, sachet label and carton labeling received on August 14, 2023, with the previous labels and labeling to determine if our previous recommendations under TTT ID No. 2022-635 are applicable to the PI, sachet label, and carton labeling received on August 14, 2023. Additionally, we reviewed the labels and labeling received on August 14, 2023, to determine if there are new areas of vulnerability that may lead to medication error.

We note the Applicant has updated the established name from the salt "acetylcysteine lysine" to "acetylcysteine." However, we did not identify concerns with this proposed revision from a medication error perspective. Thus, the previous recommendations for the PI, sachet label, and carton labeling are applicable to the new PI, sachet label, and carton labeling received on August 14, 2023.

4 CONCLUSION

The proposed PI, sachet labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We refer to our previous review completed on January 24, 2023, under TTT ID No. 2022-635, which provides the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error.

[c] Getahun, S. Label and labeling Review for Legubeti (NDA215040). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JAN 24. TTT ID No.: 2022-635.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. Product Information/Prescribing Information

Table 2 presents relevant product information for Legubeti that Galephar Pharmaceutical Research Inc. received on August 14, 2023, and the listed drug (LD).

<table>
<tr><th colspan="3">Table 4. Relevant Product Information for Listed Drug and Legubeti</th></tr>
<tr><td>Product Name</td><td>Mucomyst</td><td>Legubeti</td></tr>
<tr><td>Initial Approval Date</td><td>September 14, 1962 (Withdrawal FR Effective March 13, 2009)</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td colspan="2">Acetylcysteine</td></tr>
<tr><td>Indication</td><td><u>Inhalation:</u> indicated as adjuvant therapy for patients with abnormal, viscid, or inspissated mucous secretions in several pulmonary conditions.
<u>Orally:</u> indicated as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potential hepatotoxic quantity of acetaminophen.</td><td>Antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen.</td></tr>
<tr><td>Route of Administration</td><td>Inhalation or oral</td><td>Oral</td></tr>
<tr><td>Dosage Form</td><td>solution</td><td>Powder for oral solution</td></tr>
<tr><td>Strength</td><td>10% and 20%</td><td>500 mg and 2.5 grams</td></tr>
<tr><td>Dose and Frequency</td><td>Treatment of Acetaminophen Overdose
<table>
<tr><th colspan="2">Loading Dose</th></tr>
<tr><td>Weight (kg)</td><td>Dose (grams)</td></tr>
<tr><td>100 -109</td><td>15</td></tr>
<tr><td>90-99</td><td>198-218</td></tr>
<tr><td>80-89</td><td>176-196</td></tr>
<tr><td>70-79</td><td>154-174</td></tr>
<tr><td>60-69</td><td>132-152</td></tr>
</table></td><td><u>Pre-Treatment Assessment Following Acute Ingestion</u>:
Obtain a plasma or serum sample to assay for acetaminophen concentration at least 4 hours after ingestion.
If the time of acetaminophen ingestion is unknown:
• Administer a loading dose of LEGUBETI immediately</td></tr>
</table>

50-59	154-174
60-69	132-152
50-59	110-130
40-49	88-108
30-39	66-86
20-29	44-64

Maintenance Dose	
Weight (kg)	Dose (grams)
10-109	7.5
90-99	7
80-89	6.5
70-79	5.5
60-69	5
50-59	4
40-49	3.5
30-39	3
20-29	2

NEBULIZATION—FACE MASK, MOUTHPIECE, TRACHEOSTOMY

1 to 10 mL of the 20% solution or 2 to 20 mL of the 10% solution may be given every 2 to 6 hours; the recommended dose for most patients is 3 to 5 mL of the 20% solution or 6 to 10 mL of the 10% solution 3 to 4 times a day.

NEBULIZATION TENT, CROUPETTE

In special circumstances it may be necessary to nebulize into a tent or Croupette, and this method of use must be

- Obtain an acetaminophen concentration to determine the need for continued treatment
  If the acetaminophen concentration cannot be obtained (or is unavailable or uninterpretable) within the 8-hour time interval after acetaminophen ingestion or there is clinical evidence of acetaminophen toxicity:
- Administer a loading dose of LEGUBETI immediately and continue treatment for a total of 17 doses.
  If the patient presents more than 8 hours after ingestion and the time of acute acetaminophen ingestion is known:
- Administer a loading dose of LEGUBETI immediately
- Obtain acetaminophen concentration to determine need for continued treatment
  If the patient presents less than 8 hours after ingestion and the time of acute acetaminophen ingestion is known and the acetaminophen concentration is known:
- Use the Rumack-Matthew nomogram to determine whether or not to initiate treatment with LEGUBETI

Loading dose: 140 mg/kg

Maintenance doses: 70 mg/kg repeated every 4 hours for a total of 17 doses.

Table1: LEGUBETI Loading Dose

Dissolve LEGUBETI powder in 300 mL of diet cola or other diet soft drinks

individualized to take into account the available equipment and the patient's particular needs. This form of administration requires very large volumes of the solution, occasionally as much as 300 mL during a single treatment period.

DIRECT INSTILLATION

1 to 2 mL of a 10% to 20% solution may be given as often as every hour.

When used for the routine nursing care of patients with tracheostomy, 1 to 2 mL of a 10% to 20% solution may be given every 1 to 4 hours by instillation into the tracheostomy.

MUCOMYST may be introduced directly into a particular segment of the bronchopulmonary tree by inserting (under local anesthesia and direct vision) a small plastic catheter into the trachea. Two to 5 mL of the 20% solution may then be instilled by means of a syringe connected to the catheter.

MUCOMYST may also be given through a percutaneous intratracheal catheter. One to 2 mL of

Body weight (Kg)	Actual Acetylcysteine Dose to be Administered (grams)	Number of LEGUBETI sachets to Dissolve in diet cola or other diet soft drinks	
		2.5 grams sachets	500 mg sachets
100 or greater	15	6	0
90 to 99	14	5	3
80 to 89	13	5	1
70 to 79	11	4	2
60 to 69	10	4	0
Dissolve LEGUBETI powder in 150 mL of diet cola or other diet soft drinks			
50 to 59	8	3	1
40 to 49	7	2	4
30 to 39	6	2	2
20 to 29	4	1	3

*No specific studies have been conducted to evaluate the necessity of dose adjustments in patients weighing over 100 kg. Limited information is available regarding the dosing requirements of patients that weigh more than 100 kg.

Table 2: LEGUBETI Maintenance Dose kg and greater

Dissolve LEGUBETI powder in 300 mL of diet cola or other diet soft drinks			
Body eight Kg)	Actual Acetylcysteine Dose to be administered (grams)	umber of LEGUBETI sachets to Dissolve in diet cola or other diet soft drinks	
		2.5 grams sachets	500 mg sachets

<table>
<tr>
<td></td>
<td>the 20% or 2 to 4 mL of the 10% solution every 1 to 4 hours may then be given by a syringe attached to the catheter.

DIAGNOSTIC BRONCHOGRAMS

Two to three administrations of 1 to 2 mL of the 20% solution or 2 to 4 mL of the 10% solution should be given by nebulization or by instillation intratracheally, prior to the procedure.</td>
<td>
<table>
<tr><td>100 or greater*</td><td>7.5</td><td>3</td><td>0</td></tr>
<tr><td>90 to 99</td><td>7</td><td>2</td><td>4</td></tr>
<tr><td>80 to 89</td><td>6.5</td><td>2</td><td>3</td></tr>
<tr><td>70 to 79</td><td>5.5</td><td>2</td><td>1</td></tr>
<tr><td>60 to 69</td><td>5</td><td>2</td><td>0</td></tr>
<tr><td colspan="4">Dissolve LEGUBETI powder in 150 mL of diet cola or other diet soft drinks</td></tr>
<tr><td>50 to 59</td><td>4</td><td>1</td><td>3</td></tr>
<tr><td>40 to 49</td><td>3.5</td><td>1</td><td>2</td></tr>
<tr><td>30 to 39</td><td>3</td><td>1</td><td>1</td></tr>
<tr><td>20 to 29</td><td>2</td><td>0</td><td>4</td></tr>
</table>
*No specific studies have been conducted to evaluate the necessity of dose adjustments in patients weighing over 100 kg. Limited information is available regarding the dosing requirements of patients that weigh more than 100 kg.

For Patients weighing 1 to 19 kg
Dissolve two 2.5-gram LEGUBETI powder sachets in 100 mL of water to create a 50 mg/mL solution. Calculate the loading and maintenance doses using the patient's kilogram weight:

Loading dose: Calculate the dose by multiplying the patient's kilogram weight by 140 mg/kg and dividing by the concentration of the solution (50 mg/mL). The result is the dose in mL for administration using an oral syringe.

Maintenance dose: Calculate the dose by multiplying the patient's kilogram weight by 70 mg/kg and dividing by the concentration of the solution (50 mg/mL). The result is the dose in mL for administration using an oral syringe.
</td>
</tr>
<tr>
<td>How Supplied</td>
<td>Mucomyst®-20: 20% acetylcysteine solution (200 mg acetylcysteine per mL).</td>
<td>500 mg sachets printed with "Lot Number and Expiration Date" on one side. Each carton containing 10 or 20 sachets:
• NDC 66277-319-10: box of 10 sachets.</td>
</tr>
</table>

	NDC 0087-0570-03 Cartons of three 10 mL vials, 1 plastic dropper NDC 0087-0570-09 Cartons of three 30 mL vials NDC 0087-0570-07 Cartons of twelve 4 mL vials Mucomyst®-10: 10% acetylcysteine solution (100 mg acetylcysteine per mL). NDC 0087-0572-01 Cartons of three 10 mL vials, 1 plastic dropper NDC 0087-0572-02 Cartons of three 30 mL vials NDC 0087-0572-03 Cartons of twelve 4 mL vials	• NDC 66277-290-20: box of 20 sachets. 2.5 grams sachets printed with “Lot Number and Expiration Date” on one side. Each carton containing 10 or 20 sachets: • NDC 66277-320-10: box 10 sachets. • NDC 66277-291-20: box 20 sachets
Storage	Store unopened vials at controlled room temperature, 59°F to 86°F (15°C to 30°C). MUCOMYST does not contain an antimicrobial agent, and care must be taken to minimize contamination of the sterile solution. Dilutions of MUCOMYST should be used freshly prepared and utilized within one hour. If only a portion of the solution in a vial is used, store the remaining undiluted portion in a refrigerator and use within 96 hours.	Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature.] Protect from moisture. Store in original package until use. (b) (4) within one hour.
Container Closure	Vial	Sachet

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 26, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, acetylcysteine, acetylcysteine lysine and 215040. Our search identified one (1) previous review[d], since the date of our last search on October 5, 2022, and we considered our previous recommendations to see if they are applicable for this current review. We determined that our previous recommendations are applicable to this current review.

[d] Getahun, S. Label and Labeling Review for Legubeti (NDA 215040). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JAN 24. TTT ID No.: 2022-635.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error experiences with similar products, we reviewed the following Legubeti labels and labeling submitted by Galephar Pharmaceutical Research Inc.

- Sachet label(s) received on August 14, 2023
- Carton labeling received on August 14, 2023
- Prescribing Information (Image not shown) received on August 14, 2023, available from:
    - Annotated version: \\CDSESUB1\EVSPROD\nda215040\0016\m1\us\114-labeling\draft\labeling\draft-labelingtext-pi-redline.doc
    - Clean version: \\CDSESUB1\EVSPROD\nda215040\0016\m1\us\114-labeling\draft\labeling\draft-labeling-text-pi-ms-word.doc

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

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

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/s/

SOFANIT N GETAHUN
11/14/2023 09:05:52 AM

VALERIE S VAUGHAN
11/14/2023 09:48:15 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
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A D D E N D U M

From: Ndidi Nwokorie, MD Medical Officer
Division of Pediatrics and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
DPMH, ORPURM, OND

To: Division of Hepatology and Nutrition (DHN)
Office of Immunology and Inflammation

Subject: Addendum to April 14, 2023 Pediatric Labeling Review

Applicant: Galephar Pharmaceutical Research Inc.

Application number:	NDA 215040
Drug:	LegubetiTM (acetylcysteine-lysine)
Drug Class:	Acetaminophen Antagonist
Proposed Indication:	As an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen
Proposed Dosage:	Loading dose: 140 mg/kg Maintenance doses: 70 mg/kg repeated every 4 hours for a total of 17 doses
Route of administration:	Oral
Dosage Form:	Powder for oral solution
Dosage Strengths:	500 mg and 2.5 gm sachets

The purpose of this addendum is to correct a statement in the DPMH labeling review, entered into DARRTS under this NDA on April 14, 2023, that the Applicant retrieved 71 publications with only one article describing pediatric patients. The published systematic review[1] submitted by the Applicant on the safety of oral L-Lysine supplementation as part of a regular diet included 71 publications with five pediatric articles that described undernourished pediatric patients receiving lysine fortified supplements at lysine doses more than 25-fold lower than the proposed weight-based Legubeti dose. These articles describe supplementation of food with micronutrients containing lysine but did not clearly quantify the exact amount of lysine each participant received

[1] Kohsuke Hayamizu, Ikuyo Oshima, Makoto Nakano, Comprehensive Safety Assessment of L-Lysine Supplementation from Clinical Studies: A Systematic Review, The Journal of Nutrition, Volume 150, Issue Supplement_1, October 2020, Pages 2561S–2569S, https://doi.org/10.1093/jn/nxaa218

and did not clearly specify whether any safety monitoring relevant to the lysine content had been conducted.

Only one of the pediatric publications[2] included in the systematic literature review clearly specified that the full amount of lysine administered was completely ingested by the enrolled participants. This publication described a prospective, randomized double blinded trial conducted in the Philippines that assessed the effects of a multi-nutrient fortified juice drink on iron, zinc and anthropometric indices on children with anemia 6 to 9 years of age, who were randomized to receive fortified juice two times a day or non-fortified juice for 100 days. The juice was fortified with 133.3 µg vitamin A, 1.4 mg zinc, 1.3 mg iron, 45 mg vitamin C and 200 mg L-Lysine. The publication did not discuss the maximum amount of lysine per kilogram body weight administered to the children per day or whether the trial monitored for any adverse effects attributable to lysine.

[2] Angeles-Agdeppa I, Magsadia CR, Capanzana MV. Fortified juice drink improved iron and zinc status of schoolchildren. Asia Pac J Clin Nutr 2011;20:535–43.

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/

NDIDI N NWOKORIE
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Division of Pediatrics and Maternal Health
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M E M O R A N D U M

From: Ndidi Nwokorie, MD Medical Officer
Division of Pediatrics and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
DPMH, ORPURM, OND

John J. Alexander, MD, MPH, Deputy Director
DPMH, ORPURM, OND

To: Division of Hepatology and Nutrition (DHN)
Office of Immunology and Inflammation

Subject:	Pediatric Labeling Review
Applicant:	Galephar Pharmaceutical Research Inc.
Application number:	NDA 215040
Drug:	LegubetiTM (acetylcysteine-lysine)
Drug Class:	Acetaminophen Antagonist
Proposed Indication:	as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen
Proposed Dosage:	Loading dose: 140 mg/kg Maintenance doses: 70 mg/kg repeated every 4 hours for a total of 17 doses
Route of administration:	Oral
Dosage Form:	Powder for oral solution
Dosage Strengths:	500 mg and 2.5 gm sachets

Reference ID: 5156600

Materials Reviewed:

Documents entered in DARRTS

- Under NDA 021903
  - Clinical Review for NeoProfen entered March 1, 2006
- Under NDA 215040
  - May 18, 2016, Pre-IND Meeting Minutes on May 19, 2016
  - Agreed Initial Pediatric Study Plan on April 15, 2020
  - DPMH Consult Form on July 18, 2022
  - Filing Communication on September 9, 2022

Documents submitted to DocuBridge

- Under NDA 215040
  - Cover Letter dated July 7, 2022
  - Cover Letter dated October 21, 2022
  - Request for Waiver of Pediatric Studies for Legubeti dated July 7, 2022
  - Tolerability and Palatability Protocol v1 dated October 21, 2022
  - Response-to-filing-communication dated December 28, 2022
- Under NDA 207916
  - Request for Waiver of Pediatric Studies for Cetylev on March 30, 2015

Approved Mucomyst US Prescribing Information (PI) accessed from Drugs@FDA on December 21, 2022

Approved NeoProfen USPI accessed from Drugs @FDA on March 16, 2023

Consult Request:

DHN consulted DPMH to assist in the review of proposed NDA labeling for Legubeti to inform labeling recommendations for pediatric use.

I. Regulatory Background of Application

Galephar Pharmaceutical Research Inc.[1] submitted a new drug application (NDA) under the 505(b)(2) pathway on July 7, 2022, requesting the approval of Legubeti (acetylcysteine lysine) as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen.[2]

This Applicant is relying on FDA's previous findings of efficacy and safety for Mucomyst (acetylcysteine solution) NDA 013601 as the listed drug (LD). FDA initially approved Mucomyst in 1963 as vials containing 10 mL or 30 mL of a 10% or 20% solution of acetylcysteine as the sodium salt for inhalational use. The NDA holder for Mucomyst

[1] Referred to as Galephar or the Applicant throughout this memorandum

[2] Cover Letter dated July 7, 2022

Reference ID: 5156600

discontinued marketing this drug in 2009 not for reasons related to safety or efficacy but as a business decision (b) (4).[3] Mucomyst labeling is not in Physician Labeling Rule (PLR) format and does not mention pediatric use. In January 2016, FDA approved another acetylcysteine product, Cetylev effervescent tablets for oral solution (500 mg and 2.5 g), under NDA 207916 for the same indication. Cetylev labeling is in PLR format. In 2019, the NDA holder for Cetylev also discontinued marketing of this drug product (b) (4).[3]

Multiple ANDAs exist for acetylcysteine as an oral solution, inhalation, and as injectable solution for IV use.

The proposed product, Legubeti (acetylcysteine lysine powder for oral solution), is subject to Pediatric Research Equity Act (PREA) requirements as a new active ingredient and a new dosage form. The Applicant is proposing a new salt formulated as a powder to be reconstituted into a solution for oral ingestion. The proposed dosage is the same as that approved for Cetylev and Mucomyst. The recommended loading dose in both adults and pediatric patients is as follows:

- 140 mg/kg loading dose
- 70 mg/kg maintenance dose starting 4 hours after the loading dose and repeated every 4 hours for a total of 17 maintenance doses

The Applicant states that the powder dosage form should be dissolved in soft drinks for adults and in water for pediatric patients prior to oral ingestion. These instructions are consistent with dosing instructions included in Cetylev labeling.

An Agreed iPSP issued on April 15, 2020, contains a plan to request a partial waiver in patients weighing less than 1 kg. This iPSP also states that, if the Applicant is able to demonstrate bioequivalence to the LD, then FDA would deem Legubeti to be fully assessed in pediatric patients. Although the Division took the same approach to support the pediatric approval of Cetylev, Cetylev had ophan drug designation (ODD) and was, therefore, exempt from PREA requirements. As a result, FDA did not have the authority to require the Cetylev NDA holder to conduct additional studies for pediatric patients such as palatability assessments. Because Legubeti does not have ODD, FDA does have the authority to require additional safety assessments from the Applicant if needed.

II. Brief Overview of N-acetylcysteine

N-acetylcysteine (NAC) is the mainstay of therapy for acetaminophen (APAP) toxicity and is almost 100% effective if given within 8 hours post-ingestion.[4] APAP toxicity occurs when normal glucuronidation and sulfation pathways are saturated. Ninety percent of APAP

[3] Discussed at several internal meetings with Division as well as in an email conversation with Dr. George Makar on March 28, 2023

[4] Ershad M, Naji A, Vearrier D. N Acetylcysteine. [Updated 2022 Jun 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537183/

Reference ID: 5156600

metabolism occurs through glucuronidation and sulfation, with less than 5% occurring through oxidation by CYP450 isoform (predominately CYP2E1) to produce the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI), which is the precursor to cellular injury. At therapeutic doses, glutathione in the liver can detoxify these small quantities of NAPQI and prevent tissue damage. However, once the primary pathway is saturated by a large dose of APAP, the CYP450 pathway becomes more prominent, producing greater toxic metabolites that deplete the glutathione reserves, leading to NAPQI accumulation and ultimately tissue injury by binding to cellular macromolecules. NAC restores glutathione reserves by providing cysteine, thereby potentiating NAPQI detoxification. NAC also binds to the toxic metabolites and scavenges free radicals as well as increases oxygen delivery to tissues, increases mitochondrial ATP production, and alters the microvascular tone to increase the blood flow and oxygen delivery to the liver and other vital organs.[4]

III. Current Application

Legubeti (acetylcysteine-lysine) is a lysine salt. At the proposed dosage, adults would receive 8-13 times the dietary reference intake (DRI) of lysine per day of 38 mg/kg/d in adults[5] during the course of treatment. High-dose lysine alone can cause acute renal failure.[6] A study conducted in rats showed a pattern of persistent acute renal failure which was characterized morphologically by a picture similar to acute tubular necrosis in humans.[6]

During the filing meeting held on August 24, 2022, the Division raised concerns regarding the proposed amount of lysine per dose of this drug and about the palatability of the drug product given the unpleasant taste associated with lysine and the unpleasant taste and odor of acetylcysteine. In a Filing Communication Letter dated September 9, 2022, the Division informed the Applicant that, although its application was sufficiently complete to permit a substantive review, potential review issues were identified, and requested the following information from the Applicant:

- Provide sufficient information regarding the solubility of N-Acetylcysteine Lysine (NAL) in diet cola
- Resubmit a new reconstitution study addressing concerns regarding the ability to adequately dose the drug product by weight
- Address inconsistencies in the proposed labeled strength and the sachet composition
- Provide a thorough review of published literature regarding the safety of the proposed dosing of lysine in all age groups, including pediatric and geriatric patients as well as specific populations including, but not limited to, patients with organ impairment, pregnant women, and nursing mothers[5]
- Provide adequate data regarding the tolerability and palatability of proposed NAL doses as inability to ingest the full dose regimen, either due to inadequate palatability or inadequate

[5] Filing Communication entered in DARRTS on September 9, 2022

[6] Racusen LC, Whelton A, Solez K. Effects of lysine and other amino acids on kidney structure and function in the rat. Am J Pathol. 1985 Sep;120(3):436-42. PMID: 3929613; PMCID: PMC1887985.

Reference ID: 5156600

tolerability, poses safety concerns of inadequate treatment of acetaminophen induced toxicity and risk of aspiration from nausea and vomiting
- Provide justification, with evidence, that bridging via the relative BA study at the 1 g NAC dose ensures the comparable BA at all doses including the maximum proposed dose of 15 g NAC
- Include justification the lysine salt will not significantly affect the pharmacokinetics of acetylcysteine at doses higher than 1 g up to the maximum dose because the quantity of lysine proportionally increases with the acetylcysteine dose

In the Filing Communication, DPMH raised concerns regarding the Applicant's proposed recommendation to use water to dilute the planned powder formulation for use in pediatric patients. These concerns centered around (1) what volume of water would need to be used to fully reconstitute the drug prior to administration; and (2) whether that amount of free water would exceed daily free water limits for the youngest and lightest weight patients.

Additionally, DPMH asked the Applicant to provide evidence supporting the safety of the total amount of lysine expected to be delivered with the loading and 17 maintenance weight-based doses to patients down to 1 kg of body weight. Lastly, given the Division has conveyed during internal meetings and email communications that both Mucomyst and Cetylev were discontinued because of preferential use of the injectable dosage form, DPMH conveyed concern about the lack of data supporting the oral tolerability of Legubeti in pediatric patients.

Based on these concerns, DPMH included requests in the communication letter for the Applicant to provide the following pediatric specific information to help inform the pediatric review of this application:

- Provide a tabular summary of the anticipated reconstituted volume in which the proposed dose will be delivered to pediatric patients stratified by weight down to 1 kg.
- Identify and conduct solubility studies in age-appropriate media, such as an age-appropriate electrolyte replacement fluid, in which this product would expect to be reconstituted prior to administration in all pediatric ages as diet cola, which was identified as a medium for reconstitution in the proposed labeling, would not be appropriate for pediatric consumption. Additionally, reconstitution in water prior to administration may be problematic in patients less than one year of age in whom free water intake should be restricted because of the limited ability to excrete free water.
- Submit data demonstrating tolerability and palatability of the proposed dose in age-appropriate media for pediatric patients weighing 1 kg and greater.

The rest of this memorandum will focus on DPMH's review of the Applicant's response to the identified deficiencies in the submitted application as it pertains to the pediatric assessment.

IV. Review of Applicant's Response to Filing Communication

The Applicant submitted a response to the Filing Communication on December 30, 2022. In the response, the Applicant provided additional information about the extent of dissolution and time to solution for the product in three different media: water, pediatric electrolyte solution, and diet coke. Time to solution was evaluated at room temperature and refrigerated (5 to 7 degrees C)

Reference ID: 5156600

temperatures. The Applicant states that the results demonstrate that Legubeti powder dissolves within minutes in water, pediatric electrolyte solution, diet coke and NaCl 0.9 % and that Legubeti is about six times more soluble than the highest required loading dose. The Applicant also stated that the amount of powder required to deliver the recommended dose to a 20 kg patient can be dissolved in about 9 ml of water. The Applicant's rationale is based on results from solubility studies performed in water at various pH and temperatures as well as solubility studies performed in diet coke at different temperatures, but at coke's natural pH of 2-3. Additional solubility studies were performed with pediatric electrolyte solution and 0.9% sodium chloride solution. Time to solution was recorded for the different solvents. The results of these solubility studies showed that, amounts between 48,000 mg and 102,600 mg can be dissolved in 150 ml of water at temperatures varying from 2.5°C to 25°C. This represents a capacity of water to dissolve amounts of Legubeti of 9 to 18 times more than the required amount for dosing. Therefore, the Applicant contends the required amount of powder to deliver the intended dose can be fully dissolved in a small volume of water, Pedialyte or normal saline.

Reviewer's Comments

The small volume of media required to fully dissolve the powder is reassuring as small volumes of the drug product would be anticipated to be given to pediatric patients, averting the concern for fluid overload. Based on already approved weight-based dosing for LD Mucomyst and Cetylev, the maximum volume to be administered to a 1 kg patient is 2.8 mL as a loading dose (maximum fluid intake for day 1 of treatment: loading dose + maintenance doses will be 9.8 mL) while the maximum dose expected to be given to a 19 kg patient is 53.2 mL as a loading dose (maximum fluid intake for day 1 of treatment: loading dose + maintenance doses will be 186.2 mL or 6 ounces). See Appendix 1.

Regarding the safety of the proposed dosing of lysine in all age groups, including pediatric and geriatric patients, Gelaphar stated that (b) (4) L-Lysine is an essential amino acid[7] that must be supplied by diet since it cannot be produced by the body and is used by the body to produce peptides and proteins. L-Lysine maximum exposures following the proposed dosing regimen for both adults and children will be approximately 435 mg/kg/day on day 1 (140 mg/kg loading dose followed by 5 maintenance doses q4h), and 312 mg/kg/day on days 2-3 (6 maintenance doses q4h) for a total of 18 doses.[7]

Reviewer's Comments

The publications submitted by the Applicant failed to provide adequate evidence to support the safety of administering the proposed maximum doses of L-Lysine to patients down to 1 kg body

[7] Response-to-filing-communication submitted to DocuBridge on December 28, 2022

Reference ID: 5156600

weight. The Applicant submitted seven publications to support the use of higher doses of oral L-Lysine that consisted of the following:

- *One nonclinical study conducted in rats.*[6]
- *Two randomized clinical trials (RCT) conducted in adults*
- *A systematic literature review*
- *A consensus paper*
- *Two general reviews*

See Appendix 2. The Applicant did acknowledge that safety information pertinent to ingestion of very high daily oral doses is limited. This reviewer was unable to identify any publications describing the effects of L-Lysine in pediatric patients. This reviewer searched the Orange Book for products containing lysine and identified only one product, ibuprofen lysine (NeoProfen; NDA 021903 and ANDA 202402). NeoProfen is approved for closure of clinically significant patent ductus arteriosus (PDA) in preterm neonates weighing between 500 and 1500 g who are no more than 32 weeks gestational age when usual medical management is ineffective. NeoProfen is intended for IV use at an initial dose of 10 mg/kg followed by 2 doses of 5 mg/kg each after 24 and 48 hours. Each mL contains 17.1 mg/mL ibuprofen L-Lysine.[8] *The safety assessment of the L-Lysine salt component of ibuprofen relied on a 13-week toxicity study in which L-Lysine was fed to rats at concentrations of 5% of their diet; results reportedly showed no adverse effects. The safety assessment of the L-Lysine salt component of ibuprofen lysine relied on a 13-week toxicity study in which L-Lysine was fed to rats at concentrations of 5% of their diet; results reportedly showed no adverse effects. The NDA for NeoProfen did not contain information about the pediatric safety of the L-Lysine component of NeoProfen.*[9]

The Applicant states that the most common side effects reported from acute L-Lysine usage were nausea, diarrhea, and weakness. These side effects appeared to be lessened if doses were given with foods containing protein and divided into smaller doses. The Applicant further stated that the only reported effects of L-Lysine treatment in humans were transient GI problems in a few subjects. The Applicant submitted a published systematic review[10] on the safety of oral L-Lysine supplementation as part of a regular diet that retrieved 71 publications, one of which described pediatric patients. The safety review of the literature concluded that the observed adverse events were mainly gastrointestinal (GI) symptoms when used at doses of approximately 6 g per person per day.[10]

[8] USPI Neoprofen accessed from Drugs @FDA on 3/16/2023

[9] Clinical Review in DARRTS under NDA 021903 entered March 1, 2006

[10] Kohsuke Hayamizu, Ikuyo Oshima, Makoto Nakano, Comprehensive Safety Assessment of L-Lysine Supplementation from Clinical Studies: A Systematic Review, The Journal of Nutrition, Volume 150, Issue Supplement_1, October 2020, Pages 2561S–2569S, https://doi.org/10.1093/jn/nxaa218

Reference ID: 5156600

Reviewer's Comments

The single pediatric publication[11] was a prospective, randomized double blinded trial conducted in the Philippines that assessed the effects of a multi-nutrient fortified juice drink on iron, zinc and anthropometric indices on children with anemia6 to 9 years of age, who were randomized to receive fortified juice two times a day or non-fortified juice for 100 days. The juice was fortified with 133.3 µg vitamin A, 1.4 mg zinc, 1.3 mg iron, 45 mg vitamin C and 200 mg L-Lysine. The publication did not discuss the maximum amount of lysine per kilogram body weight administered to the children per day or whether the trial monitored for any adverse effects attributable to lysine.

The Applicant submitted a protocol proposing (b) (4) .

In response to request for further pediatric evaluation, the Applicant stated that it was their understanding that once they establish a bridge between NAL and NAC, then NAL would be considered fully assessed in the pediatric population weighing 1 kg or greater, as specified in the Agreed iPSP. Additionally, the Applicant stated that Legubeti could be given via a nasogastric tube (NGT) similar to what is recommended in the LD labeling for pediatric patients who cannot tolerate the dose. However, the use of NGTs in pediatric patients can present independent challenges related to NGT placement and retention. In addition, NGT placement often requires skilled personnel at institutions with dedicated pediatric staff who may not be available where pediatric patients initially present. Collectively, these challenges may prevent or delay administration of the full dosage regimen, resulting in inadequate treatment of acetaminophen (APAP)-induced toxicity.

The Applicant plans (b) (4) (b) (4)

[11] Angeles-Agdeppa I, Magsadia CR, Capanzana MV. Fortified juice drink improved iron and zinc status of schoolchildren. Asia Pac J Clin Nutr 2011;20:535–43.

(b) (4)

Reviewer's Comments

The Applicant's plan to not conduct a palatability and tolerability study in pediatric patients may be acceptable if the adult palatability study demonstrates that NAL does not present any palatability or tolerability issues, i.e. has no bad taste or odor.

This application was discussed with the PeRC on 3/14/2023. At the time, the Division informed the PeRC that they plan to issue a Complete Response (CR) to the application as the tolerability study would not be completed in time to allow substantive review prior to the PDUFA date. During the PeRC meeting, the Division stated that the preferred route of administration for NAC is intravenous, and the Division does not see a benefit over existing therapies for adult patients. The PeRC conveyed to the Division that IV access can be difficult to achieve in pediatric patients. Thus, the development of an oral product (b) (4) *would be beneficial to pediatric patients requiring APAP overdose treatment.*

V. Conclusion

The Applicant responded to some concerns conveyed in the Filing Communication. The Applicant conducted solubility studies, as requested, in age-appropriate media and demonstrated that the anticipated volumes needed to administer the loading dose and maintenance doses, in the smallest pediatric patients, are less than 1 ounce – and could be given in pediatric electrolyte solutions instead of water if needed. This information suggests the proposed volumes of reconstituted drug product would not be anticipated to lead to fluid overload in the youngest pediatric patients.

The Applicant maintains that the lysine component of the salt renders the NAL salt odorless and without the bad taste associated with NAC. This hypothesis will need to be confirmed by the palatability trial planned in healthy adult subjects. If the Applicant is unable to demonstrate that its product, NAL, is odorless and tasteless, the Applicant will need to provide adequate data that the product would be tolerated by pediatric patients when given orally.

There is a paucity of published data describing the safety of lysine for pediatric patients, and the Applicant did not provide adequate information supporting the safety of administering the proposed maximum doses of L-Lysine to pediatric patients weighing down to 1 kg. The maximum daily amount of L-lysine expected to be administered with Legubeti at the proposed dosage will range from 502.6 mg/kg with loading dose treatment on the first day and 313 mg/kg after completion of the maintenance dose on the last day of treatment. A publication looking at the lysine requirement of enterally fed term neonates estimated the amount to be 130 mg/kg

/day[12]. The lysine exposure in Legubeti represents 2-4 times the daily estimated intake of lysine in enterally fed term neonates of 130 mg/kg/day.

Because DHN plans to issue a CR for this application, the Division has paused labeling negotiations. If the Applicant resubmits the NDA with the completed palatability trial seeking approval down to 1 kg weight, labeling negotiations, including recommendations for pediatric use based on submission, will resume.

[12] Lisha Huang, Jacomine E Hogewind-Schoonenboom, Femke de Groof, Jos WR Twisk, Gardi J Voortman, Kristien Dorst, Henk Schierbeek, Günther Boehm, Ying Huang, Chao Chen, Johannes B van Goudoever, Lysine requirement of the enterally fed term infant in the first month of life, The American Journal of Clinical Nutrition, Volume 94, Issue 6, December 2011, Pages 1496–1503, https://doi.org/10.3945/ajcn.111.024166

Reference ID: 5156600

Appendix 1: Dosing amount for pediatric patients between 1 kg and 19 kg, expressed in mg of NAC and amount of liquid to be administered

Body Weight (kg)	Approximate age [months]	Loading Dose in ml for administration when dissolving 2.5 of acetylcysteine powder sachets in 50 ml of liquid		Maintenance Dose in ml for administration when dissolving 2.5 of acetylcysteine powder sachets in 50 ml of liquid	
		mg	ml	mg	ml
1	28*	140	2.8	70	1.4
2	34*	280	5.6	140	2.8
3	38*	420	8.4	210	4.2
4	0	560	11.2	280	5.6
5	1.5	700	14	350	7
6	2.5	840	16.8	420	8.4
7	4.5	980	19.6	490	9.8
8	5.5	1120	22.4	560	11.2
9	7.5	1260	25.2	630	12.6
10	10.5	1400	28	700	14
11	13.5	1540	30.8	770	15.4
12	17.5	1680	33.6	840	16.8
13	23.5	1820	36.4	910	18.2
14	30.5	1960	39.2	980	19.6
15	37.5	2100	42	1050	21
16	44.5	2240	44.8	1120	22.4
17	50.5	2380	47.6	1190	23.8
18	55.5	2520	50.4	1260	25.2
19	61.5	2660	53.2	1330	26.6

Source: Response-to-filing-communication-dec-28-2022

Reference ID: 5156600

Appendix 2: Publications submitted to support L-lysine use

Type of publication	Year	Title	Authors	Population	Source	Comment
General Review	2011	Medicinal Uses of L-Lysine: Past and Future.	Singh, et al	Adults and Pediatrics		Discusses the general utility of L-lysine as a supplement in various conditions. The authors acknowledged the lack of adequate safety data regarding its use particularly in special populations such as children.
General Review	1997	The Metabolic Roles, Pharmacology, and Toxicology of Lysine	Flodin, et al	Adults and Pediatrics	Journal of the American College of Nutrition	Reviewed the effect of L-lysine supplementation in poorly thriving infants who received 50-100 mg/kg of L-Lysine monohydrochloride. No systematic assessment of the safety of L-lysine was conducted.
RCT- double-blind, placebo-controlled, multicenter trial of oral L-lysine monohydrochloride for the prevention and treatment of recurrent herpes simplex (HSV) infection.	1987	Success of L-lysine therapy in frequently recurrent herpes simplex infection. Treatment and prophylaxis	Griffith, et al	Adults	Dermatologica	52 patients were randomized to 1 gm L-lysine three times a day for 6 months or placebo.
RCT- a single-blinded, randomized, cross-over pilot study	2011	L-lysine as adjunctive treatment in patients with schizophrenia: a single-blinded, randomized, cross-over pilot study	Wass, et al	Adults	BMC Med	10 Patients with schizophrenia were randomized to 6 g/day of L-lysine or placebo for four weeks, then cross-over foe additional 4 weeks. The investigators report elevated L-Lysine levels from administered L-lysine was well tolerated.
Consensus	2020	2020 Proposals for Upper Limits of Safe Intake for	Cynober, et al	Adults	The Journal of Nutrition	Authors propose NOAELs for Lysine based on research in healthy adults

		Methionine, Histidine, and Lysine in Healthy Humans				presented during the 10th Amino Acid Assessment Workshop
Systematic Literature Review	2020	Comprehensive Safety Assessment of L-lysine Supplementation from Clinical Studies: A Systematic Review	Hayamizu et al	Adults and Pediatrics	The Journal of Nutrition	This review retrieved one pediatric study, out of 71 research articles, that enrolled anemic children receiving lysine as a nutritional supplement. The dose of L-lysine was unclear. The authors concluded that observed AE in the reviewed publications was predominantly gastrointestinal symptoms.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Review

Date:	April 6, 2023
Reviewer(s):	Laura Kangas, Pharm D, Safety Evaluator* Division of Pharmacovigilance-I (DPV-I)
Team Leader(s):	Lisa Wolf, PharmD DPV-I
Acting Division Director:	Monica Munoz, PharmD, PhD DPV-I
Product Name(s):	Legubeti (N-acetylcysteine lysine powder for oral solution)
Subject:	Safety of acetylcysteine and lysine
Application Type/Number:	NDA 215040
Applicant/Sponsor:	Galephar Pharmaceutical Research Inc
TTT Record ID:	2022-1167

* Provided initial draft and analyses. Final draft completed by Lisa Wolf.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The purpose of this review is for the Division of Pharmacovigilance I (DPV-I) to provide an analysis of all adverse events (AEs) associated with N-acetylcysteine (NAC) use and lysine use in the FDA Adverse Event Reporting System (FAERS) and medical literature to inform the Division of Hepatology and Nutrition (DHN) as they review a 505(b)(2) New Drug Application (NDA 215040) for N-acetylcysteine Lysine (NAL) powder for oral solution. NAL contains the same active moiety as NAC (i.e., N-acetyl-L-cysteine), but contains the amino-acid lysine to form a salt as opposed to sodium.

We performed a high-level analysis of FAERS and medical literature reports and compared product labeling between NAC products and NAL to identify AEs of interest with NAC or lysine for further review. We identified the following AEs of interest with oral NAC: severe rash, hypersensitivity including pruritis and angioedema, DILI, and serum sickness-like reaction. In addition, we identified Fanconi's syndrome as an AE of interest of with lysine. Overall, we did not find any AEs of interest that would warrant labeling at this time for the already approved oral NAC products or warrant addition to the proposed NAL product labeling. Additional rationale is provided below:

- We identified a single case of severe skin rash with sloughing with oral NAC. Rash with or without fever is already labeled in ADVERSE REACTIONS of both the product labeling for the oral NAC products and proposed NAL product. The single case does not warrant a change to labeling at this time.

- We identified a single case of non-serious pruritis and a single case of angioedema with a serious outcome of other important medical event. These events are captured by verbiage in the WARNINGS AND PRECAUTIONS *Hypersensitivity* subsection, and a change is not warranted at this time because of the limited number of cases.

- We identified two cases of DILI in patients receiving oral and rectal NAC for treatment of an unapproved indication (meconium ileus). The lack of additional cases coupled with the fact that oral acetylcysteine is used to lessen hepatic injury in patients exposed to hepatotoxic quantities of acetaminophen, suggests no change is warranted at this time.

- We identified two cases of serum sickness-like reaction; one contained limited information and one was deemed possible because of distant administration of cefazolin, although a less likely cause. Because of the presence of only two older cases at this time, we suggest continued monitoring of this event.

- We identified a single possible case of Fanconi's syndrome associated with chronic ingestion of L-lysine at a dose slightly below the adult lysine recommended dietary allowance of 30-38 mg/kg/day, which was confounded by multiple alternative etiologies of renal failure. Taking into consideration that limited available data suggests that lysine doses of 6 g or 300-400 mg/kg is associated with mild gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) and lack of other cases of Fanconi's syndrome identified with

Reference ID: 5154528

a widely available product, we do not recommend labeling at this time. However, if NAL is approved, close monitoring of this event would be warranted.

- Of note, nausea and vomiting are labeled in the ADVERSE REACTIONS section of the proposed NAL product labeling. A coformulation of lysine and NAC could theoretically have an additive effect on nausea and vomiting and impact NAL tolerability and dose retention. Although we are unable to assess this risk from postmarketing data at this time, these events would also warrant close monitoring if NAL were approved.

Although outside of the scope of this review, we identified two potential safety signals specific to the IV formulation of NAC during our hands-on review of reports:

- We identified a case of cardiac arrest following anaphylaxis associated with FDA-approved dosages of IV NAC. Our FAERS and literature search did retrieve additional similar cases describing cardiac arrest following an anaphylactic reaction with IV NAC, however, they contained limited information for assessment (e.g., missing IV NAC dosage administered) or were likely the index case mentioned in the Acetadote product labeling. We suggest continued monitoring of this event.

- We identified cases describing overdosage of IV NAC resulting in fatal anaphylaxis, hemolytic uremic syndrome, or seizures and cerebral edema. Although some aspects of this signal are included in the current IV Acetadote product labeling (e.g., a single case of fatal anaphylaxis is included in the OVERDOSAGE section), (b) (4), (b) (5) [redacted]

1 INTRODUCTION

The purpose of this review is for the Division of Pharmacovigilance I (DPV-I) to provide an analysis of all adverse events (AEs) associated with N-acetylcysteine (NAC)[a] use and lysine use in the FDA Adverse Event Reporting System (FAERS) and medical literature to inform the Division of Hepatology and Nutrition (DHN) as they review a 505(b)(2) New Drug Application (NDA 215040) for N-acetylcysteine Lysine (NAL) powder for oral solution. NAL contains the same active moiety as NAC (i.e., N-acetyl-L-cysteine), but contains the amino-acid lysine to form a salt as opposed to sodium.

1.1 BACKGROUND AND REGULATORY HISTORY

Mucomyst (acetylcysteine solution for oral administration, NDA 013601)[b,1] was the first NAC product approved by FDA on September 14, 1963, as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen. Since that time, multiple other formulations have been FDA-approved for the same indication, including Acetadote (NDA 021539)[2], an intravenous (IV) formulation approved on January 23, 2004, and Cetylev (NDA 207916)[3], an effervescent tablet for oral solution approved on March 13, 2009. All three NAC products contain the sodium salt form of N-acetyl-L-cysteine. Of note, Mucomyst and Cetylev have been withdrawn from the market for reasons unrelated to safety and efficacy.[c,4,5] However, multiple ANDAs for NAC oral solution and IV NAC have been approved by FDA.

On July 7, 2022, the Applicant submitted NDA 215040 NAL powder for oral solution under the 505(b)(2) approval pathway relying on prior findings of safety and efficacy for the reference listed drug (RLD), Mucomyst, as summarized in the January 2001 approved Mucomyst U.S. prescribing information (PI).[1] NAL contains that same active moiety as NAC (i.e., N-acetyl-L-cysteine), but is the first product to contain the amino acid salt lysine.[6]

Lysine is primarily available in the United States in unapproved dietary supplements but has been formulated as an L-lysine salt or poly-l-lysine carrier with a few FDA-approved drug products (i.e., ibuprofen lysine, benzylpenicilloyl polylysine). Importantly, the proposed quantity of lysine a patient would receive from a treatment course of NAL would be approximately 8-13-fold greater than the recommended dietary allowance (RDA) of 38 milligram (mg)/kilogram (kg)/day in adults.[7]

On September 9, 2022, FDA requested clarification from the Applicant on why L-lysine was selected as the amino acid salt formulation of NAC and exposes patients to high quantities of lysine. On December 30, 2022, the Applicant responded that lysine:

- (b) (4)

[a] For the purposes of this review, acetylcysteine and N-acetylcysteine refer to the same product.
[b] Mucomyst solution can also be inhaled and used as a mucolytic agent. Indications relevant to inhalation are not a focus of this review.
[c] Product (withdrawal date, reason for withdrawal): Mucomyst (March 13, 2009; stopped marketing drug), Cetylev (March 4, 2022; stopped marketing drug).

Reference ID: 5154528

- (b) (4)
-

1.2 RELEVANT PRODUCT LABELING

The Applicant's proposed labeling for NAL, which is reproduced below, is based on the approved product labeling for Cetylev.[3,d] Sections from the proposed NAL product labeling (version from September 22, 2022) relevant to this review are reproduced below; see **Appendices A-C** for relevant sections from the product labeling of Cetylev, Mucomyst, and Acetadote.[1,2,3,e]

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Generalized urticaria has been observed rarely in patients receiving oral acetylcysteine for acetaminophen overdose. If this occurs or other allergic symptoms appear, treatment with ACETIECUR should be discontinued unless it is deemed essential, and the allergic symptoms can be otherwise controlled.

5.2 Risk of Upper Gastrointestinal Hemorrhage

Occasionally severe and persistent vomiting occurs as a symptom of acute acetaminophen overdose. Treatment with oral (b) (4) may aggravate the vomiting. Patients at risk of gastric hemorrhage (e.g., esophageal varices, peptic ulcers, etc.) should be evaluated concerning the risk of upper gastrointestinal hemorrhage versus the risk of developing hepatic toxicity, and treatment with (b) (4) given accordingly.

Dilution of the (b) (4) (**see Preparation of** (b) (4) **(Acetylcysteine Lysine) for Oral Solution** minimizes the propensity of oral acetylcysteine to aggravate vomiting.

6 ADVERSE REACTIONS

The following adverse reactions are described, or described in greater detail, in other sections of the labeling:

- Hypersensitivity Reactions [*see Warnings and Precautions (5.1)*]
- Risk for Upper Gastrointestinal Hemorrhage [*see Warnings and Precautions (5.2)*]

[d] The 2001 Mucomyst product labeling (i.e., RLD) was not used because the Cetylev product labeling is in Pregnancy and Lactation Labeling Rule (PLLR) format

[e] The Applicant only provided a label comparison for Cetylev and Mucomyst; Acetadote was included for completeness.

The most common adverse reactions have been identified from clinical studies or post marketing reports of acetylcysteine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The most common adverse reactions were nausea, vomiting, other gastrointestinal symptoms, and rash with or without fever.

2 METHODS AND MATERIALS

2.1 PRODUCT LABEL COMPARISON

DPV-I compared AEs listed in the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections of the proposed NAL labeling to those listed in the corresponding sections of the product labeling of Mucomyst (RLD), Cetylev, and Acetadote (see **Appendix D**).[1,2,3] AEs of interest for review included those in the proposed NAL labeling but not Mucomyst (RLD), Cetylev, or Acetadote labeling, or vice versa.

2.2 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in **Table 1.**

Because acetylcysteine is used for multiple approved (e.g., mucolytic agent) and unapproved indications (e.g., contrast-induced nephropathy), we then performed a narrative text word search[f] to identify reports in which acetylcysteine was used as an antidote for acetaminophen overdose. We performed a high-level review of the top 50 Preferred Terms (PTs) and Designated Medical Event (DME) PTs associated with this subset of reports to identify AEs of interest requiring further review. Of note, we reviewed all relevant reports, regardless of the acetylcysteine indication for use, when evaluating the AEs of interest.[g]

Table 1. FAERS Search Strategy*	
Date of search	November 22, 2022
Time period of search	September 14, 1963† - November 21, 2022
Search type	*RxLogix PV Reports Profile Report, RxLogix PV Reports Line Listing and Case Details Report*
Product terms‡	PAI: acetylcysteine, acetylcysteine sodium
MedDRA search terms (Version 25.1)	All adverse events
* See **Appendix E** for a description of the FAERS database. † Mucomyst U.S. approval date ‡ We did not perform a FAERS search with lysine because preliminary searches with lysine PAIs did not yield any useful reports. Abbreviations: PAI= Product Active Ingredient, MedDRA=Medical Dictionary for Regulatory Activities	

[f] In a stepwise approach, reports were included if they contained the words: acetaminophen, Tylenol, paracetamol, or overdose; reports were excluded if they contained the word inhalation.
[g] Potential safety signals relevant to only IV NAC were identified during the signal identification phase. It is possible that not all cases relevant to these signals were identified in this review.

Reference ID: 5154528

2.3 LITERATURE SEARCH STRATEGY

DPV-I searched the medical literature with the strategy described in **Table 2**. In contrast to the FAERS analysis, all articles were screened irrespective of the reported reason for use.

Table 2. Literature Search Strategy

	NAC		Lysine*	
	Search 1	Search 2	Search 1	Search 2
Date of search	January 5, 2023	January 5, 2023	February 7, 2023	February 7, 2023
Database	Embase	PubMed	Embase	PubMed
Search terms	('acetylcysteine'/exp OR acetylcysteine) AND ('adverse event'/exp OR 'adverse event' OR (adverse AND event)) AND ('adverse drug reaction'/exp OR 'adverse drug reaction')	(adverse drug reaction OR adverse event OR adverse effects) AND (acetylcysteine) AND (oral)	('lysine'/exp OR lysine) AND ('case report'/exp OR 'case report' OR (case AND report)) AND ('poison'/exp OR poison OR adverse OR toxic)	(lysine) AND (case report) AND (poison OR adverse OR toxic)
Years included in search	All	All	All	All
Other parameters	Case report; oral	Case report	None	None

* An independent search by the Division of Epidemiology I found no additional literature about the safety of high-dose oral L-lysine.

2.4 CAUSALITY ASSESSMENT

When applicable, reports were assessed for causal relationship between the AEs and reported product using a modified version of the World Health Organization-Uppsala Monitoring Center (WHO-CMC) causality assessment tool (see **Table 3**). Reports deemed unlikely or unassessable were excluded from further analysis.

Table 3. WHO Causality Categories[8]

Causality term	Assessment Criteria
Probable/Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake (i.e., minutes to several hours) • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake (i.e., minutes to several hours) • Could also be explained by disease or other drugs

Reference ID: 5154528

Table 3. WHO Causality Categories[8]	
Causality term	**Assessment Criteria**
	• Information on drug withdrawal may be lacking or unclear
Unlikely*	• Event or laboratory test abnormality, with a time to drug intake that makes relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unassessable*	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified
*Excluded from further analysis.	

3 RESULTS

3.1 NAC RESULTS

After completing the product labeling comparison (see **Appendix D**), performing a high-level overview of FAERS reports associated with the 50 most frequently reported PTs and reports with a DME PT (see **Appendix F**), and reviewing the medical literature for case reports with NAC (see **Appendix G**), we classified the following events as AEs of interest to inform the proposed product labeling for NAL, which are discussed in Sections 3.1.1 through 3.1.4:

- Labeled AEs with new characteristics or increased severity: severe rash, hypersensitivity including pruritis and angioedema
- Unlabeled AEs with the potential for serious outcomes: drug-induced liver injury (DILI), serum sickness-like reaction

Although not a focus of this analysis, we also identified two potential safety signals for IV NAC, which are discussed in Sections 3.1.5 and 3.1.6:

- Cardiac arrest following anaphylaxis associated with FDA-approved dosages of IV NAC
- Overdosage of IV NAC resulting in fatal anaphylaxis, hemolytic uremic syndrome, and seizures and cerebral edema

3.1.1 Severe Rash

We identified one literature case[9] of rash with new characteristics in an 81-year-old female who received oral NAC 10% 30 mL in divided doses over 2 days prior to computed tomography (CT) scan (of the chest to rule out pulmonary tumor) with intravenous contrast. The patient had stage III chronic kidney disease and NAC was given for nephroprotection. Two days after the CT scan, she presented with a diffuse skin rash on her buttocks, lower back, trunk, abdomen, upper chest and upper thighs; itching; and the sensation of 'needle pricks'. Her symptoms evolved to skin sloughing the following day. Streptococcus A and B titers and cultures were negative, and she denied fever chills, sore throat, cough, arthralgia, and ulcers and sores in the oral mucosa; her vital signs were normal. She was treated with loratadine and triamcinolone cream with symptom resolution. She had prior CT scans and never had a reaction to iodine contrast, shellfish, or food containing iodine.

Reviewer Comment: This literature case describes a probable case of skin rash with sloughing based on temporality and lack of alternative etiologies; approved labeling of oral NAC only describes rash with or without fever. We did not find any additional cases from review of reports describing the following PTs with acetylcysteine as the only suspect product[h]: Stevens-Johnson syndrome, Toxic epidermal necrolysis, Acute generalized exanthematous pustulosis, Drug reaction with eosinophilia and systemic symptoms, Severe cutaneous adverse reaction. The literature search did not identify any other possible or probable cases of rash describing new characteristics or increased severity. We did not find sufficient evidence to recommend changes to the proposed NAL or approved NAC product labeling at this time and recommend continued monitoring.

3.1.2 Hypersensitivity

We identified two possible FAERS cases describing unlabeled hypersensitivity AEs (pruritus; anaphylactoid reaction and angioedema) associated with oral NAC therapy. Proposed product labeling for NAL currently contains hypersensitivity reactions, including generalized urticaria, in WARNINGS AND PRECAUTIONS and nausea, vomiting, and rash with or without fever in ADVERSE REACTIONS, consistent with approved product labeling for other oral NAC products.

FAERS case #7364484, other, USA, 2010, PT Pruritus:
A healthcare professional reported a 23-year-old woman developed itching 10 minutes after she started drinking NAC for acetaminophen overdose.

FAERS case #3271610, other, USA, 1999, PTs Anaphylactoid reaction/Angioedema:
A literature case[10] describes a 25-year-old male who developed an anaphylactoid reaction and angioedema after receiving oral NAC 10.6 g. After receiving the initial dose of oral NAC for acetaminophen overdose of 70 to 80 g, he developed nausea, vomiting, and a fine red rash over his torso and extremities. He was given IV prochlorperazine, cimetidine, and diphenhydramine and NAC therapy was continued (70 mg/kg every 4 hours): there were no additional emesis episodes and the rash faded, but his face had some erythema and his extremities were pale. After the 8th dose of NAC, the patient's tongue swelled and the neck rash recurred. His airway remained open, and he received IV methylprednisolone and oral diphenhydramine; the angioedema decreased slowly but the rash took a prolonged period to resolve. Methylprednisolone and diphenhydramine were administered every 6 hours during the remainder of NAC therapy. All 17 maintenance doses of NAC were tolerated without further difficulty.

Reviewer comments: These two possible cases describe a temporal relationship between oral NAC administration and pruritus and angioedema but there is inadequate clinical information (e.g., IgE presence) to differentiate between an anaphylactoid and anaphylactic reaction.[11]

*Currently approved product labeling for oral NAC[1,2,3] and proposed product labeling for NAL do not specifically mention the AEs of angioedema or pruritus. However, the WARNINGS AND PRECAUTIONS Hypersensitivity subsection of these product labels do state that if generalized urticaria or **other allergic symptoms appear**, treatment with NAC or NAL should be discontinued unless it is deemed essential, and the allergic symptoms can be otherwise controlled. Based on the current labeling for NAC and NAL and*

[h] Reports with acetaminophen as a suspect product were also included for review.

Reference ID: 5154528

the limited number of AE cases of pruritis and angioedema identified, we recommend continued monitoring at this time.

3.1.3 DILI

We identified a two literature cases of DILI in pediatric patients receiving oral and rectal NAC for the unapproved use of disimpaction of meconium ileus. Current product labeling for NAC does not include DILI or elevations of liver function tests as adverse events; however, the DOSAGE and ADMINISTRATION section of the label does recommend monitoring aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, and international normalize ratio (INR) throughout NAC therapy to guide treatment.

The first literature case[12] describes a 3-year-old boy with cystic fibrosis (CF) who received nasogastric administration of NAC (50 mL of a 4% solution every 6 hours) and NAC enemas (150 mL of a 4% solution every 6 hours) for meconium ileus. He weighed 12.5 kg and received a total dose of 106 g of NAC during 3 days of treatment. Four days after beginning NAC, the patient developed markedly elevated serum transaminase levels that exceeded those normally seen in CF and were elevated from baseline; elevated gamma-glutamyl transpeptidase and persistently elevated alkaline phosphatase were most likely attributable to CF-associated hepatobiliary disease. NAC and cefaclor were discontinued, and 1 week later, his transaminases and alkaline phosphatase improved. Serologic test results for hepatitis B, hepatitis A, Epstein-Barr virus, and cytomegalovirus were negative; 4 months later, his liver function returned to baseline.

He was hospitalized 2 months later for meconium ileus equivalent and NAC enemas were given; he received a total NAC dose of 250 g during 4 days of treatment. His only other concurrent medications were theophylline and nebulized bronchodilators. Five days after admission, his liver function tests were elevated. NAC was discontinued, and 1 week later, his liver function tests had improved. A liver biopsy revealed fatty metamorphosis, mild expansion of portal areas with a neutrophilic infiltrate and rare eosinophils, and moderate bile ductular proliferation with evidence for pericholangitis. Repeat serologic test results for viral disease were negative. Four months later, his liver function tests were further improved.

The second literature case[13] describes an infant with meconium ileus secondary to CF, who was managed surgically with a double barrel ileostomy for mid-small bowel atresia and developed severe fecal impaction postoperatively. She was treated with oral NAC (2.5 mL every 8 hours) and 0.2% NAC contrast enemas (150 to 300 mL) on post-operative days 7 through 9. She responded well, but on day 10, her liver functions tests revealed dramatic increases in transaminases and bilirubin. An ultrasound of the abdomen revealed gallbladder sludge, normal liver size and echotexture with no intrahepatic biliary dilation. A Tc-99m-DISIDA scan suggested poor tracer uptake (36%, normal range >92%), which was highly suggestive of significant hepatocellular dysfunction. The transaminase and bilirubin levels showed a spontaneous improvement after peaking around day 10 after the post-operative exposure.

Reviewer comment: Although these cases are deemed possible because of the temporal relationship between the events and NAC exposure, presence of positive dechallenge, and

positive rechallenge in the first case, we do not recommend any information from these cases be added to the current labeling for oral NAC products or the proposed labeling for NAL.

Both cases describe use for an unapproved indication (meconium ileus), used oral NAC in combination with rectal NAC, and had underlying disease (CF) that could have contributed to the events. In addition, the total NAC dose (oral and rectal together) in the first case was six times the FDA-approved total dose for pediatrics receiving the product for acetaminophen overdose (for his weight of 12.5 kg).

Current approved oral NAC labeling does not describe a risk of DILI. In fact, this drug is used to lessen hepatic injury in patients exposed to hepatotoxic quantities of acetaminophen. We reviewed all FAERS reports coded with a PT possibly related to DILI (e.g., Hepatic fibrosis, Hepatic necrosis, Liver transplant, Liver and small intestine transplant, Renal and liver transplant, Hepatitis acute, Hepatitis fulminant, Drug-induced liver injury) and did not identify any additional possible or probable cases in patients receiving the product for approved or unapproved uses.

3.1.4 Serum Sickness-Like Reaction

We identified two FAERS cases, of which one was also published in the literature, describing serum sickness-like reactions associated with oral NAC therapy.

FAERS case #4816538, hospitalization, USA, 1991:
A physician reported a 23-year-old man received oral acetylcysteine for 3 days. Two days later, he developed "serum sickness-like symptoms following treatment with oral Mucomyst for acetaminophen overdose (enlarged lymph nodes, fever, body ache, rash, joint pain, etc.). Responded to antihistamine treatment."

FAERS case #5126885, life-threatening/hospitalization/required intervention, USA, 1994:
The literature case[14] describes a 29-year-old male who received NAC 5 g orally every 6 hours for acetaminophen overdose. Three days after admission, he developed fever, skin rash, arthralgia, lymphadenopathy, abdominal pain, and decreased platelet counts consistent with serum sickness-like illness. Three weeks prior to admission, he had undergone surgical repair of gunshot injuries to his abdomen and left knee and received perioperatively cefazolin, trimethoprim-sulfamethoxazole, and meperidine with no AEs. NAC was discontinued, and he received IV methylprednisolone and diphenhydramine with resolution of the abdominal pain and joint pain within 12 hours; the platelet counts gradually returned to normal. Alternative etiologies were ruled out.

Reviewer Comment: The first FAERS case is from 1991 and contains limited information to assess causality (e.g., no mention of ruling out other potential causes). This second case is deemed a possible case of serum sickness-like reaction with oral NAC because of the temporal association between oral NAC administration and the signs and symptoms; distant prior administration of cefazolin is a possible, but unlikely, alternative etiology. Based on these two older cases, we suggest continued monitoring for this event at this time.

3.1.5 Cardiac Arrest Following Anaphylaxis Associated With FDA-Approved Dosages of IV NAC

Current IV NAC product labeling contains hypersensitivity reactions in WARNINGS AND PRECAUTIONS, but only describes the risk of death in one patient with asthma who developed bronchospasm after IV NAC administration. We identified one additional case of this reaction in a patient without asthma, which is detailed below.

FAERS case #6876881, hospitalization/life-threatening, IRL, 2008:
This literature case[15] describes a 38-year-old male (86 kg) who developed cardiac arrest following the administration of a therapeutic dose of IV acetylcysteine for a paracetamol overdose; he also took 9 mg of bromazepam. He had a history of depression and suicidal ideation but not allergies, asthma, or atopy. His normal medications of lithium 250 mg daily and citalopram 30 mg daily were not taken in overdose. His initial symptoms included one episode of vomiting, normal vital signs, and normal Glasgow Coma Scale. Liver and renal function tests were within normal limits; a serum lithium concentration was not reported. Soon after administration of the NAC loading dose (12,900 mg in 200 mL 5% dextrose over 20 minutes), the patient developed flushing, urticaria, hypotension, respiratory depression, and bradycardia culminating in asystole. The NAC infusion was stopped, adrenaline and hydrocortisone were given, and he was resuscitated by precordial thump with full recovery and symptom resolution. Oral methionine was given as an alternative paracetamol antidote, and he remained well with normal liver function tests.

Reviewer Comment: This possible case of cardiac arrest following an anaphylactic reaction is supported by a temporal association of IV NAC administration and a constellation of symptoms culminating in cardiac arrest. This case does contain other factors that may have contributed to the events (e.g., bromazepam). Our FAERS and literature search did retrieve additional similar cases describing cardiac arrest following an anaphylactic reaction with IV NAC, however, they contained limited information for assessment (e.g., missing IV NAC dosage administered) or were likely the index case mentioned in the Acetadote product labeling. We suggest continued monitoring for this event at this time.

3.1.6 Overdosage of IV NAC Resulting in Fatal Anaphylaxis, Hemolytic Uremic Syndrome, and Seizures and Cerebral Edema

The OVERDOSAGE section of the current IV Acetadote product labeling describes a single patient who received a 10-fold higher than prescribed dose, resulting in an acute inflammatory reaction and death. We identified additional cases[i] of overdosages of IV NAC resulting in the following events: fatal anaphylaxis, hemolytic uremic syndrome, and seizures and cerebral edema.

[i] It is possible that not all cases were evaluated as part of this review.

Reference ID: 5154528

Fatal anaphylactic shock

We identified an additional case of overdosage of IV NAC, resulting in death after developing anaphylaxis, which is described below.

FAERS case #8138765, death, USA, 2011:

This literature case[16] describes a 53-year-old male (84 kg) who died after receiving a 10-fold overdose of IV NAC. His medical history included chronic obstructive pulmonary disease, hepatitis C, alcohol abuse, and chronic back pain, but not cardiovascular disease. The patient presented with altered mental status and pinpoint pupils after likely overdosing on acetaminophen/hydrocodone and carisoprodol; transaminase levels and coagulation factors were within normal limits and troponin was 0.012 ng/mL. He was given naloxone and ordered IV NAC 150 mg/kg (12,600 mg) but was actually given 126,000 mg; immediately after NAC initiation, he developed periorbital edema, rash, and hypotension; NAC was stopped, he was intubated and given normal saline and phenylephrine. An electrocardiogram showed pronounced ST segment elevation in the inferior leads and an echocardiogram showed global severe hypokinesis with an ejection fraction of less than 20%. The patient was given aspirin and heparin, but his troponin rose to 658 ng/mL over the following 10 hours, and he died 17 hours after the initiation of IV NAC.

Hemolytic Uremic Syndrome

We identified three cases of hemolytic uremic syndrome in patients who received overdosages of IV NAC, which are described below.

FAERS case #11243357, hospitalization/death, IRN, 2015:

A literature case[17] describes a 23-year-old woman (65 kg) who died after receiving an overdose of IV NAC for paracetamol ingestion. The patient presented with weakness, lethargy, nausea, and dizziness; arterial blood gas and vital signs were normal. She was given activated charcoal and IV NAC (10 g loading dose given over 30 minutes, followed by a 9.5 g maintenance dose given over 20 hours) but developed agitation, nausea, vomiting, dyspnea, tachypnea, hypotension, drowsiness, and periorbital edema; she was treated for a suspected drug allergy but it was discovered that she received a 100 g NAC loading dose instead of 10 g. The patient then developed decreased consciousness with normal pupil reaction, severe hypotension, unpalpable radial pulse, hypernatremia, elevated creatinine and transaminases, increased respiratory rate, and required intubation. Her clinical condition over the next few days included normalization of elevated transaminases, generalized edema, oliguria, and decreased hemoglobin, hematocrit, and platelets; treatments included hemodialysis, “peak cell injection”, platelets, and fresh frozen plasma. Schistocytes seen on peripheral blood confirmed hemolytic anemia and plasmapheresis was started. Despite the interventions and normal liver function tests, she clinically deteriorated (e.g., brain edema seen on computed tomography, increased respiratory rate, metabolic acidosis, respiratory alkalosis), and died from hemolytic uremic syndrome. The discussion in the literature case mentions that glucose-6 phosphate deficiency (G6PD) was not confirmed in the patient and decreased hemoglobin, hematocrit, and platelets levels, the presence of schistocytes on peripheral blood smear, along with a negative Coombs test, hemolytic anemia, and thrombotic thrombocytopenic purpura suggested hemolytic uremic syndrome cause by NAC overdose.

FAERS case #19933685, disability/hospitalization/life-threatening/other, IRN, 2021:

A literature case[18] describes a 15-year-old girl (unknown weight) who experienced acute renal failure and hemolytic uremic syndrome after receiving a 10-fold acetylcysteine overdose. Gastric lavage, activated charcoal, and IV NAC (150 mg/kg for 1 hour followed by 9 mg/kg over 20 hours) were initiated for treatment of acetaminophen ingestion; she received a 90 g bolus of IV NAC but only 450 mg of a 90 g maintenance dose due to development of allergic reaction symptoms (e.g., nausea, hot flashes, erythema, and pruritus). Hydrocortisone was given and she was transferred to a poison center; the poison center was not informed of the NAC overdose and restarted NAC (5 mg/kg in 500 mL dextrose 5% over 24 hours) for symptoms of abdominal pain, nausea, vomiting, and elevated liver enzymes; serum amylase and lipase were normal. On the second day of hospitalization, her abdominal pain improved and NAC was discontinued but lab work showed elevated serum creatinine levels (Scr), decreased urine output, decreased hemoglobin and platelets, and schistocytes seen on peripheral blood smear; she was diagnosed with hemolytic uremic syndrome and received hemodialysis without improvement of her Scr and plasmapheresis. She also developed dyspnea, acute pulmonary edema, and hemoptysis requiring ventilation, antibiotic therapy, and bronchoscopy procedures; echocardiography performed "on the 11th, 24th, and 38th days that showed 50%, 35% and 40%, respectively". A secondary workup for high Sr levels showed: "C3 and C4 were less than standard" but normal antinuclear antibody, perinuclear antineutrophil cytoplasmic antibody, cytoplasmic-anti neutrophilic cytoplasmic antibodies, anti-double stranded DNA, and hemolytic complement levels; a renal biopsy showed pathological processes consistent with hemolytic uremic syndrome, glomerular ischemia, glomerulosclerosis, and acute tubular necrosis. The patient was eventually discharged on permanent dialysis.

FAERS case #8293384, hospitalization, USA, 2011:
A literature case[19] describes a 21-year-old woman who developed hemolytic uremic syndrome after receiving a 5-fold acetylcysteine overdose during treatment for an acetaminophen and ethanol overdose. Her medical history included depression and asthma treated with sertraline, venlafaxine, and montelukast; she also used tobacco, alcohol, and marijuana. Her initial evaluation showed tachycardia on examination with normal lab work (complete blood count, basic metabolic panel, hepatic panel, salicylate, urinalysis, urine pregnancy test, and urine drug screen). She was ordered IV NAC (150 mg/kg for 1 hour followed by 50 mg/kg over 4 hours followed by 100 mg/kg over 16 hours) but it was discontinued 20 minutes into the second infusion when she developed nausea, vomiting, and transient hypotension. She was given ondansetron, diphenhydramine, methylprednisolone, normal saline, inhaled albuterol with ipratropium, and dopamine and epinephrine infusion with improvement in her blood pressure. It was then discovered that she incorrectly received a 5-fold overdose of NAC (52.5 g in 500 mL of NS over 1 hour followed by 17.5 g in 500 mL over 4 hours). Over the next 3 days, her lab work showed decreased acetaminophen, hemoglobin, and hematocrit levels, increased transaminase and creatinine levels, and urinalysis positive for blood; she was treated with hemodialysis, packed red blood cell transfusions, and plasmapheresis for potential thrombotic thrombocytopenic purpura. Hematology tests (e.g., peripheral blood smear with schistocytes, negative direct Coombs, negative indirect Coombs, normal activity of A Disintegrin and Metalloproteinase with Thrombospondin motifs) confirmed a diagnosis of hemolytic uremic syndrome. At follow-up 3 and 6 months later, she had normal renal function and blood cell counts and additional testing showed normal G6PD activity.

Seizures and Cerebral Edema

We identified three cases in which patients received overdosages of IV NAC and experienced seizures and cerebral edema, which are described below.

FAERS case #8217268, hospitalization, USA, 2011:

A literature case[20] describes a 21-year-old female (42 kg) who developed delirium and seizures that progressed to cerebral edema, uncal herniation, and severe brain injury after receiving an overdose of IV NAC for acetaminophen ingestion; she received approximately 150 g of NAC over 32 hours when she was only supposed to receive a total dosage of approximately 14 g. The discussion of the case mentions, "The patient was in good health prior to presentation, had no history of seizures and there was no clinical evidence of infectious, metabolic, or other toxic causes of seizures."

FAERS case #19085077, death, CAN, 2021:

A literature case[21] describes a 17-year-old female (48.3 kg) who experienced confusion with shallow respirations, followed by agitation, diaphoresis, and seizures, and ultimately cerebral edema, cerebellar tonsillar herniation, and brain death after receiving an overdose of IV NAC for acetaminophen ingestion; she received 1,242.2 mg/kg of NAC over 8.3 hours (approximately 60 g) when she was only supposed to receive approximately 10.7 g over that time period.

FAERS case #5656539/5656962/5674244, death, USA, 2004:

A literature case[22] describes a healthy 30-month-old girl given an accidental overdose of IV NAC (2,450 mg/kg instead of 208 mg/kg total) for acetaminophen overdose which led to seizures, intracranial hypertension, and death. She had allegedly ingested acetaminophen 418 mg/kg. She was treated with two doses of activated charcoal followed by a 20.5 hour IV NAC protocol (stopped after 6.5 hours when error was identified, which was 14.5 hour post-acetaminophen ingestion). She was asymptomatic during the infusions, and vital signs remained normal. Thirty minutes after the third infusion was stopped, the nurse noticed some red lesions on her face and neck. One hour after the infusion was stopped, her face was slightly edematous. Five hours after the error was detected, she developed myoclonus on the left side of her body, with left eye deviation. This condition persisted intermittently for 3 hours despite treatment with diazepam, lorazepam, and phenytoin. A computed tomography (CT) scan result was normal. A few hours later, she sustained shorter recurrences of the myoclonus. At 30 hours after ingestion, she started to have irregular breathing and became unresponsive to pain. A repeat CT scan showed diffuse cerebral edema. A postmortem examination showed the presence of acute anoxic encephalopathy with marked cerebral edema and the beginning of uncal herniation that confirmed the clinical diagnosis of intracranial hypertension and brain death.

Reviewer Comment: As stated above, the OVERDOSAGE section of the current IV Acetadote product labeling describes only 1 case of death from acute inflammatory reaction in a patient who received a 10-fold higher than prescribed dose (an initial 150 mg/kg dose of acetylcysteine for a patient weighting 106 kg was mistakenly calculated as 160 g); despite treatment of anaphylaxis (e.g., generalized heat sensation, body pain, widespread urticaria, hypotension), the patient died. In this review, we identified an additional case of fatal anaphylaxis.

In addition, we identified events (e.g., hemolytic uremic syndrome, seizures, cerebral edema) that are currently not included in the OVERDOSAGE section of the IV Acetadote product labeling. It is difficult to assess the causality between these events and the IV NAC overdosage because similar events have been reported with acetaminophen toxicity alone. For example, there are published cases of acetaminophen overdosage resulting in hemolytic anemia in patients with confirmed G6PD.[23,24] However, two of the three cases summarized above described the development of hemolytic uremic syndrome (i.e., hemolytic anemia, thrombocytopenia, and renal dysfunction) in patients without G6PD who received unintentional overdosages of IV NAC for treatment of acetaminophen overdose; one case did not report G6PD status.

NAC is used to prevent progression of hepatotoxicity in patients with acetaminophen overdosage. However, patients who develop acute liver failure following acetaminophen overdose may experience complications, such as cerebral edema and multisystem organ failure.[25] The information provided in the three cases above of seizures and cerebral edema did not suggest the patients had progressed to hepatic failure, making this cause of the events less likely.

(b) (4), (b) (5)

3.2 LYSINE RESULTS

Our search of the literature for lysine-associated AEs identified one relevant case report summarized below.

The literature case[26] describes a 44-year-old female (104 kg) evaluated for polyuria, polydipsia, fatigue, and renal insufficiency after taking 3,000 mg L-lysine daily for 5 years as oral herpes prophylaxis. Her medical history was significant for a "kidney infection" at age 14, presenting with gross hematuria after an upper respiratory tract infection; she was treated with a prolonged course of antibiotics and recovered without sequelae. Concurrent medications included ibuprofen 600 mg, 4 to 6 tablets per day during menstruation. Her substance abuse history included remote prior use of alcohol, cocaine, amphetamine, and heroin injection. Her family history was remarkable for adult-onset diabetes but there was no history of renal or metabolic disease. Her physical examination was unremarkable with the exception of 1+ pedal edema. Laboratory testing yielded the following: blood urea nitrogen 18 mg/dL; creatinine 1.8 mg/dL; sodium 140 mmol; potassium 3.8 mmol/L; chloride 111 mmol/L; bicarbonate 22 mmol/L; glucose 79 mg/dL; calcium 8.6 mg/dL; phosphate 2.4 mg/dL; uric acid 2.5 mg/dL; albumin 3.8 g/dL; hemoglobin A1c 4.3%; hematocrit 37%; ALT 29 U/L; AST 40 U/L; lactate dehydrogenase 240 U/L; bilirubin 0.2 mg/dL; and alkaline phosphatase 190 U/L. Hepatitis testing revealed: hepatitis B seronegative, hepatitis B surface antigen negative, and hepatitis C seropositive. Urinalysis showed a pH of 7.0 with 2+ proteinuria, 0.05 g/dL glycosuria, 250 erythrocyte/μL hematuria, and no casts. A 24- hour urine collection was notable for a creatinine clearance of 54 mL/min, 1.98 g protein, and fractional excretions of uric acid and phosphorus of 57.3% and 34.5%, respectively. An abdominal ultrasound showed echogenic kidneys approximately 9 cm in length bilaterally. Additional studies included an elevated erythrocyte sedimentation rate (92 mm/hr), negative antinuclear antibody, rheumatoid factor, and antineutrophil cytoplasmic antibody,

negative Lyme titer, and normal serum complements and C3 fraction (CH50 262 mg/dL, C3 117 mg/dL). There was a mildly elevated gamma globulin fraction, but no monoclonal spike was evident on serum or urine immunoelectrophoresis. Cryoglobulins were not detected. A heavy metal screen, including cadmium, lead, mercury, and arsenic, was unremarkable. Serum ceruloplasmin was mildly elevated. An abdominal fat pad aspirate showed no evidence of amyloid.

Her azotemia progressed over the next 4 months, and repeat urinalyses showed 3+ proteinuria and 2+ hematuria with an inactive sediment. Repeat laboratory tests were notable for hypocomplementemia (CH50 <20, C4 20, C3 146, C5 12, C2 1.05, and C7 33 mg/dL), negative antinuclear antibody, negative cryoglobulins, and persistent glycosuria, hypophosphatemia (range, 1.9 to 2.4 mg/dL) and hypouricemia (range, 1.7 to 3.3 mg/dL), despite gradually worsening renal function (serum creatinine concentration range, 1.8 to 3.3 mg/dL); At the time, her serum creatinine was 3.3 mg/dL; serum bicarbonate, 15 mmol/L; anion gap, 13 mmol/L; serum phosphate, 2.3 mg/dL; and serum uric acid, 3.6 mg/dL. Human immunodeficiency virus testing was negative. A renal biopsy was performed and showed chronic vascular injury with marked interstitial fibrosis, tubular atrophy, prominence of lysosomes in the proximal tubules, and immune complex-mediated glomerular injury with electron-dense deposits in the mesangium and subendothelium; their appearance suggested a remote process without evidence of active inflammation. Segmental areas of hyalinosis were seen in the arteries and arterioles, indicative of a remote but now inactive vascular process. Immunofluorescence was notable for glomerular reactivity to immunoglobulin (Ig) G, and C3 deposition along the arteriolar walls. Congo Red stain was negative.

The patient discontinued L-lysine therapy and subjectively reported improvement in her energy level; follow-up laboratory data showed creatinine, 6.7 mg/dL; blood urea nitrogen, 57 mg/dL; bicarbonate, 19 mmol/L; anion gap, 5 mmol/L; calcium, 8.0 mg/dL; phosphate, 3.8 mg/dL; and uric acid, 6.1 mg/dL, with only trace glycosuria, 2+ hematuria, and no casts. Although proximal tubule function did improve, her renal failure progressed to end-stage in 5 months from the time of biopsy, eventually requiring the initiation of peritoneal dialysis. Cryoglobulins were later found to be transiently positive at l%, and immune complex-mediated glomerular injury, though previously quiescent, was thought to be a possible explanation for the subsequent deterioration in renal function. Complements remained low. A liver biopsy was consistent with mild chronic viral hepatitis.

Reviewer comment: This literature case describes possible causal association between Fanconi's syndrome and chronic ingestion of L-lysine. The patient received 3 g of lysine per day (28.8 mg/kg/day), slightly below the RDA of lysine (30-38 mg/kg/daily). Per the authors of the publication, although a temporal relationship is present and pathological findings suggest toxic injury, the case is limited by multiple alternative etiologies of renal injury (e.g., ibuprofen, alcohol, cocaine, amphetamine, heroin, vasculitis, hepatitis C-associated cryoglobulinemia, postinfectious glomerulonephritis); additionally, in the absence of preexisting renal disease, it is expected that L-lysine would produce a reversible proximal renal tubular acidosis without necessarily causing progressive renal insufficiency.

Data from a systematic review of the safety of L-lysine supplemented to a regular diet suggests an L-lysine hydrochloride dose of 6 g per day is safe for long-term use and is associated with subjective gastrointestinal tract symptoms, such as nausea, stomachache, and diarrhea.[27]

Based on the currently available data, this safety signal warrants close monitoring if NAL is approved, however, we do not recommend adding this AE to labeling at this time based on this single case that describes chronic exposure to lysine and potential alternative causes for the event.

4 DISCUSSION

In response to the consult from DHN, we performed a high-level analysis of FAERS reports and medical literature and compared product labeling between NAC products and NAL to identify AEs of interest with NAC or lysine for further review. We identified the following AEs of interest with oral NAC: severe rash, hypersensitivity including pruritis and angioedema, DILI, and serum sickness-like reaction. In addition, we identified the AE of interest of Fanconi's syndrome with lysine. Overall, we did not find any AEs of interest that would warrant labeling at this time for the already approved oral NAC products or warrant addition to the proposed NAL product labeling. Additional rationale is provided below:

- We identified a single case of severe skin rash with sloughing with oral NAC. Rash with or without fever is already labeled in ADVERSE REACTIONS of both the product labeling for the oral NAC products and proposed NAL product. The single case does not warrant a change to labeling at this time.

- We identified a single case of non-serious pruritis and a single case of angioedema with a serious outcome of other important medical event. These events are captured by verbiage in the WARNINGS AND PRECAUTIONS *Hypersensitivity* subsection, and a change is not warranted at this time because of the limited number of cases.

- We identified two cases of DILI in patients receiving oral and rectal NAC for treatment of an unapproved indication (meconium ileus). The lack of additional cases coupled with the fact that oral acetylcysteine is used to lessen hepatic injury in patients exposed to hepatotoxic quantities of acetaminophen, suggests no change is warranted at this time.

- We identified two cases of serum sickness-like reaction; one contained limited information and one was deemed possible because of distant administration of cefazolin, although a less likely cause. Because of the presence of only two older cases at this time, we suggest continued monitoring of this event.

- We identified a single possible case of Fanconi's syndrome associated with chronic ingestion of L-lysine at a dose slightly below the adult lysine RDA of 30-38 mg/kg/day, which was confounded by multiple alternative etiologies of renal failure. Taking into consideration that limited available data suggests that lysine doses of 6 g or 300-400 mg/kg is associated with mild gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) and lack of other cases of Fanconi's syndrome identified with a widely

available product, we do not recommend labeling at this time. However, if NAL is approved, close monitoring of this event would be warranted.

- Of note, nausea and vomiting are labeled in the ADVERSE REACTIONS section of the proposed NAL product labeling. A coformulation of lysine and NAC could theoretically have an additive effect on nausea and vomiting and impact NAL tolerability and dose retention. Although we are unable to assess this risk from postmarketing data at this time, these events would also warrant close monitoring if NAL were approved.

Although outside of the scope of this review, we identified two potential safety signals specific to the IV formulation of NAC during our hands-on review of reports:

- We identified a case of cardiac arrest following anaphylaxis associated with FDA-approved dosages of IV NAC. Our FAERS and literature search did retrieve additional similar cases describing cardiac arrest following an anaphylactic reaction with IV NAC, however, they contained limited information for assessment (e.g., missing IV NAC dosage administered) or were likely the index case mentioned in the Acetadote product labeling. We suggest continued monitoring of this event.

- We identified cases describing overdosage of IV NAC resulting in fatal anaphylaxis, hemolytic uremic syndrome, or seizures and cerebral edema. Although some aspects of this signal are included in the current IV Acetadote product labeling (e.g., a single case of fatal anaphylaxis is included in the OVERDOSAGE section), (b) (4), (b) (5)

5 CONCLUSION

In conclusion, we did not identify any new postmarketing safety issues with oral NAC warranting changes to the current oral NAC product labeling or the proposed NAL product labeling. We did not identify any safety signals with lysine that would impact the proposed NAL product labeling. (b) (4), (b) (5)

6 REFERENCES

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7 APPENDICES

7.1 APPENDIX A. PERTINENT CETYLEV SAFETY LABELING

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including generalized urticaria have been observed in patients receiving oral acetylcysteine for acetaminophen overdose. If hypersensitivity reactions occur, CETYLEV should be discontinued unless it is deemed essential for patient management and the reactions can be otherwise controlled.

5.2 Risk of Upper Gastrointestinal Hemorrhage

Occasionally severe and persistent vomiting occurs as a symptom of acute acetaminophen overdose. Treatment with CETYLEV may aggravate the vomiting and increase the risk of upper gastrointestinal hemorrhage in at risk patients (e.g., those with esophageal varices, peptic ulcers, etc.). Consider the risk/benefit for patients at risk of hemorrhage versus the risk of developing hepatic toxicity, and treat with CETYLEV as needed.

6 ADVERSE REACTIONS

The following adverse reactions are described, or described in greater detail, in other sections of the labeling:

• Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
• Risk for Upper Gastrointestinal Hemorrhage *[see Warnings and Precautions (5.2)]*

The most common adverse reactions have been identified from clinical studies or postmarketing reports of acetylcysteine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The most common adverse reactions were nausea, vomiting, other gastrointestinal symptoms, and rash with or without fever.

7.2 APPENDIX B. PERTINENT MUCOMYST SAFETY LABELING

CONTRAINDICATIONS
There are no contraindications to oral administration of acetylcysteine in the treatment of acetaminophen overdose.

Reference ID: 5154528

WARNINGS
Generalized urticaria has been observed rarely in patients receiving oral acetylcysteine for acetaminophen overdose. If this occurs or other allergic symptoms appear, treatment with acetylcysteine should be discontinued unless it is deemed essential and the allergic symptoms can be otherwise controlled.

If encephalopathy due to hepatic failure becomes evident, acetylcysteine treatment should be discontinued to avoid further administration of nitrogenous substances. There are no data indicating that acetylcysteine adversely influences hepatic failure, but this remains a theoretical possibility.

PRECAUTIONS
Occasionally severe and persistent vomiting occurs as a symptom of acute acetaminophen overdose. Treatment with oral acetylcysteine may aggravate the vomiting. Patients at risk of gastric hemorrhage (e.g., esophageal varices, peptic ulcers, etc.) should be evaluated concerning the risk of upper gastrointestinal hemorrhage versus the risk of developing hepatic toxicity, and treatment with acetylcysteine given accordingly.

Dilution of the acetylcysteine (SEE PREPARATION OF ACETYLCYSTEINE FOR ORAL ADMINISTRATION) minimizes the propensity of oral acetylcysteine to aggravate vomiting.

ADVERSE REACTIONS
Oral administration of acetylcysteine, especially in the large doses needed to treat acetaminophen
overdose, may result in nausea, vomiting and other gastrointestinal symptoms. Rash with or without mild fever has been observed rarely.

7.3 APPENDIX C. PERTINENT ACETADOTE SAFETY LABELING

4 CONTRAINDICATIONS
ACETADOTE is contraindicated in patients with a previous hypersensitivity reaction to acetylcysteine [see Warnings and Precautions (5.1)].

5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reactions
Serious acute hypersensitivity reactions during acetylcysteine administration including rash, hypotension, wheezing, and/or shortness of breath, have been observed in patients receiving intravenous acetylcysteine for acetaminophen overdose and occurred soon after initiation of the infusion [see Adverse Reactions (6.1)]. If a severe hypersensitivity reaction occurs, immediately stop the infusion of ACETADOTE and initiate appropriate treatment.

One patient with asthma developed bronchospasm and died after intravenous administration of acetylcysteine. ACETADOTE should be used with caution in patients with asthma, or where there is a history of bronchospasm. Patients with asthma should be closely monitored during initiation of ACETADOTE therapy and throughout ACETADOTE therapy.

Acute flushing and erythema of the skin may occur in patients receiving acetylcysteine intravenously. These reactions usually occur 30 to 60 minutes after initiating the infusion and often resolve spontaneously despite continued infusion of acetylcysteine. If a reaction to acetylcysteine involves more than simply flushing and erythema of the skin, it should be treated as a hypersensitivity reaction.

Management of less severe hypersensitivity reactions should be based upon the severity of the reaction and include temporary interruption of the infusion and/or administration of antihistaminic drugs. The ACETADOTE infusion may be carefully restarted after treatment of the hypersensitivity symptoms has been initiated; however, if the hypersensitivity reaction returns upon re-initiation of treatment or increases in severity, ACETADOTE should be discontinued and alternative patient management should be considered.

5.2 Fluid Overload

The total volume of ACETADOTE administered should be adjusted for patients less than 40 kg and for those requiring fluid restriction. To avoid fluid overload, the volume of diluent should be reduced as needed [see Dosage and Administration (2)]. If volume is not adjusted fluid overload can occur, potentially resulting in hyponatremia, seizure and death.

Intravenous administration of ACETADOTE can cause fluid overload, potentially resulting in hyponatremia, seizure and death. To avoid fluid overload, use the recommended dilution shown in Tables 2, 3 and 4 [see Dosage and Administration (2.4)].

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the literature the most frequently reported adverse reactions attributed to intravenous acetylcysteine administration were rash, urticaria and pruritus. The frequency of adverse reactions has been reported to be between 0.2% and 21%, and they most commonly occur during the initial loading dose of acetylcysteine.

Loading Dose/Infusion Rate Study

In a randomized, open-label, multi-center clinical study conducted in Australia in patients with acetaminophen poisoning, the rates of hypersensitivity reactions between a 15-minute and 60-minute intravenous infusion for the 150 mg/kg loading dose of acetylcysteine were compared.

The incidence of drug-related adverse reactions occurring within the first 2 hours following acetylcysteine administration is presented in Table 5. Overall, 17% of patients developed an acute hypersensitivity reaction (18% in the 15-minute infusion group; 14% in the 60-minute infusion group) [see Warnings and Precautions (5.1), Clinical Studies (14)].

Table 5. Incidence of Drug-Related Adverse Reactions Occurring Within the First 2 Hours Following Study Drug Administration by Preferred Term: Loading Dose/Infusion Rate Study

Treatment Group	15-minutes				60-minutes			
Number of Patients	n=109				n=71			
Cardiac disorders	5 (5%)				2 (3%)			
Severity:	*Unkn*	*Mild*	*Moderate*	*Severe*	*Unkn*	*Mild*	*Moderate*	*Severe*
Tachycardia NOS		4 (4%)	1 (1%)			2 (3%)		
Gastrointestinal disorders	16 (15%)				7 (10%)			
Severity:	*Unkn*	*Mild*	*Moderate*	*Severe*	*Unkn*	*Mild*	*Moderate*	*Severe*
Nausea	1 (1%)		6 (6%)			1 (1%)	1 (1%)	
Vomiting NOS		2 (2%)	11 (10%)			2 (3%)	4 (6%)	
Immune System Disorders	20 (18%)				10 (14%)			
Severity:	*Unkn*	*Mild*	*Moderate*	*Severe*	*Unkn*	*Mild*	*Moderate*	*Severe*
Hypersensitivity reaction	2 (2%)	6 (6%)	11 (10%)	1 (1%)		4 (6%)	5 (7%)	1 (1%)
Respiratory, thoracic and mediastinal disorders	2 (2%)				2 (3%)			
Severity:	*Unkn*	*Mild*	*Moderate*	*Severe*	*Unkn*	*Mild*	*Moderate*	*Severe*
Pharyngitis			1 (1%)					
Rhinorrhea		1 (1%)						
Rhonchi						1 (1%)		
Throat tightness						1 (1%)		
Skin & subcutaneous tissue disorders	6 (6%)				5 (7%)			
Severity:	*Unkn*	*Mild*	*Moderate*	*Severe*	*Unkn*	*Mild*	*Moderate*	*Severe*
Pruritus		1 (1%)				2 (3%)		
Rash NOS		3 (3%)	2 (2%)			3 (4%)		
Vascular disorders	2 (2%)				3 (4%)			
Severity:	*Unkn*	*Mild*	*Moderate*	*Severe*	*Unkn*	*Mild*	*Moderate*	*Severe*
Flushing		1 (1%)	1 (1%)			2 (3%)	1 (1%)	

Unkn= Unknown; NOS= not otherwise specified

Safety Study

A large multi-center study was performed in Canada where data were collected from patients who were treated with intravenous acetylcysteine for acetaminophen overdose between 1980 and 2005. This study evaluated 4709 adult cases and 1905 pediatric cases. The incidence of hypersensitivity reactions in adult (overall incidence 8%) and pediatric (overall incidence 10%) patients is presented in Tables 6 and 7.

Reference ID: 5154528

Table 6. Distribution of reported hypersensitivity reactions in adult patients receiving intravenous acetylcysteine

Reaction	Incidence (%) n=4709
Urticaria/Facial Flushing	6.1%
Pruritus	4.3%
Respiratory Symptoms*	1.9%
Edema	1.6%
Hypotension	0.1%
Anaphylaxis	0.1%

Table 7. Distribution of reported hypersensitivity reactions in pediatric patients receiving intravenous acetylcysteine

Reaction	Incidence (%) n=1905
Urticaria/Facial Flushing	7.6%
Pruritus	4.1%
Respiratory Symptoms*	2.2%
Edema	1.2%
Anaphylaxis	0.2%
Hypotension	0.1%

*Respiratory symptoms are defined as presence of any of the following: cough, wheezing, stridor, shortness of breath, chest tightness, respiratory distress, or bronchospasm.

7.4 APPENDIX D. RESULTS OF PRODUCT LABELING COMPARISON

No AEs of interest were identified from comparison of the NAL proposed product labeling to Mucomyst or Cetylev product labeling. See below for the details of the product labeling comparison.

- Contraindications:
  - Acetadote is contraindicated for use in patients with a previous hypersensitivity reaction to acetylcysteine; NAL, Mucomyst, and Cetylev product labeling does not contain a contraindication for use.
- Warnings and Precautions:
  - Acetadote describes hypersensitivity reactions as serious acute (rash, hypotension, wheezing, and/or shortness of breath), bronchospasm, acute flushing and erythema of skin; NAL, Mucomyst, and Cetylev describe hypersensitivity reactions of generalized urticaria.
  - NAL, Mucomyst, and Cetylev contain a subsection for upper gastrointestinal hemorrhage; Acetadote does not.
  - Mucomyst describes discontinuing use in the setting of encephalopathy due to hepatic failure; NAL, Mucomyst, and Cetylev do not.
  - Acetadote contains a subsection for fluid overload; NAL, Mucomyst, and Cetylev do not.
- Adverse Reactions:
  - NAL, Mucomyst, and Cetylev contain other gastrointestinal symptoms; Acetadote does not.
  - NAL, Mucomyst, and Cetylev contain rash with or without fever; Acetadote contains rash only.
  - Acetadote contains urticaria, pruritus, tachycardia NOS, hypersensitivity reaction, pharyngitis, rhinorrhea, rhonchi, throat tightness, flushing, edema, hypotension, anaphylaxis; NAL, Mucomyst, and Cetylev do not.

Reference ID: 5154528

7.5 APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) AND OSE DESIGNATED MEDICAL EVENTS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

List of OSE Designated Medical Events

System Organ Class	Preferred Terms (MedDRA version 23.0)
Blood and lymphatic system disorders	Agranulocytosis
	Aplastic anaemia
	Bone marrow failure
	Coombs negative haemolytic anaemia
	Coombs positive haemolytic anaemia
	Haemolytic anaemia
	Pancytopenia
	Thrombotic thrombocytopenic purpura
Cardiac disorders	Torsade de pointes
	Ventricular fibrillation
Ear and labyrinth disorders	Deafness
	Deafness bilateral
	Deafness neurosensory
	Deafness permanent
	Deafness transitory
	Deafness unilateral
	Ototoxicity
	Sudden hearing loss
Eye disorders	Blindness
	Blindness transient
	Blindness unilateral

Reference ID: 5154528

System Organ Class	Preferred Terms (MedDRA version 23.0)
	Optic ischaemic neuropathy
	Sudden visual loss
	Toxic optic neuropathy
Gastrointestinal disorders	Haemorrhagic necrotic pancreatitis
	Pancreatic necrosis
	Pancreatitis haemorrhagic
	Pancreatitis necrotising
General disorders and administration site conditions	Sudden cardiac death
	Sudden death
Hepatobiliary disorders	Acute hepatic failure
	Drug-induced liver injury
	Hepatic failure
	Hepatic necrosis
	Hepatitis fulminant
Immune system disorders	Anaphylactic reaction
	Anaphylactic shock
	Anaphylactoid reaction
	Anaphylactoid shock
Infections and infestations	Progressive multifocal leukoencephalopathy
	Suspected transmission of an infectious agent via product
	Transmission of an infectious agent via product
Investigations	Electrocardiogram QT prolonged
Musculoskeletal and connective tissue disorders	Myopathy toxic
	Rhabdomyolysis
Nervous system disorders	Generalised tonic-clonic seizure
	Seizure
	Serotonin syndrome
	Status epilepticus
Product issues	Product compounding quality issue
	Product contamination
	Product contamination chemical
	Product contamination microbial
	Product contamination physical
Psychiatric disorders	Completed suicide
Renal and urinary disorders	Acute kidney injury
Skin and subcutaneous tissue disorders	Acute generalised exanthematous pustulosis
	Drug reaction with eosinophilia and systemic symptoms
	Stevens-Johnson syndrome
	Toxic epidermal necrolysis
Surgical and medical procedures	Liver transplant

Reference ID: 5154528

7.6 APPENDIX F. FAERS SEARCH RESULTS

The FAERS search on November 22, 2022, yielded 3,073 reports, of which 883 were retrieved after performing the narrative text word search to identify reports in which acetylcysteine was used for treatment of acetaminophen overdose. Report counts may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse), miscoded reports, or unrelated reports. Reported outcomes for this section are the coded outcomes (see **Appendix E** for FAERS limitations).

Table 4 provides the descriptive characteristics of the FAERS reports retrieved by the search strategy described in Table 1.

Table 4. Descriptive Characteristics of FAERS Reports With NAC, Received by FDA From September 14, 1963 to November 21, 2022

		N=883*
Sex	Male	304
	Female	488
	Unknown	91
Age	< 1 year	22
	1 to <3 years	37
	3 to < 7 years	7
	7 to <17 years	76
	17 to <65 years	477
	≥ 65 years	136
	Unknown	128
Country	United States	340
	Foreign	541
	Unknown	2
Report type	Expedited	793
	Direct	63
	Periodic	26
Serious outcomes† (n=849)	Death	184
	Life-threatening	137
	Hospitalization	526
	Disability	20
	Congenital anomaly	10
	Required intervention	38
	Other serious	397

* May include duplicates.
† For the purposes of this document, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A report can have one or more outcome.
Abbreviations: NAC=Acetylcysteine

Reviewer comment: The majority (849/883) of reports were coded with a Serious Outcome. Patients <17 years of age accounted for 16% (142/883) of all reports.

Reference ID: 5154528

Table 5 lists the top 25 most frequently reported MedDRA preferred terms (PTs) and the labeling status of each PT.

Table 5. Top 25 Most Frequently Reported MedDRA PTs With NAC, Received by FDA From September 14, 1963, to November 21, 2022, Sorted by Decreasing Number of FAERS Reports per PT

MedDRA PT	Total Number of FAERS Reports*	Labeled (Yes/No); Location† or Other Category; Comment	
		NAC, Mucomyst, Cetylev (Possible or probable cases identified)	Acetadote
Toxicity to various agents	147	N; U	No; U
Overdose	204	No; Alt Ex (0)	No; Alt Ex‡
Drug ineffective	92	No; U	No; U
Vomiting	76	Yes; W/P; (0)	Yes; AR
Intentional overdose	73	No; U	No; U
Pruritus	66	No; (1); **See Section 3**	Yes; AR
Hypotension	65	No; Alt Ex; (0)	Yes; AR
Stevens-Johnson syndrome	62	No; Alt Ex; (0)	No; Alt Ex
Metabolic acidosis	50	No; Alt Ex; (0)	No; Alt Ex
Dyspnoea	48	No; Alt Ex; (0)	Yes; W/P
Nausea	48	Yes; AR; (0)	Yes; AR
Rash	48	Yes; AR; (0)	Yes; W/P
Acute kidney injury	45	No; Alt Ex; (0)	No; Alt Ex
Medication error	41	No; Alt Ex; See PT Overdose footnote	No; Alt Ex; See PT Overdose footnote
Suicide attempt	40	No; Alt Ex	No; Alt Ex
Anaphylactoid reaction	36	No; (1); **See Section 3**	No; U§
Pyrexia	35	Yes (with rash); AR; (0)	No; Alt Ex
Hepatotoxicity	34	No; Alt Ex; (0)	No; Alt Ex
Urticaria	34	Yes; W/P; (1)	Yes; AR
Acute hepatic failure	33	No; Alt Ex; (0)	No; Alt Ex
Angioedema	33	No; (1); **See Section 3**	No; Alt Ex‖
Flushing	32	No; (0)	Yes; W/P
Coma	31	No; Alt Ex; (0)	No; Alt Ex
Toxic epidermal necrolysis	30	No; Alt Ex; (0)	No; Alt Ex
Anaphylactic reaction	29	No; (0)	Yes; AR; **See Section 3**

* A report can contain more than one MedDRA PT.
† If the event is included in multiple sections of labeling, only the section of highest importance is listed.

‡ Multiple reports of NAC dosing errors leading to NAC overdose were identified. (b) (4)

§ Anaphylactoid reactions could not be differentiated from anaphylaxis due to limited information; anaphylaxis was added to the Acetadote labeling on Jun 5, 2013, and anaphylactoid reactions were removed from the label on July 29 2016.

‖ Angioedema was reported as sequelae of hypersensitivity reactions.

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term, NAC=N-acetylcysteine, U=Uninformative, Alt Ex=Alternative explanation (disease-related, indication-related, or concomitant medication-related), W/P =Warnings and Precautions, AR=Adverse Reaction

Designated Medical Events (DMEs) are adverse events that are considered serious and, from a pharmacovigilance perspective, may often be caused by exposure to drugs from many pharmacological or therapeutic classes. Identification of these events is a priority, even when the number of cases is small, and before there is evidence of disproportional reporting. DMEs are not intended to include events with a high prevalence in the general population. See **Appendix F** for a list of the Office of Surveillance and Epidemiology's (OSE) DMEs.

Table 6 lists the most frequently reported DMEs and the labeling status of each. Only PTs with a frequency ≥ 9 are listed in the table and reviewed for new potential safety signals.

Table 6. Most Frequently Reported DMEs With NAC, Received by FDA From September 14, 1963 to November 21, 2022, Sorted by Decreasing Number of FAERS Reports per PT

DME MedDRA PT	Total Number of FAERS Reports*	Labeled (Yes/No); Location† or Other Category; Comment	
		NAC, Mucomyst, Cetylev (Possible or probable cases identified)	Acetadote
Stevens-Johnson syndrome	62	No; Alt Ex; (0)	No; Alt Ex
Acute kidney injury	45	No; Alt Ex; (0)	No; Alt Ex
Anaphylactoid reaction	36	No; (1); **See Section 3**	No; U‡
Acute hepatic failure	33	No; Alt Ex; (0)	No; Alt Ex
Toxic epidermal necrolysis	30	No; Alt Ex; (0)	No; Alt Ex
Anaphylactic reaction	29	No; (0)	Yes; AR; **See section 3**
Seizure	16	No; (0)	No; **See Section 3**
Hepatic failure	14	No; Alt Ex; (0)	No; Alt Ex
Generalized tonic-clonic seizure	12	No; (0)	No; **See Section 3**
Drug-induced liver injury	10	No; Alt Ex; (0)	No; Alt Ex
Haemolytic uraemic syndrome	10	No; (0)	No; **See Section 3**

Table 6. Most Frequently Reported DMEs With NAC, Received by FDA From September 14, 1963 to November 21, 2022, Sorted by Decreasing Number of FAERS Reports per PT

DME MedDRA PT	Total Number of FAERS Reports*	Labeled (Yes/No); Location† or Other Category; Comment	
		NAC, Mucomyst, Cetylev (Possible or probable cases identified)	Acetadote
Anaphylactic shock	9	No; (0)	No; **See Section 3**
Electrocardiogram QT prolonged	9	No; Alt Ex;(0)	No; Alt Ex
Status epilepticus	8	No; (0)	No; **See Section 3**
Agranulocytosis	6	No; Alt Ex; (0)	No; Alt Ex
Rhabdomyolysis	6	No; U; (0)	No; U
Ventricular fibrillation	6	No; Alt Ex; (0)	No; Alt Ex
Completed suicide	5	No; Alt Ex; (0)	No; Alt Ex
Serotonin syndrome	5	N; Alt Ex; (0)	No; Alt Ex
Acute generalized exanthematous pustulosis	4	No; Alt Ex; (0)	No; Alt Ex
Blindness	4	No; Alt Ex; (0)	No; Alt Ex
Drug reaction with eosinophilia and systemic symptoms	4	No; Alt Ex; (0)	No; Alt Ex
Haemolytic anaemia	4	No; (0)	No; **See Section 3**
Hepatitis fulminant	3	No; Alt Ex; (0)	No; Alt Ex
Liver transplant	3	No; Alt Ex; (0)	No; Alt Ex
Pancytopenia	3	No; U; (0)	No; U
Thrombotic thrombocytopenic purpura	3	No; (0)	No; **See Section 3**
Hepatic necrosis	2	No; Alt Ex; (0)	No; Alt Ex
Aplastic anaemia	1	No; U; (0)	No; U
Bone marrow failure	1	No; U; (0)	No; U
Deafness	1	No; U; (0)	No; U; Alt Ex
Severe cutaneous adverse reaction	1	No; Alt Ex; (0)	No; Alt Ex
Torsades de pointes	1	No; Alt Ex; (0)	No; Alt Ex

* A report can contain more than one MedDRA PT.
† If the event is included in multiple sections of labeling, only the section of highest importance is listed.
‡ Anaphylactoid reactions could not be differentiated from anaphylaxis due to limited information; anaphylaxis was added to the Acetadote labeling on Jun 5, 2013 and anaphylactoid reactions were removed from the label on July 29 2016.

Table 6. Most Frequently Reported DMEs With NAC, Received by FDA From September 14, 1963 to November 21, 2022, Sorted by Decreasing Number of FAERS Reports per PT			
DME MedDRA PT	**Total Number of FAERS Reports***	**Labeled (Yes/No); Location† or Other Category; Comment**	
		NAC, Mucomyst, Cetylev (Possible or probable cases identified)	**Acetadote**
Abbreviations: NAC=N-acetylcysteine, DME=Designated Medical Event, MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term, Alt Ex=Alternative explanation (disease-related, indication-related, or concomitant medication-related), AR=Adverse Reaction, U=Uninformative			

7.7 APPENDIX G. LITERATURE SEARCH RESULTS

Table 7 lists medical literature articles with relevant new safety findings.

Table 7. Medical Literature Articles with Relevant New Safety Findings for NAC			
Citation	**Adverse Event(s)**	**Labeled (Yes/No); Location, or Other Category; Comment**	
		NAC, Mucomyst Cetylev (Possible or probable cases identified)	**Acetadote**
Langford JS, Sheikh S. An adolescent case of sulfhemoglobinemia associated with high-dose metoclopramide and N-acetylcysteine. *Ann Emerg Med* 1999;34(4 Pt 1):538-41.	Sulfhemoglobinemia	No; (0)	No
Jabr FI. Skin rash after oral N-acetylcysteine for kidney protection. *Int J Dermatol* 2014;53(3):e189-190.	Skin rash	Yes; AR; (1); **See Section 3**	Yes; W/P
Mroz LS, Benitez JG, Krenzelok EP. Angioedema with oral N-acetylcysteine. *Ann Emerg Med* 1997;30(2):240-1.	Anaphylactoid reaction with angioedema	No (1, duplicate of FAERS case #3271610); **See Section 3**	No
Bailey DJ, Andres JM. Liver injury after oral and rectal administration of N-acetylcysteine for meconium ileus equivalent in a patient with cystic fibrosis. *Pediatrics* 1987;79(2):281-2.	DILI	No*	No

Cooke A, Deshpande AV, Wong CKF, Cohen R. Hepatic derangement following N-acetylcysteine enemas in an infant with cystic fibrosis. *J Paediatrics and Child Health* 2008;44:673-5.	DILI	No*	No
Mohammed S, Jamal AZ, Robison LR. Serum sickness-like illness associated with N-acetylcysteine therapy. *Ann Pharmacother* 1994;28(2):285.	Serum sickness	No; (1); **See Section 3**	No
* The two cases (Bailey et al. and Cooke et al.) describe patients with meconium ileus treated with oral and rectal NAC who developed DILI; we will continue to monitor for this event in an unapproved population. Abbreviations: NAC=N-acetylcysteine			

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/

LISA M WOLF
04/06/2023 04:20:48 PM

MONICA MUNOZ
04/06/2023 04:31:16 PM

M E M O R A N D U M

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

DATE: March 10, 2023

TO: Frank Anania, MD, FACP, AGAF, FAASLD
(Acting) Director
Division of Hepatology and Nutrition (DHN)
Office of Immunology and Inflammation (OII)
Office of New Drugs (OND)

FROM: Monica Javidnia, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun Julia Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: Routine inspection of Pharma Medica Research Inc., Toronto, Ontario, Canada.

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of study 2021-5140 (NDA 215040, IND 130190) conducted by CI Janice Faulknor, MD at Pharma Medica Research Inc., Toronto, Ontario, Canada.

No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-out. There were two discussion items related to suggested Standard Operating Procedure (SOP) revisions, detailed below in Section 3.

After reviewing the inspectional findings, I conclude the data from the audited study 2021-5140 are reliable, with the exception of Subject (b) (6). I recommend the review division consider the eligibility of Subject (b) (6) based on our inability to verify their eligibility following concerns raised during the inspection (see Discussion Item 2).

2. Inspected Studies:

NDA 215040, IND 130190

Study Number: 2021-5140
Study Title: A Single-Dose, Bioequivalence Study of Two Formulations of Acetylcysteine 1000 mg under Fasting Conditions
Dates of conduct: 12/06/2021 – 12/30/2021

Clinical site: Pharma Medica Research, Inc.
4770 Sheppard Avenue East
Toronto, Ontario, Canada

3. Inspectional Findings

Pharma Medica Research Inc., Toronto, Ontario, Canada

ORA investigator Lori Gioia inspected Pharma Medica Research Inc., Toronto, Ontario, Canada from December 05-08, 2022.

The previous OSIS inspection of Pharma Medica Research Inc. was conducted from January 06-10, 2020. At the conclusion of the inspection, Form FDA 483 was not issued, and there were no discussion items. The final classification was NAI, No Action Indicated.

The current inspection included auditing the following items:
-Informed consent forms
-Institutional review board approvals
-Adverse events (AEs)
-Test article accountability and storage
-PK sampling
-Dosing
-Protocol deviations
-Study source records (all 24 randomized subjects)
-Electronic case report forms (eCRFs)
-SOPs
-Calibration records for centrifuges and freezers

At the conclusion of the inspection, investigator Lori Gioia did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site. However, there were two discussion items described at the conclusion of the inspection.

Discussion Item 1: The ORA investigator suggested updating the Standard Operating Procedure (SOP) related to the Adverse Event (AE) follow-up interval because the time period between an initial AE report for Subject (b) (6) and the follow-up was greater than 30 days.

Reference ID: 5139561

Firm Response: The firm did not provide a response to the discussion item.

OSIS Evaluation: The protocol for study 2021-5140 does not require a specific window for AE follow-up, and after review of documentation collected during the inspection, I conclude that that clinical site appropriately conducted the AE follow-up for Subject (b) (6). Although it may be a good practice to standardize a time period for conducting an AE follow-up, there is no requirement to do so under this specific study protocol.

Discussion Item 2: The ORA investigator suggested updating the subject screening SOP because there was some confusion as to the eligibility of Subject (b) (6). The study protocol exclusion criteria states subjects may not be enrolled if they have a blood loss or donation ≥500 mL within 56 days prior to drug administration. During the inspection, the ORA investigator initially identified Subject (b) (6) as being ineligible due to a record noting blood loss of >500 mL. However, following a review of "prior study" records, the ORA investigator determined that this blood loss occurred over the entire study, which is beyond the 56-day limitation.

Firm Response: The firm did not provide a response to the discussion item.

OSIS Evaluation: The protocol required that the CI exclude any subject from enrollment if they donated/lost ≥500 mL of blood within 56 days prior to drug administration. Based on the EIR statements, Subject (b) (6) was enrolled and dosed despite documentation of >500 mL blood loss. However, ORA determined that the initial calculation of blood loss (>500 ml) was incorrect.

The inspection did not collect study records to support this discussion item, and we contacted ORA for clarification on how they (ORA and the site) performed the blood loss calculation during the inspection [**Attachment 1**]. The ORA investigator stated she reviewed timepoints from the protocol from a "prior study" in which the subject participated in. Since there were no records collected from the inspection, I recommend the review division consider the eligibility of Subject (b) (6) because I am unable to verify the calculation of the blood loss associated with the exclusion criteria.

Monica Javidnia, Ph.D.
Staff Fellow

Reference ID: 5139561

Draft: MJ 03/02/2023, 03/07/2023, 03/08/2023
Edit: DP 03/03/2023, 03/07/2023; JC 3/3/2023 3/8/2023

OSIS File #: BE 9646

eNSpect Assignment ID: 206618
eNSpect OpID: 233491

Attachment 1: Email Communication with ORA Investigator Regarding Review of Subject (b) (6) s Study Records

Reference ID: 5139561

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/

MONICA JAVIDNIA
03/10/2023 09:17:24 AM

DOUGLAS B PHAM
03/10/2023 09:19:15 AM

SEONGEUN CHO
03/10/2023 10:29:40 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology Literature Review

Date:	March 1, 2023
Reviewer:	Joel L. Weissfeld, MD MPH Division of Epidemiology I
Team Leader:	Benjamin J. Booth, PhD MS Division of Epidemiology I
Associate Director:	Wei Hua, MD PhD MS MHS Division of Epidemiology I
Drug Name:	acetylcysteine lysine (Legubeti)
Subject:	Efficacy and safety of N-acetylcysteine when used to treat acetaminophen overdose
Application Type/Number:	NDA 215040
Applicant/sponsor:	Galephar
TTT ID #:	2022-629

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The Division of Epidemiology I (DEPI) responded to a request from the Division of Hepatology and Nutrition (DHN) for an assessment of published literature used by an NDA applicant (Galephar) to support the effectiveness and safety of acetylcysteine lysine.

Galephar submitted NDA 215040, a Section 505(b)(2) application for acetylcysteine lysine powder (presented as an orally administered antidote for acetaminophen poisoning). DHN asked DEPI to (1) address literature submitted in NDA 215040 to support efficacy and safety of the reference listed drug (N-acetylcysteine; NAC) and (2) identify additional studies possibly missed by Galephar.

Galephar described a wide ranging search for public information about the safety and efficacy of NAC as an antidote for acetaminophen poisoning. This search identified reports from eight non-randomized studies of oral NAC. DEPI combined four approaches to canvass medical literature for possibly relevant studies missed by Galephar. DEPI's search identified 46 additional articles but none considered superior to articles identified by Galephar.

DEPI recommended that DHN regard the literature presentations by Galephar as practically complete for purposes of NDA review and product labeling.

1 INTRODUCTION

The Division of Epidemiology I (DEPI) responds to a request from the Division of Hepatology and Nutrition (DHN) for an assessment of published literature used by an NDA applicant (Galephar) to support the effectiveness and safety of acetylcysteine lysine.

On July 7, 2022, Galephar submitted NDA 215040 for acetylcysteine lysine powder as an orally administered "antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen."[a] As a Section 505(b)(2) application, NDA 215040 relies on FDA's previous findings of safety and effectiveness for the Reference Listed Drug (LD) MUCOMYST (acetylcysteine solution; NDA 013601). Galephar's Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS) additionally support effectiveness and safety by including "information in the public literature."[b]

On August 31, 2022, DHN filed a Request of Consultation, which asks DEPI to address "the methodology and approach in literature submitted [in NDA 215040] to support the efficacy and safety of the LD, N-acetylcysteine including implications and limitations."[c] The Request for

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[a] Draft Prescribing Information for [redacted] (b) (4) (acetylcysteine lysine) powder for oral solution, submitted to NDA 215040, eCTD 0000, Module 1.14, on July 7, 2022.

[b] Introduction to Summary, submitted to NDA 215040, eCTD 0000, Module 2.2, on July 7, 2022.

[c] Request for Consultation, filed under NDA 215040 on August 31, 2022 (DARRTS Reference ID: 5039251).

Reference ID: 5134103

Consultation also asks DEPI to identify "additional studies/trials that the Applicant may have missed."[d]

2 REVIEW METHODS AND MATERIALS

DEPI identified relevant articles cited in the NDA's SCE (Module 2.7.3), SCS (Module 2.7.4), or Literature References (Module 2.7.5). DEPI identified other possibly relevant articles by examining 109 full-text articles submitted to NDA Module 5.4.

To identify additional studies or trials missed by the Applicant, DEPI:

- Used the text words *acetylcysteine*, *acetaminophen*, and *paracetamol* to search the Cochrane Database of Systematic Reviews (CDSR; https://www.cochranelibrary.com/cdsr/reviews).
- Examined literature cited by clinical reviews of CETYLEV®, another oral acetylcysteine product approved (on January 29, 2016) by the OND Division of Gastroenterology and Inborn Error Products (DGIEP).[e]
- Used the query string '(acetaminophen) AND (acetylcysteine)' to search PubMed (https://pubmed.ncbi.nlm.nih.gov/) for articles published in 2014 or later (**APPENDIX 1**).[f]
- Assessed articles covered by a 2013 systematic review of oral and intravenous (IV) acetylcysteine for treatment of acetaminophen toxicity [1].[g]

3 REVIEW RESULTS

3.1 Applicant's Methodology

As reproduced verbatim below, the SCS (pp 4-5) presents a 4-part search strategy for "information in the public domain to support the safety and efficacy" of NAC as an antidote for acetaminophen poisoning:

i. a PubMed search for publications from Jan 1, 1960, to October 2021 which contained 'acetylcysteine' in the title or abstract, review of the abstracts from these documents and

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[d] DHN also requested a literature review on lysine safety. DEPI will address this request by separate memorandum.

[e] Dimick-Santos L and SO Omokaro, Clinical Review for N-acetylcysteine (CETYLEV®), filed under NDA 207916 on November 20, 2015 (DARRTS Reference ID: 3850258).

Korvick J, Division Director (Signatory) Summary Review for Regulatory Action, filed under NDA 207916 on January 29, 2016 (DARRTS Reference ID: 3879846).

[f] DEPI's search strategy assumed complete awareness in DGIEP of relevant literature published before 2013 (>2 years before DGIEP's January 2016 approval of CETYLEV®).

[g] Referenced by **Schwarz 2014** [2], commentary identified by PubMed search.

Reference ID: 5134103

collection of publications which appeared to have relevant information regarding the pharmacology, absorption, distribution, metabolism, excretion, and toxicity of acetylcysteine for detailed review

ii. review of those references cited in the bibliography of the selected publications from (i) above and collection of the publications for those references which appeared to have pertinent information but were not captured in the PubMed search

iii. review of publications cited in the prior IND application for [redacted] (b) (4) that were not captured from (i) or (ii) above[h]

iv. review of the documents from the FDA review of NDA 207916 for CETYLEV available through Drugs@FDA and collection of any publications cited in those documents that were not captured in (i) or (ii) above. A review of the bibliographies of any publications obtained through this process was conducted as described in (ii) above

3.2 Summary of Clinical Efficacy

As summarized below, the SCE presents three articles to support the effectiveness of NAC as an antidote for acetaminophen poisoning.

Prescott 1979 [3]. Clinicians at a U.K. medical center used IV NAC (300 mg/kg over 20 hours) to treat 100 instances of acetaminophen poisoning. Unlike 57 historical controls given supportive treatment only, severe liver damage occurred infrequently in patients initiating NAC within 10 hours of acetaminophen ingestion (Table 1).

Table 1: Severe liver damage from acetaminophen poisoning, in patients treated with intravenous N-acetylcysteine (N=100) and historical controls (N=57), by degree of poisoning and timing of treatment.

		Severe liver damage	
	N	**n**	**%**
High-risk poisoning			
Rx <10 hours	33	1	3.0
Rx 10-24 hours	27	18	66.7
Historical control	28	25	89.3

[h] [redacted] (b) (4) – proprietary name initially proposed by Galephar for acetylcysteine lysine.

Reference ID: 5134103

	N	Severe liver damage	
		n	%
Intermediate-risk poisoning			
Rx <10 hours	29	0	0.0
Rx 10-24 hours	11	2	18.2
Historical control	29	8	27.6

SOURCE: **Prescott 1979** [3].
FOOTNOTES:
1. Poisoning defined by plasma acetaminophen concentration above a line (on a semilogarithmic graph) joining 200 mg/L and 30 mg/L at 4 and 15 hours post ingestion, respectively.
2. High-risk poisoning defined by plasma acetaminophen concentration above a line (on a semilogarithmic graph) joining 300 mg/L and 45 mg/L at 4 and 15 hours post ingestion, respectively.
3. Severe liver damage defined by aspartate transaminase (AST) or alanine transaminase (ALT) blood concentration >1000 IU/L.
4. The row stubs *Rx <10 hours* and *Rx 10-24 hours* indicate time between acetaminophen ingestion and start of treatment with N-acetylcysteine. The source publication simply states that "most [historical control] patients presented early."

Smilkstein 1988 [4]. Between September 1976 and February 1985, investigators at the Rocky Mountain Poison and Drug Center prospectively identified 2,540 patients (3.3% under 5 years in age) with the following characteristics:

- history of single, acute acetaminophen overdose,
- plasma acetaminophen concentration measured at least once between 4 and 24 hours after ingestion,
- complete course of treatment with oral NAC (140 mg/kg loading dose followed by 17 doses at 70 mg/kg administered at 4-hour intervals), and
- aspartate transaminase (AST) measurements sufficient to determine hepatotoxicity outcomes.

Table 2 summarizes occurrences of hepatotoxicity in risk categories defined by **Prescott 1979** [3].

Reference ID: 5134103

Table 2: Hepatotoxicity from acetaminophen poisoning, in patients treated with oral N-acetyl-cysteine, by degree of poisoning and timing of treatment.

		Severe liver damage	
	N	**n**	**%**
High-risk poisoning			
Rx <10 hours	206	17	8.3
Rx 10-24 hours	578	199	34.4
Intermediate-risk poisoning			
Rx <10 hours	527	32	6.1
Rx 10-24 hours	935	247	26.4

SOURCE: **Smilkstein 1988** [4].
FOOTNOTES:
1. Poisoning defined by plasma acetaminophen concentration above a line (on a semilogarithmic graph) joining 200 mg/L and 30 mg/L at 4 and 15 hours post ingestion, respectively.
2. High-risk poisoning defined by plasma acetaminophen concentration above a line (on a semilogarithmic graph) joining 300 mg/L and 45 mg/L at 4 and 15 hours post ingestion, respectively.
3. Severe liver damage defined by aspartate transaminase (AST) or alanine transaminase (ALT) blood concentration >1000 IU/L.
4. The row stubs *Rx <10 hours* and *Rx 10-24 hours* indicate time between acetaminophen ingestion and start of treatment with N-acetylcysteine.

Williamson 2013 [5]. Investigators at the Illinois Poison Center retrospectively identified a consecutive series of 795 patients with the following characteristics:

- age ≥12 years,
- NAC started within 8 hours of a single, acute acetaminophen ingestion (January 2002 – December 2007),
- acetaminophen concentration 4 hours post-ingestion at 150 mg/L or equivalent level according to Rumack-Matthew nomogram, and
- complete course of NAC treatment according to one of three standard protocols (2 oral and 1 IV).

Table 3 summarizes outcomes according to NAC treatment.

Reference ID: 5134103

Table 3: Number of patients with (1) death or liver transplantation (LT), (2) hepatic encephalopathy grade III or IV (HE), creatinine (Cr) >3.4 mg/dL, or international normalized ratio (INR) >6.5, and (3) acidosis, in patients completing a course of N-acetylcysteine treatment according to one of three standard protocols.

N-acetylcysteine treatment protocol	N	Number of patients with outcome		
		Death or LT	HE, high Cr, or INR >6.5	Acidosis (pH <7.3)
20-hour intravenous	213	0	0	3
36-hour oral	213	0	0	0
72-hour oral	369	0	0	1

SOURCE: **Williamson 2013** [5].

3.3 Summary of Clinical Safety

The SCE cites 39 articles to support the safety of NAC [6-44]. As summarized below, 5 articles concerned oral NAC [7,20,21,36,38], 20 articles concerned IV NAC [8,9,11,14,17,22,24-29,32-35,37,40,42,44], and 14 articles concerned matters of indirect importance to NAC safety [6,10,12,13,15,16,18,19,23,30,31,39,41,43].

3.3.1 Safety of Oral NAC for Acetaminophen Poisoning

Miller 1983 [7]. In a study sponsored by industry and directed by the Rocky Mountain Poison Center, investigators recorded adverse events experienced by 1,329 patients started on oral NAC (standard 72-hour regimen) for acetaminophen poisoning. Monitoring included periodic laboratory testing and electrocardiography according to protocol schedule. Vomiting and diarrhea occurred frequently (Table 4). **Miller 1983** regarded oral NAC as the principal cause for diarrhea and a contributing cause for vomiting.

Table 4: Patients with acetaminophen overdose (N), number and percent (n, %) with vomiting and diarrhea, by oral N-acetylcysteine dose category (number of doses administered).

Dose Category	N	Vomiting		Diarrhea	
		n	%	n	%
0	46	9	19.6	1	2.2
1-5	405	89	22.0	72	17.8
6-8	204	62	30.4	61	29.9
9-11	102	34	33.3	32	31.4
12-14	57	20	35.1	22	38.6
≥15	515	262	50.9	224	43.5
ALL	1,329	476	35.8	412	31.0

SOURCE: **Miller 1983** [7].

Reference ID: 5134103

Mroz 1997 [20]. Investigators from Children's Hospital of Pittsburgh reported a case of anaphylactoid reaction with angioedema in a 25-year-old man treated with oral NAC for acetaminophen poisoning.

Bailey 1998 [21]. Investigators from a children's hospital in Toronto retrospectively identified 60 patients treated over a 6 year period (1990 – 1995) with oral or IV NAC for acetaminophen overdose. Medical charts documented an adverse reaction in 11 patients. Adverse reactions included flushing, urticaria, angioedema, and wheezing. Zero of 16 patients developed an adverse reaction during oral NAC.

Sandilands 2009 [36]. Authors of a systematic review of literature (through 2008) determined that "no formal comparative study has ever been performed between oral and intravenous [NAC] therapy." Adverse reactions to NAC, as commonly reported in literature, included nausea and vomiting ("particularly with the oral antidote") and anaphylactoid reactions—flushing, rash, pruritus, angioedema, bronchospasm, chest pain, and hypotension (rarely).

Bebarta 2010 [38]. Investigators at 11 U.S. centers retrospectively identified 503 patients treated with NAC for acetaminophen overdose (June 2006 – December 2007). Standardized chart reviews identified no serious adverse events related to NAC. Table 5 summarizes the number of patients with at least one related (nonserious) adverse event, by route of NAC administration.

Table 5: Patients treated with intravenous NAC only or oral NAC only, number (n) and percent (%) with at least one adverse event.

	Route of Administration			
	IV N=306		**Oral N=145**	
Adverse Event	**n**	**%**	**n**	**%**
Gastrointestinal	27	8.8	33	22.8
Anaphylactoid	18	5.9	3	2.1
Other AE	9	2.9	3	2.1
Any AE	42	13.7	37	25.5

SOURCE: **Bebarta 2010** [38].
ABBREVIATIONS: AE – adverse event; NAC – N-acetylcysteine
FOOTNOTES:
1. Patients treated with both intravenous and oral NAC (N=52) excluded from analysis.
2. Gastrointestinal AEs: nausea and vomiting.
3. Anaphylactoid AEs: bronchospasm, pruritus, flushing, urticaria, other rash, chest tightness, and hypotension.
4. Other AEs: tachycardia, presyncope, syncope, and anxiety.

Reference ID: 5134103

3.3.2 Safety of IV NAC for Acetaminophen Poisoning

Bateman 1984 [8]. U.K. investigators described adverse events (nausea, rash, fall in blood pressure, and bronchospasm) in seven patients treated with IV NAC for acetaminophen poisoning.

Mant 1984 [9]. Combining reports over a 5-year study period (1979-1983) to the U.K. National Poisons Information Service and a drug manufacturer, investigators identified 38 instances of anaphylactoid reaction (rash, nausea/vomiting, angioedema, hypotension, bronchospasm, flushing, and tachycardia) to IV NAC and 19 instances of NAC overdose due to medical error.

Dawson 1989 [11]. Investigators in Australia summarized 30 voluntary reports of adverse reactions (rash, pruritus, nausea, vomiting, bronchospasm, tachycardia, hypotension, and hypertension) to IV NAC for acetaminophen poisoning (January 1979 – September 1987).

Smilkstein 1991 [14]. U.S. investigators described outcomes from a prospective, multicenter, single-arm clinical trial of 48-hour IV NAC for acute acetaminophen overdose (June 1984 – March 1990). An adverse event possibly related to IV NAC occurred in 32 of 223 patients (14.3%). A potentially life threatening reaction (edema, diffuse rash, wheezing, throat tightness, and itching) occurred in a patient who improperly received 12 g NAC (instead of 3.6 g NAC) as a fifth dose.

Chan 1994 [17]. Investigators in Hong Kong described fever or rash as adverse reactions in 8 of 56 patients (14.3%) treated with IV NAC for acetaminophen poisoning (1989-1992).

Yip 1998 [22]. Investigators at the Rocky Mountain Poison and Drug Center reviewed records in a Toxic Exposure Surveillance System to identify 76 patients administered an oral NAC preparation by an IV route (1992 – 1993). An adverse reaction occurred in four patients (5.3%).

Lifshitz 2000 [24]. Investigators in Israel used medical records to document adverse reaction (rash, urticaria, or pruritus) in 3 of 92 patients (3.2%) treated with IV NAC for acetaminophen overdose (1994 – 1998).

Schmidt 2001 [25]. Investigators in Denmark searched diagnosis codes in a hospital database to identify 529 patients admitted for acetaminophen poisoning and treated with IV NAC (January 1994 – June 1999). Medical records documented any adverse reaction in 45 patients (8.5%), cutaneous adverse reaction (rash, pruritus, or flushing) in 42 patients (7.9%), and systemic adverse reaction (bronchospasm, angioedema, nausea, vomiting, dizziness, hypotension, fever, sweating, coughing, or chest pain) in 18 patients (3.4%).

Kao 2003 [26]. Investigators searched a clinical database and pharmacy records for an academic medical center in Indiana to identify 187 patients intravenously administered an oral NAC product for acetaminophen poisoning (September 1995 – September 2001). Review of medical records identified 7 patients (3.7%) with adverse event possibly or probably related to IV NAC. Among these patients, six presented with cutaneous anaphylactoid adverse events. Life-

Reference ID: 5134103

threatening apnea and bradycardia occurred in a 37-year-old man 1 hour after start of NAC infusion.

Lynch 2004 [27]. Investigators prospectively identified "a convenience sample" of 64 patients treated (in a short-stay ward for the Hull Royal Infirmary in Pontefract, England) with IV NAC for acetaminophen poisoning (January 1997 – June 1999). Thirty-one patients (48.4%) experienced a non-severe anaphylactoid reaction (rash, flushing, nausea, vomiting, pruritus, or bronchospasm).

Gheshlagi 2005 [28]. Investigators from Iran published a research abstract, which reported side effects (nausea, vomiting, flushing, bronchospasm, vertigo, skin rash, or hypotension) in 77 of 173 patients (44.5%) treated with IV NAC for acetaminophen poisoning.

Kerr 2005 [29]. Investigators at 7 urban referral hospitals in Australia randomized 180 patients to 1 of 2 IV NAC dosing regimens for acetaminophen poisoning (2-year enrollment period ending in 2003). A (nonserious) drug-related adverse event occurred in 49 of 109 (45.0%) and 27 of 71 (38.0%) patients administered IV NAC loading doses (150 mg/kg) over 15 and 60 minutes, respectively.

Merl 2007 [32]. Investigators searched an institutional database for a community teaching hospital in Australia to identify 470 patients with a principal discharge diagnosis indicating acetaminophen overdose (July 1995 – June 2004). A review of medical records documented adverse drug reaction (urticaria, flushing, bronchospasm, pruritus, chest pain, hypotension, or facial angioedema) in 36 of 320 patients (11.2%) treated with IV NAC. The investigators identified a major adverse drug reaction in 2 patients (0.6%; hypotension and facial angioedema).

Whyte 2007 [33]. Investigators used a clinical database managed by a regional toxicology treatment unit in Australia to identify 399 patients treated with IV NAC for acetaminophen poisoning (January 13, 1987 – January 10, 2003). The database recorded adverse drug reaction to IV NAC in 37 patients (9.3%) and anaphylactoid adverse drug reaction in 7 patients (1.8%).[i]

Pakravan 2008 [34]. Investigators at the Royal Infirmary of Edinburgh (United Kingdom) prospectively monitored 169 patients treated with IV NAC for acetaminophen overdose (July 2006 – May 2007). Monitoring documented a prespecified adverse reaction in 130 patients (76.9%), including 17 (10.1%) and 51 (30.2%) patients (classified by most severe reaction) with severe and moderately severe reaction, respectively.[j]

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[i] Analysis restricted to first instance of IV NAC for acetaminophen poisoning.

[j] Criteria for severe reaction: NAC infusion stopped because of severe flushing, respiratory distress, moderate to severe chest pain, >50% reduction in peak expiratory flow rate, or hypotension (systolic blood pressure <90 mmHg or diastolic blood pressure <50 mmHg).

Waring 2008 [35]. Investigators at the Royal Infirmary of Edinburgh (United Kingdom) prospectively monitored 362 patients treated with IV NAC for acetaminophen overdose (March 2005 – June 2006). Study-specific data collection documented adverse reaction to IV NAC in 147 patients (40.6%), anaphylactoid reaction in 54 patients (14.9%), and gastrointestinal reaction in 90 patients (24.9%).

Yarema 2009 [37]. Investigators for the Canadian Acetaminophen Overdose Study used a 75-item data collection form to abstract medical records for patients evaluated at 34 Canadian hospitals for possible acetaminophen poisoning (1980 – 2005). Analyses included 2,086 patients with a toxic concentration of acetaminophen in blood, IV NAC initiated between 4 and 24 hours after acetaminophen ingestion, and known hepatic outcome. Medical records documented an anaphylactoid reaction (pruritus, urticaria, facial flushing, edema, stridor, shortness of breath, wheezing, cough, or low blood pressure) in 148 patients (7.1%) and anaphylactoid reaction with systemic symptoms (respiratory symptoms or hypotension) in 33 patients (1.6%).[k]

Zyoud 2010 [40]. Investigators reviewed medical records for 125 patients admitted to a hospital in Malaysia and treated with IV NAC for acetaminophen overdose (2005 – 2008). When classified by the most severe reaction, 12 (9.6%), 17 (13.6%), and 54 (34.2%) patients experienced severe, moderate, and mild reactions, respectively.[l]

Mahmoudi 2015 [42]. Mahmoudi, et al., reported a case of fatal IV NAC overdose due to medical error (100 g instead of 10 g loading dose). Complications included hemolysis, thrombocytopenia, and acute renal failure.

Yarema 2018 [44]. The Canadian Acetaminophen Overdose Study reported cutaneous reaction only, systemic reaction only, and both cutaneous and systemic reactions in 398 (6.2%), 34 (0.5%), and 96 (1.5%) of 6,455 patients started on IV NAC for acetaminophen poisoning (1980 – 2005).[m]

3.3.3 Miscellaneous Articles

The SCS cited 14 miscellaneous articles, which addressed matters such as (1) NAC transfer to newborn by placental route [18], (2) NAC pharmacokinetics (PK) in pre-term infants [23], (3) NAC PK in patients with hepatic [19] or renal failure [31,39,41], (4) drug-drug interaction [10,43], (5) NAC effects on hemostatic parameters in healthy subjects [30], (6) effects of

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[k] For external control, **Yarema 2009** presented results from the National Multicenter Study. See, **Smilkstein 1988** [4].

[l] Severe reaction – severe chest pain, angioedema, or hypotension; moderate reaction – flushing, pruritus, rash, or mild chest pain; mild reaction – nausea or vomiting.

[m] Unlike **Yarema 2009** [37], **Yarema 2018** [44] included all patients treated with IV NAC (21-hour protocol), regardless of acetaminophen blood concentration values, timing of NAC infusions in relation to acetaminophen ingestions, and availability of data for determining hepatic outcome.

acetaminophen on platelet [12] or leukocyte function [15], (7) ECG abnormality in patients with hepatic failure [6], and (8) distinguishing features of anaphylactoid reaction [13] and anaphylaxis [16].

3.4 DEPI Search for Studies Missed by Applicant

3.4.1 Cochrane Database of Systematic Reviews

DEPI identified one systemic review in CDSR of interventions for acetaminophen overdose (**Chiew 2018** [45]). **Chiew 2018** identified 11 randomized clinical trials (RCTs) overall, including 6 RCTs with a NAC-treatment arm.

Two RCTs (both conducted in Iran) compared oral vs. IV NAC. **Chiew 2018** assessed risk of bias as high for both RCTs.

- **Arefi 2013** [46] randomized 66 patients to receive either oral or IV NAC for acetaminophen overdose. Nausea occurred more frequently in patients treated with oral NAC.

- **Eizadi-Mood 2013** [47] randomized 50 patients to receive a first NAC dose by either oral or IV route. Patients in both arms completed NAC treatment by IV route. Anaphylactoid reaction occurred more frequently in patients initiating treatment intravenously.[n]

Four RCTs assessed some aspect of IV NAC for acetaminophen overdose.

- **Keays 1991** [48] randomized 50 patients presenting in fulminant hepatic failure to receive either IV NAC or supportive care only.

- **Kerr 2005** [28] randomized 180 patients to receive IV NAC with initial dose (150 mg/kg) administered over either 15 or 60 minutes.[o]

- **Bateman 2014** [49] randomized 222 patients to receive IV NAC (300 mg/kg total) administered according to either modified 12-hour or standard 20-hour schedule.[p] **Bateman 2014** assessed the primary outcome (vomiting, retching, or antiemetic-drug rescue) during first 2 hours of IV NAC. The primary outcome occurred in 39 of 108 (36.1%) and 71 of 109 (65.1%) evaluable patients initiating IV NAC according to modified and standard schedule, respectively.

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[n] Analysis excluded (post randomization) patients unable to tolerate oral NAC.

[o] The SCS cited **Kerr 2005** [28]. See Section 3.3.2.

[p] Modified IV NAC sequence: (a) 100 mg/kg in 200 mL over 2 hours, (b) 200 mg/kg in 1000 mL over 10 hours. Standard IV-NAC sequence: (a) 150 mg/kg in 200 mL over 15 minutes, (b) 50 mg/kg in 500 mL over 4 hours, (c) 100 mg/kg in 1000 mL over 16 hours.

Reference ID: 5134103

- **Cumberland Pharmaceutical 2014** [50] randomized 17 patients to receive IV NAC (ACETADOTE®) formulated either with ethylenediaminetetraacetic acid (EDTA) or without EDTA.

A regularly updated online medical resource (UpToDate®) confirms that "there are no randomized, placebo-controlled trials evaluating the efficacy of N-acetylcysteine for the prevention of hepatic injury from acetaminophen poisoning."[q]

3.4.2 DGIEP Reviews for NDA 207916

The Division Director Summary Review for NDA 207916 cited a review article (**Rumack 1975** [51]) as support presentation of the Rumack-Matthew nomogram in the CETYLEV® label.

The Clinical Review for NDA 207916 cited 20 articles [48,52-70], including articles to support (1) NAC treatment for acute acetaminophen ingestion [54,57,58,61,65,66,68], (2) NAC treatment for repeated ingestion of supratherapeutic amounts of acetaminophen [53,54,57,58,60,61,65,66,68], (3) prolonging NAC treatment in certain patients with acetaminophen still detected in blood after initial treatment [48,53,54,58,59,61-63,65,66,69], and (4) NAC dosing for patients ≥100 kg in body weight [56,65,67,70].[r]

Together, the Clinical and Summary Reviews for NDA 207916 cited 21 articles classified (by DEPI) into 6 categories:

- 9 reviews of general scope [51,54,55,57,61,65,66,68,69].
- 4 reviews directed toward pediatrics [58,60,63,64].
- 1 study assessing a method to prevent IV NAC dosing and administration errors [56].
- 1 RCT (**Keays 1991** [48]) summarized above under Section 3.4.1.
- 1 case report describing occurrence of hepatotoxicity attributed to premature discontinuation of IV NAC [59].
- 5 observational studies [52,53,62,67,70] summarized below.

Rumack 1978 [52]. Investigators from the Rocky Mountain Poison Center reported results from

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[q] Heard K and R Dart. Acetaminophen (paracetamol) poisoning in adults: Treatment. In SJ Traub (Ed.), *UpToDate*®, Waltham, MA. https://www.uptodate.com/contents/acetaminophen-paracetamol-poisoning-in-adults-treatment. (Accessed on February 1, 2023.)

[r] A footnote to Table 1 in Prescribing Information for CETYLEV® presents two statements. (1) No specific studies have been conducted to evaluate the necessity of dose adjustments in patients weighing over 100 kg. (2) Limited information is available regarding the dosing requirements of patients that weigh more than 100 kg.

a U.S. multi-clinic open study (initiated in September 1976) of 100 patients treated with oral NAC for acetaminophen overdose. **Rumack 1978** observed hepatotoxicity (serum glutamic-oxaloacetic transaminase (SGOT) >1000 IU/L) less frequently in patients initiating treatment within 10 hours than patients initiating treatment 10-24 hours after acetaminophen ingestion (17% vs. 45%).[s]

Daly 2004 [53]. Investigators from the Rocky Mountain Poison Center reported results from a prospective study of 249 ≥12-year-old patients presenting to local medical facilities with history of repeated supratherapeutic acetaminophen ingestion (May 1998 – December 1999).[t] Hepato-toxicity (AST >1000 IU/L) developed in 7 of 47 patients (15%) selected for protocol-based NAC treatment because of presenting AST >50 IU/L.

Doyon 2009 [62]. Investigators from the Maryland Poison Center reported results from a retrospective review of poison center records for 77 patients who completed IV NAC initiated within 8 hours of a toxic acetaminophen ingestion (June 2004 – July 2007). Four patients (5.2%) developed hepatotoxicity (AST or ALT >1000 IU/L).

Varney 2014 [67]. Investigators from the Rocky Mountain Poison and Drug Center described demographics, outcomes, and adverse events for 37 patients (>100 kg in body weight) treated with NAC (14 oral, 22 IV, and 1 unknown route) for acetaminophen overdose (June 2006 – February 2008).[u]

Radosevich 2016 [70]. Investigators from a U.S. academic medical center reported results from a retrospective review of medical records for 40 non-obese and 40 obese patients (median body weight 64 and 98 kg, respectively) treated with IV NAC for acetaminophen overdose (June 2005 – August 2012).

3.4.3 PubMed

PubMed search (**APPENDIX 1**) identified seven recently published reports in humans of oral NAC for acetaminophen poisoning.

Kasmi 2015 [71]. Investigators in Albania reported a 5-year old girl presenting in fulminant hepatic failure after the unintentional repeated supratherapeutic ingestion of acetaminophen (4.8 gm total over 3 days). She received 18 NAC doses orally and recovered fully.

Greene 2017 [72]. Investigators reported (in 30 healthy volunteers) the relative oral bioavail-ability of 2 NAC formulations, effervescent NAC (CETYLEV®) and NAC solution.[v] One

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[s] Possibly an early report from the same study reported by **Smilkstein 1988** [4].

[t] Defined as >1 ingestion of acetaminophen during >8-hour period with cumulative dose >4.0 g per 24 hours.

[u] A patient subset from **Bebarta 2010** [38].

[v] Submitted as Study AR10.001 to NDA 207916. See Dimick-Santos, *op. cit.*, pp 17-31.

Reference ID: 5134103

patient experienced (24 hours after a single administration of 11 gm NAC oral solution) a nonserious adverse event described as syncope and seizure-like activity without postictal period.

Benlamkaddem 2018 [73]. Investigators in Morocco reported a 24-year-old female successfully treated with oral NAC for acute massive acetaminophen overdose (50 gm total).

Chefirat 2020 [74]. Investigators from Oran University Hospital (Algeria) reported 400 cases of acute acetaminophen poisoning (2010 – 2017), including 77 patients treated with oral NAC. **Chefirat 2020** recorded liver injury in 8 patients (2%), including 2 patients treated with oral NAC.

Mehpour 2021 [75]. Investigators identified 39,022 reports of acetaminophen exposure (2012 – 2017) to the U.S. National Poison Data System (NPDS). NPDS recorded death or outcome with major effect in 395 of 3,874 patients (10.2%) treated with oral NAC.[w]

Yarema 2021 [76]. The Canadian Acetaminophen Overdose Study identified 162 in-hospital deaths associated with acetaminophen ingestion (1980 – 2010). This case series included 128 (79%), 6 (4%), 4 (2%), and 24 (15%) patients treated with IV NAC (21-hour protocol), oral NAC (72-hour protocol), other NAC protocol, and no or unknown NAC protocol, respectively.

Lewis 2022 [77]. Investigators used data from the California Poison Control System to conduct a retrospective observational cohort study of three NAC-treatment protocols initiated within 24 hours of an acute single-agent massive overdose with acetaminophen (single substance or combination product; 2007 – 2020).[x] Table 6 summarizes hepatotoxicity outcomes from each protocol in patients grouped by time between acetaminophen ingestion and start of treatment. A multinomial logistic regression estimated risks for hepatotoxicity—odds ratios (ORs) and 95% confidence intervals (CIs)—relative to standard-dose IV NAC:

- oral NAC: OR 0.68 (95% CI 0.25-1.90) and
- high-dose IV NAC: OR 1.27 (95% CI 0.49-3.29).[y]

[w] NPDS definition of medical outcome with major effect: The patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement.

[x] Massive overdose defined as acetaminophen blood concentration ≥2 times Rumack-Matthew threshold (150 µg/mL at 4 hours).

[y] Adjusted for (1) acetaminophen formulation (single-agent or combination product), (2) acetaminophen blood concentration (expressed as a multiple of the Rumack-Matthew threshold—150 µg/mL at 4 hours), (3) initial AST or ALT (elevated or not elevated), and (4) time between acetaminophen ingestion and start of treatment (<8 hours or 8-24 hours after ingestion).

Table 6: Patients (n, %) developing hepatotoxicity (AST or ALT > 1000 IU/L), by (1) time between acute single-agent massive acetaminophen overdose and start of treatment and (2) NAC-treatment protocol.

Time to NAC Start	NAC-Treatment Protocol	N	Hepato-toxicity		Risk Ratio	
			n	%	EST	95% CI
<8 hours	Oral	45	1	2.2	1.07	0.07-16.6
	High-dose IV	56	1	1.8	0.86	0.06-13.3
	Standard-dose IV	48	1	2.1	REF	
8-24 hours	Oral	76	12	15.8	0.72	0.38-1.39
	High-dose IV	61	17	27.9	1.28	0.72-2.25
	Standard-dose IV	87	19	21.8	REF	

SOURCE: **Lewis 2022** [77].
ABBREVIATIONS: ALT – alanine transaminase; AST – aspartate transaminase; CI – confidence interval; EST – estimate; IV – intravenous; NAC – N-acetylcysteine; REF – reference category
FOOTNOTE: Oral NAC – 140 mg/kg loading dose followed by 70 mg/kg every 4 hours for 4 doses; High-dose IV NAC – 150 mg/kg loading dose followed by 50 mg/kg over 4 hours and 200 mg/kg over 16 hours; Standard-dose IV NAC – 150 mg/kg loading dose followed by 50 mg/kg over 4 hours and 100 mg/kg over 16 hours. Each protocol allowed continued treatment with NAC if blood acetaminophen still detectable or liver enzymes elevated.

3.4.4 Systematic Review by Green 2013

A systematic search reported in **Green 2013** [1] identified 20 English-language reports (published before 2010) from 16 studies of oral or IV NAC for treatment of acetaminophen toxicity [4,14,33,37,52,62,78-91]. **Green 2013** included only studies of acute acetaminophen overdose treated with oral or IV NAC in consecutively enrolled patients (N ≥20) with toxic acetaminophen blood concentrations (per Rumack-Matthew nomogram) and no pre-treatment hepatotoxicity. None of the individual studies used an internally derived control group to compare effectiveness of oral vs. IV NAC. For each study in **Green 2013**, Table 7 shows the proportion of patients developing hepatotoxicity, by timing of treatment and route of NAC administration.

Table 7: Number (n) and proportion (%) of patients with hepatotoxicity (AST or ALT >1000 IU/L) after acute acetaminophen overdose, by time between acetaminophen ingestion and start of treatment, route of NAC administration, and source of information (Author Year).

Part A: NAC initiated early (within 10 hours or as defined by author)				
Author Year	**N**	**n**	**%**	**95% CI**
IV NAC				
Prescott 1981 [78]	62	1	1.6	0.2-10.6
Smilkstein 1991 [14]	73	6	8.2	3.7-17.1

Reference ID: 5134103

Buckley 1999 [83]	49	2	4.1	1.0-14.9
Whyte 2007 [33]	59	2	3.4	0.8-12.6
Doyon 2009 [62]	77	4	5.2	2.0-13.0
Oral NAC				
Smilkstein 1988 [4]	527	32	6.1	4.3-8.5
Spiller 2006 [90]	57	2	3.5	0.9-13.0
Part B: NAC initiated late (more than 10 hours or as defined by author				
Author Year	**N**	**n**	**%**	**95% CI**
IV NAC				
Prescott 1981 [78]	38	20	52.6	37.0-67.7
Parker 1990 [80]	20	7	35.0	17.7-57.4
Smilkstein 1991 [14]	106	24	22.6	15.7-31.6
Buckley 1999 [83]	37	3	8.1	2.6-22.3
Whyte 2007 [33]	69	8	11.6	5.9-21.5
Oral NAC				
Smilkstein 1988 [4]	935	247	26.4	23.7-29.3
Spiller 2006 [90]	88	22	25.0	17.1-35.1
Part C: Timing not reported by author				
Author Year	**N**	**n**	**%**	**95% CI**
IV NAC				
Chan 1995 [82]	24	5	20.8	8.9-41.3
Yarema 2009 [37]	2,086	289	13.9	12.4-15.4
Klein-Schwartz [91]	28	4	14.3	5.5-32.4
Oral NAC				
Spiller 1994 [81]	122	6	4.9	2.2-10.5
Wright 1999 [84]	42	3	7.1	2.3-19.9
Woo 2000 [85]	75	6	8.0	3.6-16.7
Yip 2003 [86]	33	0	0.0	0.0-19.6
Tsai 2004 [87]	30	9	30.0	16.4-48.3
Tsai 2005 [89]	27	6	22.2	10.3-41.4
Yarema 2009 [37]	1,962	310	15.8	14.4-17.5

SOURCE: **Green 2013** [1].
ABBREVIATIONS: ALT – alanine transaminase; AST – aspartate transaminase; CI – confidence interval; IV – intravenous; N – number of patients studied; NAC – N-acetylcysteine
FOOTNOTES:
1. Prescott 1981 [78] – also reported in Prescott 1979 [3] and summarized in SCE. See Section 3.2.
2. Smilkstein 1988 [4] – also summarized in SCE. Results shown correspond to intermediate risk category in Table 2 in Section 3.2 (above).

Reference ID: 5134103

3. 95% CIs as reported in **Green 2013** (logit confidence limits for binomial proportion).

4 DISCUSSION

DEPI assessed literature about the efficacy and safety of NAC for preventing hepatic injury from acetaminophen poisoning.

4.1 Applicant's Methodology and Approach

The SCS (pp 4-5) describes a wide ranging search for "information in the public domain to support the safety and efficacy" of NAC as an antidote for acetaminophen poisoning. The SCS communicates an additional intent to find information about NAC pharmacology possibly relevant to potential for drug-drug interaction or use in special populations (e.g., patients with impaired renal or hepatic function).

DEPI assesses as selective the presentations (in SCE and SCS) from this wide ranging search. In DEPI's judgement, the SCE and SCS deliberately identify and summarize (without critical analysis) only the best evidence available.

4.2 Implications and Limitations

The SCE and SCS cite three [3-5] and five non-randomized studies [7,20,21,36,38] to support efficacy and safety of oral NAC, respectively. One study (**Williamson 2013** [5]) used retrospectively collected data to assess NAC-treatment effectiveness in patients treated according to one of three standard protocols (two oral and one IV). A second study (**Bebarta 2010** [38]) used retrospectively collected data to assess NAC safety in patients treated with oral or IV NAC. Other studies cited in the SCE and SCS can be described as observational in design without concurrent control.

As noted by authoritative sources and confirmed by DEPI search, notions about NAC efficacy emerge not from randomized, placebo-controlled trials.[z] Rather, confidence in NAC as an effective antidote for acetaminophen overdose emerges from (1) knowledge about the mechanism of NAC's action (e.g., replenish hepatic glutathione needed to detoxify N-acetyl-p-benzoquinoneimine, an electrophilic acetaminophen metabolite), (2) a single-arm study with historical control (**Prescott 1979** [3]), and (3) consistent clinical experience demonstrating better outcomes in patients started on NAC soon after acetaminophen overdose (e.g., **Smilkstein 1988** [4]). Current treatment guidelines—concerning patient selection for NAC treatment, preferred route of NAC administration (oral or IV), and NAC dosing—reflect expert opinion informed by clinical experience and not evidence from literature as derived from well controlled studies [92].

[z] Heard K and R Dart, *op. cit.*

Reference ID: 5134103

4.3 Missed Articles

DEPI combined four approaches to canvass medical literature for possibly relevant studies missed by SCE or SCS. Together, these approaches identified 46 additional articles [46-91]. None provided evidence considered superior to evidence presented in SCE or SCE. None provided evidence that changed DEPI's understanding of NAC efficacy or safety. Notably, DEPI identified only one previously unknown observational study with concurrent control (**Lewis 2022** [77]).

4.4 Implications

Draft Prescribing Information for acetylcysteine lysine (NDA 215040, eCTD 0000) presents two types of serious adverse reaction: (1) Hypersensitivity Reactions (generalized urticaria and other allergic reactions) and (2) Upper Gastrointestinal Hemorrhage as a consequence of severe or persistent vomiting. DEPI's search identified no serious adverse reactions to oral NAC other than (1) hypersensitivity (manifestations of anaphylactoid reaction or non-IgE mediated anaphylaxis) and (2) nausea and vomiting as gastrointestinal complications.

5 CONCLUSIONS AND RECOMMENDATIONS

NDA 215040 selectively identifies and summarizes (without critical analysis) the best evidence available in literature about the efficacy and safety of oral NAC as an antidote for acetaminophen poisoning. DEPI recommends that DHN regard literature presentations in the SCE and SCS as practically complete for purposes of NDA review and product labeling.

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CC: Sandhu S / Hua W / Booth B / Peprah S / Wang X / Wolf L / Kangas L / Jackson S / Calloway P (OSE)

Makar G / Dhawan A / Ebonine C (DHN)

APPENDIX 1: PubMed Search

PubMed search (on January 25, 2023) using query string '(acetaminophen) AND (acetylcysteine)' identified 580 records with publication year ≥2014.

A DEPI analyst examined article titles and abstracts to exclude 526 records from further review for 1 of 5 reasons: (1) publication in language other than English (18 records), (2) non-human study (147 records), (3) review article or commentary (70 records), (4) not relevant to review question—oral NAC for acetaminophen poisoning in humans (285 records), and (5) previously captured by another method [41,42,44,67,70,93].

After examining article full text, the same DEPI analyst excluded 47 records (listed below) for 1 of 3 reasons: (1) review article, commentary, or article erratum (4 records), (2) non-informative case report (1 record), and (3) not relevant to review question (42 records).

DEPI summarized seven articles not excluded after examination of full text [71-77]. See Section 3.4.3.

Listing of 47 articles excluded from further analysis after examination of full text.

Group1: Review article, commentary, or article erratum

1. Huang JW, et al. A systematic review of the effect of N-acetylcysteine on serum creatinine and cystatin C measurements. Kidney Int Rep. 2021;6:396-403.
2. Tillmann BW, et al. Acetylcysteine for acetaminophen overdose in patients who weigh >100 kg. Am J Ther. 2016;23:e244-5.
3. Vargha R, et al. Correction: Treatment with N-acetylcystein and total plasma exchange for extracorporeal liver support in children with paracetamol intoxication. Klin Padiatr. 2014;226:e1.
4. Schwarz E, et al. Is intravenous acetylcysteine more effective than oral administration for the prevention of hepatotoxicity in acetaminophen overdose? Ann Emerg Med. 2014;63:79-80.

Group 2: Non-informative case report

5. Quartuccio L, et al. Acetaminophen-induced liver injury in a woman with febrile flare of systemic lupus erythematosus. J Clin Rheumatol. 2014;20:349-51.

Group 3: Not relevant to review question—oral NAC for acetaminophen poisoning in humans

6. Amer H, et al. Paracetamol toxicity in mild overdose in combination with opioids: A retrospective observational study. Br J Clin Pharmacol. 2022;88:1258-1267.
7. Bateman DN, et al. Impact of reducing the threshold for acetylcysteine treatment in acute paracetamol poisoning: The recent United Kingdom experience. Clin Toxicol (Phila).

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16. Dan-Nielsen S, et al. Retrospective study of paracetamol poisoning in children aged zero to six years found no cases of liver injury. Acta Paediatr. 2018;107:1775-1780.
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18. Egan H, et al. Retrospective evaluation of repeated supratherapeutic ingestion (RSTI) of paracetamol. Clin Toxicol (Phila). 2019;57:703-711.
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20. Graudins A. Overdose with modified-release paracetamol (Panadol Osteo®) presenting to a metropolitan emergency medicine network: A case series. Emerg Med Australas. 2014;26:398-402.
21. Graudins A. Paracetamol poisoning in adolescents in an Australian setting: Not quite adults. Emerg Med Australas. 2015;27:139-44.
22. Hedeland RL, et al. Early predictors of severe acetaminophen-induced hepatotoxicity in a paediatric population referred to a tertiary paediatric department. Acta Paediatr. 2014;103:1179-86.

23. Hedeland RL, et al. Early risk factors of moderate/severe hepatotoxicity after suicide attempts with acetaminophen in 11- to 15-year-old children. Glob Pediatr Health. 2014;1-11 (DOI: 10.1177/2333794x14552897).

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36. Seifert SA, et al. Acetaminophen concentrations prior to 4 hours of ingestion: Impact on diagnostic decision-making and treatment. Clin Toxicol (Phila). 2015;53:618-23.

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39. Stollings JL, et al. Incidence and characterization of acute kidney injury after acetaminophen overdose. J Crit Care. 2016;35:191-4.
40. Tan CJ, et al. Characterisation and outcomes of adult patients with paracetamol overdose presenting to a tertiary hospital in Singapore. Singapore Med J. 2017;58:695-702.
41. Thusius NJ, et al. Intentional or inadvertent acetaminophen overdose-how lethal it really is? Psychosomatics. 2019;60:574-581.
42. Urban M, et al. Paracetamol poisonings in the Czech and Slovak republic and N-acetylcysteine treatment. Data analysis. Neuro Endocrinol Lett. 2014;35 Suppl 2:180-5.
43. Vargha R, et al. Treatment with N-acetylcystein and total plasma exchange for extracorporeal liver support in children with paracetamol intoxication. Klin Padiatr. 2014;226:84-5.
44. Wong A, et al. Paracetamol toxicity: What would be the implications of a change in Australian treatment guidelines? Emerg Med Australas. 2014;26:183-7.
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/s/

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03/01/2023 08:41:44 AM

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03/01/2023 10:52:17 AM

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Division of Pediatrics and Maternal Health Review

Date: 2/22/2023 **Date consulted:** 7/18/2022

From: Katherine Kratz, M.D., Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Hepatology and Nutrition (DHN)

Drug: Legubeti (acetylcysteine lysine) powder for oral solution

NDA: 215040

Applicant: Galephar Pharmaceutical Research Inc.

Subject: Pregnancy and Lactation Labeling

Indication: Antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen

Materials Reviewed:

- DPMH consult request dated July 18, 2022. DARRTS Reference ID 5014778.
- Applicant's submitted background package and proposed labeling for NDA 215040, SN 0000, dated July 7, 2022.
- DPMH review of Acetadote (acetylcysteine) injection, NDA 021539 by Leyla Sahin, M.D., dated June 15, 2016. DARRTS Reference ID 3944775.
- U.S. Prescribing Information (USPI) for Acetadote (acetylcysteine) injection, for intravenous use.

Reference ID: 5130357

- DPMH review of Cetylev (acetylcysteine) effervescent tablets for oral solution, NDA 207916 by Suchitra M. Balakrishnan, M.D., dated November 12, 2015. DARRTS Reference ID 3845243.
- U.S. Prescribing Information (USPI) for Cetylev (acetylcysteine) effervescent tablets for oral solution.

Consult Question: Provide assistance in reviewing the PLLR (Pregnancy and Lactation Labeling Rule) sections of Legubeti (acetylcysteine lysine) labeling.

I. INTRODUCTION AND BACKGROUND

On July 7, 2022, the applicant, Galephar Pharmaceuticals Research Inc., submitted a 505(b)(2) NDA for Legubeti (N-acetylcysteine lysine, NAL) powder indicated as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen. The application relies on FDA's previous findings of safety and effectiveness for the reference listed drug (RLD), Mucomyst (acetylcysteine solution), approved under NDA 013601 and withdrawn from the market not for safety or efficacy reasons. To bridge to FDA's finding of safety and efficacy for the RLD, the applicant has conducted a comparative bioavailability study of Legubeti (Study 2021-5140). The Division of Hepatology and Nutrition (DHN) consulted the Division of Pediatrics and Maternal Health (DPMH) on July 18, 2022, to assist with the Pregnancy and Lactation subsections of labeling.

Relevant Regulatory History

- 1963: Mucomyst (acetylcysteine) solution was approved under NDA 013601.
- 2004: Acetadote (acetylcysteine) intravenous injection was approved under NDA 215040.
- 2009: Mucomyst (acetylcysteine) solution was withdrawn from the market.
- 2016: Cetylev (acetylcysteine) oral effervescent tablet was approved under NDA 207916.
- 2022: Cetylev (acetylcysteine) oral effervescent tablet was withdrawn from the market for business, not safety, reasons.[1]

Drug Characteristics[2]

Drug class	Acetaminophen antidote
Mechanism of action	Protects the liver by maintaining or restoring the glutathione levels, or by acting as an alternative substrate for conjugation with, and thus detoxification of, the reactive metabolite of acetaminophen.
Dosing regimen	Total dose: 1330 mg/kg PO over 72 hours Loading dose: 140 mg/kg PO x 1 Maintenance doses: 70 mg/kg PO 4 hours after loading dose and q4hours for a total of 17 doses
Molecular weight	309.38 Daltons[3]

[1] NDA 207916, Cover Letter dated May 18, 2021. SN 0063.
[2] Applicant's submitted background package, Draft labeling, pending verification by the review team.
[3] Applicant's submitted background package, Module 2.5 Clinical Overview, page 9.

Reference ID: 5130357

Half-life	3.30 hours
% protein bound	66-87%
Bioavailability	~ 4 to ~ 10%[4]

Current state of labeling for oral acetylcysteine[5,6]

- The approved labeling is in the PLLR format.
- There is no boxed warning for embryo-fetal toxicity.
- There is no contraindication for pregnancy or lactation.
- Serious adverse reactions:
    - Hypersensitivity reactions, including urticaria
    - Gastrointestinal hemorrhage
- Subsection 8.1, Pregnancy:
    - Human data are insufficient: "Limited published case reports and case series…"
    - Clinical Considerations: "*Disease-Associated Maternal and/or Embryo/Fetal Risk* "Acetaminophen and acetylcysteine cross the placenta. Delaying treatment in pregnant women with acetaminophen overdose and potentially toxic acetaminophen plasma levels may increase the risk of maternal and fetal morbidity and mortality."
- Subsection 8.2, Lactation:
    - There are no human data.
    - Labeling includes the standard risk/benefit statement: "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ACETADOTE and any potential adverse effects on the breastfed child from ACETADOTE or from the underlying maternal condition."
    - There is a Clinical Considerations statement in Acetadote that notes: "Based on the pharmacokinetic data, acetylcysteine should be nearly completely cleared 30 hours after administration. Breastfeeding women may consider pumping and discarding their milk for 30 hours after administration." This language does not appear in labeling for Cetylev.
- There is no pregnancy testing or contraception recommendation.
- There are no known drug-drug interactions with hormonal contraceptives.

[4] Applicant's submitted background package, Module 2.5 Clinical Overview, page 5.
[5] U.S. Prescribing Information (USPI) for Cetylev (acetylcysteine) effervescent tablets for oral solution. Revised 4/18/2017. Drugs@FDA. Accessed 8/3/22.
[6] U.S. Prescribing Information (USPI) for Acetadote (acetylcysteine) injection, for intravenous use. Revised 10/30/2019. Drugs@FDA. Accessed 8/3/22.

II. REVIEW

PREGNANCY

Acetaminophen overdose in pregnancy

Acetaminophen overdose in pregnancy has been previously described in DPMH reviews.[7,8] As an update to the previous DPMH reviews, in 2020, according to the American Association of Poison Control Centers' National Poison Data System, exposures to poisonous substances occurred in 5832 pregnant individuals with known gestational age at the time of exposure.[9] Analgesics, including acetaminophen, were the most common drugs involved in pregnant exposures; among 5489 single substance exposures in pregnancy in 2020, 501 (9.1%) of them were related to analgesics.[10] While acetaminophen is the most common drug overdose in pregnancy,[10] the exact number of overdoses due to acetaminophen annually is unknown. Acetaminophen crosses the placenta,[11] and treatment with acetylcysteine is indicated if the serum acetaminophen concentration is greater than 20 mcg/mL or the serum transaminase concentration is elevated (>50 international unit/L).[12] The dosing and duration of treatment do not differ in the pregnant patient as compared to the non-pregnant patient.[13] N-acetylcysteine (NAC) therapy appears to be protective for both the mother and fetus.[14] The probability of fetal death in one study was increased with a delay in NAC treatment after overdose and with overdose early in gestation.[15]

> ***Reviewer comment:***
> *Acetaminophen overdose may be life-threatening to the mother and fetus, and treatment for acetaminophen overdose in pregnancy is needed to protect the mother and the fetus. The overall number of pregnant individuals who overdose on acetaminophen annually is unknown but can be estimated to be small (≤501 individuals) based on the 2020 annual*

[7] DPMH review of Acetadote (acetylcysteine) injection, NDA 021539 by Leyla Sahin, M.D., dated June 15, 2016. DARRTS Reference ID 3944775.
[8] DPMH review of Cetylev (acetylcysteine) effervescent tablets for oral solution, NDA 207916 by Suchitra M. Balakrishnan, M.D., dated November 12, 2015. DARRTS Reference ID 3845243.
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report from the American Association of Poison Control Centers' National Poison Data System.

Nonclinical Experience

No teratogenic effects were observed in embryo-fetal development studies in rats at oral doses up to 2000 mg/kg/day (0.6 times the maximum recommended human dose based on body surface area) or in rabbits at oral doses up to 1000 mg/kg/day (0.6 times the maximum recommended human dose based on body surface area) administered during organogenesis.[2,5]

Reviewer comment:
DPMH discussed the nonclinical data presented above with the DHN Pharmacology/Toxicology team. These data are identical to those that appear in the Cetylev labeling. The Pharmacology/Toxicology team explained that the Cetylev label should be used as the standard for the nonclinical review of the Legubeti label. For additional information, the reader is referred to the full Pharmacology/Toxicology review by Dr. Rosalyn Jurjus.

Review of Pharmacovigilance Database

The applicant did not provide pharmacovigilance data.

Review of Literature

Applicant's review:

The applicant cited one publication by Horowitz et al.[16] and stated the following to summarize the study:[17] "Four pregnant women with acetaminophen toxicity who delivered their infants while receiving treatment with NAC were studied. Maternal and cord blood from 3 viable infants, and cardiac blood sampled during an autopsy on the fourth, were analyzed for NAC using HPLC [high-performance liquid chromatography]. NAC was detected in the cord blood of the three viable infants and in the cardiac blood of the fourth infant sampled at the time of autopsy."

Reviewer comment:
The applicant's literature search was limited to one publication. The applicant did not draw any conclusions from their review of this publication. From this publication, DPMH concludes that NAC crosses the placenta.

DPMH review:

The published data on NAC in pregnancy were previously reviewed by DPMH for the review of Cetylev (acetylcysteine effervescent tablets) and Acetadote (acetylcysteine injection) in 2015 and 2016, respectively.[7,8] Three case series and one prospective, double-blind pilot study were reviewed by DPMH in 2015 and 2016, and synopses of these publications were formatted into a table by this reviewer and placed in Appendix A of this document. In summary, the published literature previously reviewed by DPMH in 2015 and 2016 demonstrated the following:

[16] Horowitz RS, Dart RC, Jarvie DR, Bearer CF, Gupta U. Placental Transfer of N-Acetylcysteine Following Human Maternal Acetaminophen Toxicity. Clinical Toxicology, 1997;35:447-451.
[17] Applicant's submitted background package, Module 2.7.2 Summary of Clinical Pharmacology, page 12.

Reference ID: 5130357

- 61 pregnant women were exposed to NAC for the treatment of acetaminophen overdose.
- The outcomes of the 61 pregnancies exposed to NAC were:
    - 42 viable infants
        - 41 without congenital anomalies
        - 1 with hypospadias
    - 10 elective abortions
    - 8 spontaneous abortions
    - 1 stillborn

DPMH conducted a search of published human studies related to acetylcysteine and pregnancy in PubMed and Embase from 2016 to the present, using the search terms "acetylcysteine" and "pregnancy," "pregnancy outcomes," "birth defects," "stillbirth," and "spontaneous abortion." One clinical trial was found and is summarized below:

- Buhimschi et al.[18] conducted a single-center, quadruple-blind, placebo-controlled trial of pregnant women with amniocentesis-confirmed intra-amniotic infection (IAI). Participants (n=67) were randomized to an intravenous infusion of NAC or placebo using the same regimen as is used to treat acetaminophen overdose. NAC was selected for treatment due to its anti-inflammatory activities and possible protective effect against inflammation-induced brain injury in neonates born prematurely due to IAI. No major maternal adverse reactions were reported in the NAC treatment group, and premature babies exposed to NAC *in utero* had improved status at birth compared to those exposed to placebo.

Four case reports were retrieved, which are summarized in Appendix B, and described pregnant women with acetaminophen overdose treated with NAC who did not experience adverse events and delivered healthy infants.

DPMH also searched Micromedex,[19] TERIS, [20] and Reprotox.[21] The following information, which was not reported by other sources in this review, was noted:

- Micromedex: "There are no adequate or well controlled studies of acetylcysteine use in human pregnancy. One study concluded that acetylcysteine could be given to women in various stages of pregnancy who had taken excessive amounts of acetaminophen. The complete follow-up of 59 patients (18 in the first trimester, 23 in the second trimester, and 18 in the third trimester) revealed that 42 patients delivered infants with no documented neonatal abnormalities; 12 women had elective or spontaneous abortions; one fetal/natural death occurred; and one patient delivered a 32-week stillborn fetus.[22]"

[18] Buhimschi, C.S., Bahtiyar, M.O., Zhao, G. et al. Antenatal N-acetylcysteine to improve outcomes of premature infants with intra-amniotic infection and inflammation (Triple I): randomized clinical trial. Pediatr Res 89, 175–184 (2021). https://doi.org/10.1038/s41390-020-01106-w
[19] Truven Health Analytics information, http://www.micromedexsolutions.com. Accessed 8/3/22.
[20] TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 8/4/22.
[21] Reprotox Website: www.Reprotox.org. Accessed 8/3/22.
[22] Holdiness MR: Clinical pharmacokinetics of N-acetylcysteine. Clin Pharmacokinet 1991; 20:123-134.

Reference ID: 5130357

- TERIS: Congenital anomalies were not reported among 57 infants born to women who had been treated with NAC beginning very early in pregnancy in a controlled therapeutic trial for recurrent miscarriage.[23]

- Reprotox: No additional information was obtained.

Reviewer comment:
Case reports, case series, and a prospective pilot study of acetaminophen overdose in pregnancy treated with NAC prior to delivery have not identified any new findings in a total of 124 patients (61 patients reported in 2015 and 2016 DPMH reviews + 4 case reports summarized above + 59 patients in Micromedex information). In addition, when NAC IV was used intrapartum for IAI in the randomized controlled trial by Buhimschi et al. and for recurrent miscarriage in the study by Amin et al., there were no adverse maternal or fetal outcomes in 67 and 57 patients, respectively. See the Discussion and Conclusions section of this document for DPMH recommendations about language to include in subsection 8.1.

LACTATION

Nonclinical Experience
Nonclinical data are not available related to NAC and lactation.

The reader is referred to the full Pharmacology/Toxicology review by Dr. Rosalyn Jurjus.

Review of Pharmacovigilance Database
The applicant did not provide pharmacovigilance data.

Review of Literature
Applicant's review:
The applicant did not provide a literature search related to NAC and lactation.

DPMH review:
The 2015 and 2016 DPMH reviews for Cetylev and Acetadote did not identify published literature on NAC and lactation. For the current review, DPMH conducted a search for published human studies from 2016 to present in PubMed and Embase, using the search terms: "acetylcysteine" and "lactation" and "breastfeeding." No publications were found.

In addition, DPMH conducted a search for "acetylcysteine" in Hale's *Medications and Mothers' Milk*,[24] Briggs *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal*

[23] Amin AF, Shaaban OM, Bediawy MA: N-acetyl cysteine for treatment of recurrent unexplained pregnancy loss. Reprod Biomed Online 17(5):722-726, 2008.
[24] Hale, Thomas W. Hale's Medications & Mothers' Milk 2021: A Manual of Lactational Pharmacology. 19th ed. New York: Springer Publishing Company, 2020. www.halesmeds.com

Reference ID: 5130357

Risk,[25] Micromedex, the Drugs and Lactation Database (LactMed),[26] and Reprotox. A review of Hale's and Brigg's publications were not conducted for the 2015 or 2016 DPMH reviews. The results of the search are as follows:

- Hale's: "Based on this medication's small molecular weight and low volume of distribution it most likely will enter milk; however, its bioavailability is low (10-30%), thus the amount the infant will be exposed to should be low. The manufacturer reports that N-acetylcysteine should be completely cleared by 30 hours after the last dose; however, when administering this medication to a breastfeeding woman for an acetaminophen overdose, breastfeeding may need to be withheld due to the amount of acetaminophen in milk, and potential risk of adverse effects to the infant. It may be best to resume breastfeeding once acetaminophen levels are undetectable."

- No additional information was found in Briggs, Micromedex, LactMed, or Reprotox.

  Reviewer comment:
  Hale's explained that NAC will likely enter milk due to its small molecular weight and low volume of distribution; however, the molecular weight that Hale's refers to is 162.3 and the molecular weight of the proposed product is 309.38. The proposed product, with a larger molecular weight, may not pass as easily into human milk as the product with a smaller molecular weight.

  Hale's also raises the issue that breastfeeding may need to be withheld due to the amount of acetaminophen in milk after maternal overdose and that it may be best to resume breastfeeding once maternal acetaminophen levels are undetectable. The DPMH Maternal Health Team discussed this issue with the DPMH Pediatrics Team, and the Pediatrics Team agreed that acetaminophen in breastmilk following maternal overdose may result in toxic levels of acetaminophen in the breastmilk. However, the Pediatrics Team also noted that infants have a relative immaturity in CYP2E1 metabolism, which would substantially reduce the production of the toxic metabolite (NAPQI) of acetaminophen, and that severe acetaminophen intoxication in children seems to be less frequent compared with adults. CYP2E1 reaches adult levels by 1 year of age.[27] Although infants exposed to breastmilk containing acetaminophen may be protected in the first year of life, the significance of this relative protection in a substantial acetaminophen overdose is unknown. Additionally, infants who are still being breastfed after 1 year of life could be at risk for acetaminophen exposure through milk. See the Discussion and Conclusions section of this document for DPMH recommendations about language to include in subsection 8.2.

[25] Briggs, Gerald G., Craig V. Towers, and Alicia B. Forinash. Briggs Drugs in Pregnancy and Lactation: a Reference Guide to Fetal and Neonatal Risk. 12th edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2021. Print.
[26] Drugs and Lactation Database (LactMed). Accessed 7/26/22.
[27] Ogilvie et al. Acetaminophen overdose in children. CMAJ. 2012, 184 (13). 1492-1496.

- Briggs: "IV acetylcysteine has been administered directly to preterm neonates for therapeutic indications, without causing toxicity, at doses far above those that would be obtained from milk"[28,29]

- Micromedex: "It is unknown whether acetylcysteine is excreted into human breast milk or affects milk production or the breastfed infant. No information regarding lactation pharmacokinetics is available."

- LactMed and Reprotox: No additional information was found.

Reviewer comment:
Although there are no human data on the presence of NAC in human milk, the effects of NAC on the breastfed infant, or its effects on milk production, NAC is approved for treatment of acetaminophen overdose of infants down to1 kg.[5]

Additionally, two case reports by McDougall et al.[39] *and Pavlek et al.*[42] *(reviewed in Appendix B of this document) and other reports*[30,31,32] *demonstrate that neonates (including premature and low birth weight neonates) did not have adverse events when NAC was administered to them after delivery. See the Discussion and Conclusions section of this document for DPMH recommendations about language to include in subsection 8.2.*

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience
The labeling for Cetylev[5] states the following in section 13, Nonclinical Toxicology: "In a fertility study of acetylcysteine in rats, intravenous administration of 1000 mg/kg/day (0.3 times the recommended human oral dose based on body surface area) caused a profound reduction of fertility in females, which was correlated with morphological changes in oocytes and severe impairment of implantation (18 of 20 mated females had no implantations). The reversibility of this effect was not evaluated. No effects on fertility were observed in female rats at intravenous doses up to 300 mg/kg/day (0.1 times the recommended human oral dose based on body surface area), or in male rats at intravenous doses up to 1000 mg/kg/day. Mating was unaffected in this study.

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[28] Ahola TM, Fellman V, Laaksonen R, Laitila J, Lapatto R, Neuvonen PJ, Raivio KO. Pharmacokinetics of intravenous N-acetylcysteine in preterm neonates (abstract). Pediatr Res 1998;43(Suppl 2):163.
[29] Isbister GK, Bucens IK, Whyte IM. Paracetamol overdose in a preterm neonate. Arch Dis Child Fetal Neonat Ed 2001;85:F70-2.
[30] Savva DA, Crist M, Lardieri A. N-Acetylcysteine for Gastric Lactobezoars in a 1-Month-Old. J Pediatr Pharmacol Ther. 2019 May-Jun;24(3):247-250. doi: 10.5863/1551-6776-24.3.247. PMID: 31093026; PMCID: PMC6510517.
[31] Kiuru A, Ahola T, Klenberg L, Tommiska V, Lano A, Kleemola P, Haavisto A, Fellman V. Postnatal N-acetylcysteine does not provide neuroprotection in extremely low birth weight infants: A follow-up of a randomized controlled trial. Early Hum Dev. 2019 May;132:13-17. doi: 10.1016/j.earlhumdev.2019.03.006. Epub 2019 Mar 28. Erratum in: Early Hum Dev. 2019 Jul;134:12. PMID: 30927687.
[32] Ahola T, Lapatto R, Raivio KO, Selander B, Stigson L, Jonsson B, Jonsbo F, Esberg G, Stövring S, Kjartansson S, Stiris T, Lossius K, Virkola K, Fellman V. N-acetylcysteine does not prevent bronchopulmonary dysplasia in immature infants: a randomized controlled trial. J Pediatr. 2003 Dec;143(6):713-9. doi: 10.1067/S0022-3476(03)00419-0. PMID: 14657813.

In a reproduction study of acetylcysteine, male rats were treated orally for 15 weeks prior to mating and during the mating period. A slight non-dose related reduction in fertility was observed at oral doses of 500 and 1000 mg/kg/day (0.1 and 0.3 times the recommended human dose, respectively, based on body surface area)."

> ***Reviewer comment:***
> *DPMH discussed the nonclinical data outlined above with the DHN Pharmacology/Toxicology team. The Pharmacology/Toxicology team agrees with the nonclinical data from the Cetylev labeling. For additional information, the reader is referred to the full Pharmacology/Toxicology review by Dr. Rosalyn Jurjus.*

Review of Pharmacovigilance Database
The applicant did not provide pharmacovigilance data.

Review of Literature
Applicant's review:
The applicant did not provide a literature search related to NAC and reproductive potential.

DPMH review:
DPMH conducted a literature search for studies in humans using PubMed and Embase, using the search terms "acetylcysteine" and "fertility," "contraception," "oral contraceptives," and "infertility." Two publications that have not been previously reviewed by DPMH were found as follows:

- Thakkar et al.[33] published a systematic review and meta-analysis of randomized controlled trials to review the benefits and harms of NAC in women with polycystic ovary syndrome (PCOS). Eight studies with a total of 910 women (including 180 women from the study by Salehpour et al. cited by Reprotox below) with PCOS were randomized to NAC or other treatments/placebo. Women with NAC had higher odds of having a live birth, getting pregnant, and ovulation as compared to placebo. However, women with NAC were less likely to have pregnancy or ovulation as compared to metformin. There was no significant difference in rates of the miscarriage, menstrual regulation, acne, hirsutism, and adverse events, or change in body mass index, testosterone, and insulin levels with NAC as compared to placebo. Limitations of the studies reviewed included a high risk of selection, performance, and attrition bias in two studies; a high risk of reporting bias in four studies; small numbers of participants and wide confidence intervals in some studies, which limited the precision and confidence of the conclusions. Overall, the systematic review failed to obtain the primary study data in analyzable format, so an independent analysis could not be conducted.

[33] Thakker D, Raval A, Patel I, Walia R. N-acetylcysteine for polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled clinical trials. Obstet Gynecol Int. 2015;2015:817849. doi: 10.1155/2015/817849. Epub 2015 Jan 8. PMID: 25653680; PMCID: PMC4306416.

Reference ID: 5130357

- Song et al.[34] published a systemic review and meta-analysis of randomized controlled trials to evaluate the clinical effectiveness and safety of NAC versus metformin in PCOS patients. 10 studies, involving 486 patients exposed to NAC and 476 patients exposed to PCOS, were considered eligible for inclusion. NAC significantly reduced body mass index (BMI) and total testosterone; there was no significant difference in pregnancy rate, serum LH level, fasting insulin, and LH/FSH ratio. There were no adverse events reported related to NAC exposure. The authors concluded that NAC may be considered as an alternative supplement to metformin, but large-scale randomized controlled trials are needed to assess the efficacy and safety of NAC in PCOS patients. This meta-analysis was limited by heterogeneity between the studies included. Several of the results were constrained due to the limited number of trials available and the number of patients in each trial. In addition, bias may have been introduced in six of the trials, as the double-blinded method of randomization was used in four trials only. Finally, the dosages of NAC and metformin used are not the same across studies.

DPMH also conducted a search in Reprotox, Micromedex, and TERIS.[35] The results are shown below:

- Reprotox: In a 2012 Iranian randomized clinical trial, 180 infertile patients with polycystic ovary syndrome were randomly divided into two groups for induction of ovulation: patients in group 1 received clomiphene citrate 100 mg/day plus NAC 1.2 g/day and patients in group 2 received clomiphene citrate plus placebo for 5 days starting at day 3 of the cycle.[36] The number of ripe follicles, endometrial thickness, and ovulation and pregnancy rates were all significantly higher in the group that received the NAC supplement. No adverse side effects were reported.

- Micromedex and TERIS: no additional information found.

  Reviewer comment:
  The literature review did not identify adverse effects on fertility in female patients with PCOS. There were no data found on the effects of NAC on male fertility.

  One systematic review by Thakkar et al. suggested that NAC may improve reproductive function (ovulation, getting pregnant, and live birth) in female patients with PCOS as compared to placebo however, there were several limitations of these data as outlined above. The other study by Song et al. did not include a placebo comparator cohort; therefore, data related to fertility between subjects exposed to NAC versus unexposed subjects are not available from the Song publication.

[34] Song Y, Wang H, Huang H, Zhu Z. Comparison of the efficacy between NAC and metformin in treating PCOS patients: a meta-analysis. Gynecol Endocrinol. 2020 Mar;36(3):204-210. doi: 10.1080/09513590.2019.1689553. Epub 2019 Nov 21. PMID: 31749393.
[35] TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 8/4/22.
[36] Salehpour S, Sene AA, Saharkhiz N, Sohrabi MR, Moghimian F. N-Acetylcysteine as an adjuvant to clomiphene citrate for successful induction of ovulation in infertile patients with polycystic ovary syndrome. J Obstet Gynaecol Res. 2012 Sep;38(9):1182-6. PMID: 22540635.

Reference ID: 5130357

III. DISCUSSION AND CONCLUSIONS

Pregnancy

Acetaminophen overdose is the most common overdose in pregnancy, and NAC is the accepted treatment for acetaminophen overdose in pregnant individuals. NAC has been marketed in an intravenous or oral formulation for almost six decades. Data about the use of NAC during pregnancy to treat acetaminophen overdose are limited. Among 124 published cases in case reports, case series, and a prospective pilot study, no adverse maternal outcomes have been reported. Withholding NAC treatment for acetaminophen overdose in pregnancy increases the probability of fetal death.[15] Therefore, DPMH recommends the following language under the Risk Summary in subsection 8.1: "Available data from published case reports and case series over decades of use with acetylcysteine during pregnancy have not identified an increased risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes."

Given that acetaminophen overdose in pregnancy is life-threatening requires urgent treatment, DPMH recommends the same language as used for other NAC products[5,6] under the Risk Summary in subsection 8.1 as follows: "Treatment of acetaminophen overdose should not be delayed because potentially toxic acetaminophen plasma levels may increase the risk of maternal or fetal morbidity and mortality *(see Clinical Considerations)*."

Under Clinical Considerations, the same language as used for other NAC products[5,6] is recommended: "Although acetaminophen and acetylcysteine cross the placenta, there have been no adverse maternal or fetal outcomes associated with acetylcysteine use during pregnancy. Treatment in pregnant women with acetaminophen overdose should not be delayed because potentially toxic acetaminophen plasma levels may increase the risk of maternal and fetal morbidity and mortality."

Given that NAC has been marketed for decades and a review of the literature did not identify any new safety concerns related to its use in pregnancy, DPMH does not recommend any additional post-marketing pregnancy safety studies at this time.

Lactation

There are no human data available about the presence of NAC in human milk, or its effect on the breast fed infant or on milk production. Therefore, under the Risk Summary in subsection 8.2, DPMH recommends the following language: "There is no information regarding the presence of acetylcysteine in human milk, or the effects of acetylcysteine on the breastfed infant or on milk production."

Given that infants who have direct systemic exposure to NAC did not demonstrate toxicity and no risks have been identified that would preclude breastfeeding, it is appropriate to include a risk/benefit statement as follows: "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LEGUBETI and any potential adverse effects on the breastfed child from LEGUBETI or from the underlying maternal condition."

The DPMH Maternal Health discussed the issue of acetaminophen levels in breastmilk with the DPMH Pediatrics Team. Although there is evidence that the CYP2E1 metabolism is immature in infants and would reduce the production of toxic metabolites in infants, the significance of this relative protection in a substantial acetaminophen overdose is unknown. There is a potential for toxic maternal levels of acetaminophen to be harmful for the breastfed infant; therefore, the healthcare provider should consider the underlying maternal condition as conveyed by the risk/benefit statement provided in the preceding paragraph.

Given that NAC has been approved for decades and no significant reports of adverse effects on breastfed infants have been found, DPMH does not recommend that the applicant conduct a clinical lactation study at this time.

Females and Males of Reproductive Potential
DPMH concludes that the infertility findings in female rats are not clinically relevant because clinical studies exploring NAC for treatment of infertility contradict the nonclinical findings. NAC does not cause embryo-fetal toxicity or genotoxicity.[5,6] For these reasons, DPMH recommends omitting subsection 8.3 from labeling.

LABELING RECOMMENDATIONS
DPMH provided labeling recommendations for subsections 8.1 and 8.2. DPMH discussed our labeling recommendations with the Division on 2/3/2023 and 2/15/2023. DPMH recommendations are below. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling
Labeling for Legubeti was modeled after the labeling for Cetylev and Acetadote.

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Available data from published case reports and case series over decades of use with acetylcysteine during pregnancy have not identified an increased risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Treatment of acetaminophen overdose should not be delayed because potentially toxic acetaminophen plasma levels may increase the risk of maternal or fetal morbidity and mortality *(see Clinical Considerations)*. In animal reproduction studies, no teratogenic effects were observed with oral administration of acetylcysteine to pregnant rats and rabbits during organogenesis at doses up to 0.6 times the maximum recommended human dose (based on body surface area) of about 560 mg/kg (total dose on first day of treatment) *[see Data]*. Acetylcysteine lysine, the active ingredient in LEGUBETI, was not tested in animal reproduction studies.

The background risk of major birth defects and miscarriage for the indicated population 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 defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Although acetaminophen and acetylcysteine cross the placenta, there have been no adverse maternal or fetal outcomes associated with acetylcysteine use during pregnancy. Treatment in pregnant women with acetaminophen overdose should not be delayed because potentially toxic acetaminophen plasma levels may increase the risk of maternal and fetal morbidity and mortality.

Data

Animal Data

No teratogenic effects were observed in embryo-fetal development studies of acetylcysteine in rats at oral doses up to 2000 mg/kg/day (0.6 times the maximum recommended human dose based on body surface area) or in rabbits at oral doses up to 1000 mg/kg/day (0.6 times the maximum recommended human dose based on body surface area) administered during organogenesis.

8.2 Lactation

Risk Summary

There is no information regarding the presence of acetylcysteine in human milk, or the effects of acetylcysteine on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LEGUBETI and any potential adverse effects on the breastfed child from LEGUBETI or from the underlying maternal condition.

APPENDIX A – Reviewer-generated table of publications reviewed by DPMH in 2015 and 2016

Publication author Date Country	Type of study	Population	Exposure/dose	Results/ Pregnancy outcome
Wiest et al.[37] 2014 USA	Prospective double-blind pilot study PK study	11 pregnant women with chorioamnionitis treated with NAC	NAC IV	There is placental transfer of acetylcysteine, which occurs rapidly and substantially after 1 dose. No data were provided regarding fetal outcomes.
Horowitz et al.[16] 1997 USA and Scotland	Case series PK study	4 pregnant women with acetaminophen overdose treated with NAC	NAC IV (1 subject) or PO (3 subjects)	Acetylcysteine was detected in the cord blood of 3 viable infants and in the cardiac blood of the fourth infant sampled at time of autopsy (SAB at 22 weeks); the mean acetylcysteine cord blood concentration was within the range associated with adult therapeutic doses. There were no adverse sequelae in the 3 viable infants.
McElhatton et al.[38] 1997 England	Case series	33 pregnant women with acetaminophen overdose either alone or as part of combined preparations treated with NAC	NAC	24 normal infants 1 male infant with hypospadias 3 SABs 5 elective terminations for "social" reasons not for anomalies
Riggs et al.[15] 1989 USA	Case series	24 pregnant women with acetaminophen overdose treated with NAC	1) 10 subjects received NAC PO within 10 hours of acetaminophen ingestion	1)7 full-term, normal infants; 1 pre-term (37 weeks), normal infant; 2 elective terminations

[37] Wiest DB, Chang E, Fanning D, Garner S, Cox T, Jenkins DD. Antenatal Pharmacokinetics and Placental Transfer of N-Acetylcysteine in Chorioamnionitis for Fetal Neuroprotection. J Pediatr, 2014;165:672-677.
[38] McElhatton PR, Sullivan FM, Volans GN. Paracetamol Overdose In Pregnancy; Analysis Of The Outcomes Of 300 Cases Referred To The Teratology Information Service. Reproductive Toxicology, 1997; 11:85-94

Reference ID: 5130357

			2) 10 subjects received NAC PO 10-16 hours post-ingestion of acetaminophen 3) 4 subjects received NAC PO 15-24 hours post-ingestion of acetaminophen	2) 4 full-term, normal infants; 1 pre-term, normal infant; 3 SABs; 2 elective terminations 3) 1 normal infant; 1 maternal death with SAB; 1 stillbirth; 1 elective termination

Reference ID: 5130357

APPENDIX B – Reviewer-generated table of case reports reviewed by DPMH

Author	Description of case
McDougall et al.[39]	A 31-year-old pregnant female at 33 weeks gestation was admitted for acetaminophen overdose. Soon after admission, a Cesarean section was performed for a prolonged fetal heart rate deceleration. At the time of delivery, the neonate was severely depressed and required intubation. The umbilical cord arterial blood gas was 6.70, consistent with fetal acidosis. The infant had an elevated serum acetaminophen concentration and elevated ALT, AST, bilirubin, and INR. Postpartum, both the mother and infant were treated with NAC intravenously (IV). The mother was discharged on post-operative day 10 and the infant was discharged on day 12 of life with normal labs and exam findings.
Dom et al.[40]	A 25-year-old pregnant female at 30 weeks gestation presented with acetaminophen overdose. She was treated with NAC IV, and delivered a viable neonate without anomalies approximately 2 weeks later.
Reale et al.[41]	A 28-year-old pregnant female at 33 weeks gestation presented to the hospital after ingesting acetaminophen 50 grams and aspirin 5 grams within the preceding hour. NAC was administered. Twenty-four hours later, the fetus had repetitive late decelerations and an urgent Cesarean section was performed. The umbilical cord arterial blood gas was 7.11, reflecting fetal acidosis. The neonate experienced respiratory distress requiring intubation at 4 hours after birth. The infant had a mild transaminitis on day 1 of life. The neonate was discharged from the hospital at 3 weeks of life without residual toxic effects from acetaminophen exposure. The mother's status normalized within 48 hours of delivery.
Pavlek et al.[42]	A 26-year-old pregnant female at 26 weeks of gestation was admitted to the intensive care unit for respiratory failure requiring intubation due to a suicide attempt involving ingestion of a large quantity of Tylenol, aspirin, quetiapine, and prenatal vitamins. Prior to delivery, NAC IV was administered to treat maternal acetaminophen overdose. Due to persistent fetal bradycardia, the infant was delivered via emergency c-section at 26 1/7 weeks of gestation with Apgar scores of 2 and 3 at 1 and 5 minutes, respectively. The infant required resuscitation with positive pressure

[39] McDougall G, Murphy NG, Loubani O. N-Acetylcysteine treatment of neonatal acetaminophen toxicity caused by transplacental transfer - a case report. Clin Toxicol (Phila). 2021 Sep;59(9):840-842. doi: 10.1080/15563650.2021.1874405. Epub 2021 Feb 2. PMID: 33527858.
[40] Dom AM, Royzer R, Olson-Chen C: Malnourishment-associated acetaminophen toxicity in pregnancy. Obstet Gynecol 137(5):877-880, 2021.
[41] Reale SC, Gray KJ, Boyer EW, Arce DY, Farber MK. Toxic Ingestion of Acetaminophen and Acetylsalicylic Acid in a Parturient at 33 Weeks Gestation: A Case Report. A A Pract. 2019 May 1;12(9):302-304. doi: 10.1213/XAA.0000000000000915. PMID: 30312176; PMCID: PMC7088459.
[42] Pavlek L, Kraft M, Simmons C, et al. Acetaminophen and acetylsalicylic acid exposure in a preterm infant after maternal overdose. Am J Perinatol. 2018 Jun 26. doi: 10.1055/s-0038-1661405.

Reference ID: 5130357

	ventilation and intubation. APAP level was elevated at 17 hours of life, and NAC IV was administered to the 870 gram neonate without adverse events.

Reference ID: 5130357

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/s/

KATHERINE G KRATZ
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LYNNE P YAO
02/23/2023 10:56:24 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	January 24, 2023
Requesting Office or Division:	Division of Hepatology and Nutrition (DHN)
Application Type and Number:	NDA 215040
Product Name and Strength:	Legubeti (acetylcysteine lysine) powder for solution, 500 mg and 2.5 grams
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Galephar Pharmaceutical Research Inc.
FDA Received Date:	July 7, 2022, August 16, 2022, September 22, 2022, and October 7, 2022
TTT ID #:	2022-635
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD., BCPS.
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD.

Reference ID: 5114849

1 REASON FOR REVIEW

As part of the approval process for Legubeti (acetylcysteine lysine) powder for solution, the Division of Hepatology and Nutrition (DHN) requested that we review the proposed Legubeti prescribing information (PI), sachet labels and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

NDA 215040 is a 505(b)(2) NDA and the listed drug product is Mucomyst, NDA 01361.

On May 18, 2016, the Agency held pre-NDA meeting where the Agency commented on medication error concern regarding the dosage and preparation table that was provided at the time. We notified the Applicant that "we may recommend additional data (such as labeling comprehension study) to ensure that healthcare providers can safely and effectively prescribe and prepare doses of NAL based on the dosage guide and preparation table."[a]

2 MATERIALS 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
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

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

[a] Davis-Williams, A. Meeting Minutes for N-Acetylcysteine Lysine (NAL). Silver Spring (MD): FDA, CDER, OSE (US); 2016 MAY 19. IND 130190.

Reference ID: 5114849

3 DISCUSSION

At the initial phase of our review, we noted that *Section 2.3 Recommended Dosage and Preparation and Administration Instruction in Adults and Pediatrics for Acute Acetaminophen Ingestion* of the Full Prescribing Information (FPI) includes complex dosing that requires combining one or more of each the 2.5 gram and 500 mg sachets to prepare a single dose of Legubeti. As such, there is concern the complexity of the dosing regimen could increase the risk of wrong dose medication errors. Thus, we sent an information request (IR) to the Applicant to confirm the intended users and use environment for the proposed product. The Applicant clarified that the proposed product "is intended for administration to patients in an emergency care setting. The product is a [prescription] product intended for use in hospitals, or other emergency care settings under close supervision of a Physician."[b]

Based on our overall assessment, we provide recommendations below to revise *Table 1. LEGUBETI Loading Dose* and *Table 2. LEGUBETI Maintenance Dose* of the FPI to minimize the risk of dosing errors.

4 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), sachet label, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Galephar Pharmaceutical Research Inc.

[b] Chinedu, E. FDA Communication: Information Request for NDA 215040 acetylcysteine due 12.19.22. Silver Spring (MD): FDA, CDER, OSE (US), 2022 DEC 14. NDA 215040

5 RECOMMEDATIONS FOR DIVISION OF HEPATOLOGY AND NUTRITION (DHN)

Table 2. Identified Issues and Recommendations for Division of Hepatology and Nutrition (DHN)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
Full Prescribing Information – Section 2 Dosage and Administration			
1.	We note that *Table 1. LEGUBETI Loading Dose* and *Table 2: LEGUBETI Maintenance Dose* of Section 2.3 *Recommended Dosage, Preparation and Administration Instructions in Adults and Pediatrics for Acute Acetaminophen Ingestion* can be improved for clarity.	Given the complex dosing regimen of the proposed product, providing the weight range within the subheadings for the recommended loading and maintenance dose, including the units of measurement following the numeric portion of each dose, and bolding the statements "2.5 grams (b) (4)" and "500 mg (b) (4)" could help to provide clarity and minimize the risk for dosing errors.	See recommended revisions in Figure 1.
2.	We note that, under *Section 2.3 Recommended Dosage and Preparation and Administration Instructions in Adults and Pediatrics for Acute Acetaminophen Ingestion,* the dosing instructions for Patients Weighing 1 to 19 kg, which states, (b) (4) ," could be improved for clarity.	To mitigate the risk for dosing errors, the total amount of drug product needed to prepare the 50 mg/mL solution should be stated.	

Table 2. Identified Issues and Recommendations for Division of Hepatology and Nutrition (DHN)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION

Figure 1. Suggested edits for Section 2.3 Recommended Dosage, Preparation and Administration Instructions in Adults and Pediatrics for Acute Acetaminophen Ingestion

Table 1: LEGUBETI Loading Dose

For patients weighing **60 kg or greater**, Dissolve LEGUBETI powder in **300 mL** of diet cola or other diet soft drinks

Body weight (Kg)	Actual Acetylcysteine Dose to be Administered (b) (4)	Number of LEGUBETI (b) (4) to Dissolve in diet cola or other diet soft drinks	
		2.5 grams (b) (4)	**500 mg** (b) (4)
100 or greater	15 grams	6	0
90 to 99	14 grams	5	3
80 to 89	13 grams	5	1
70 to 79	11 grams	4	2
60 to 69	10 grams	4	0
For patients weighing **20 kg to 59 kg**, Dissolve LEGUBETI powder in **150 mL** of diet cola or other diet soft drinks			
50 to 59	8 grams	3	1
40 to 49	7 grams	2	4
30 to 39	6 grams	2	2
20 to 29	4 grams	1	3

*No specific studies have been conducted to evaluate the necessity of dose adjustments in patients weighing over 100 kg. Limited information is available regarding the dosing requirements of patients that weigh more than 100 kg.

Table 2: LEGUBETI Maintenance Dose

For patients weighing **60 kg or greater**, Dissolve LEGUBETI powder in **300 mL** of diet cola or other diet soft drinks

Body weight (Kg)	Actual Acetylcysteine Dose to be administered (b) (4)	Number of LEGUBETI (b) (4) to Dissolve in diet cola or other diet soft drinks	
		2.5 grams (b) (4)	**500 mg** (b) (4)
100 or greater	7.5 grams	3	0
90 to 99	7 grams	2	4
80 to 89	6.5 grams	2	3
70 to 79	5.5 grams	2	1
60 to 69	5 grams	2	0
For patients weighing **20 kg to 59 kg**, Dissolve LEGUBETI powder in **150 mL** of diet cola or other diet soft drinks			
50 to 59	4 grams	1	3
40 to 49	3.5 grams	1	2
30 to 39	3 grams	1	1
20 to 29	2 grams	0	4

*No specific studies have been conducted to evaluate the necessity of dose adjustments in patients weighing over 100 kg. Limited information is available regarding the dosing requirements of patients that weigh more than 100 kg.

Patients Weighing 1 to 19 kg

Dissolve 5 grams (equivalent to two 2.5-gram LEGUBETI powder (b) (4) in 100 mL of water to create a 50 mg/mL solution. Calculate the loading and maintenance doses using the patient's kilogram weight:

6 RECOMMENDATIONS FOR GALEPHAR PHARMACEUTICAL RESEARCH INC.

Table 3. Identified Issues and Recommendations for Galephar Pharmaceutical Research Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Sachet Label(s) and Carton Labeling			
1.	The format for expiration date is not defined.	A clearly defined expiration date will minimize confusion and risk for deteriorated drug medication errors.	Define the expiration date 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: 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 forward slash be used to separate the portions of the expiration date.
2.	As currently presented, the storage statement on the carton labeling is not consistent with the Storage and Handling statement in Section 16 of the PI.	Inconsistency between storage statements may lead to confusion.	We recommend revising and including the storage and handling statement on the sachet labels and carton labeling.

Reference ID: 5114849

Table 3. Identified Issues and Recommendations for Galephar Pharmaceutical Research Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	Additionally, the storage and handling statement is not included on the sachet labels.		"Store at 20ºC to 25ºC (68ºF to 77ºF), excursions permitted to 15ºC to 30ºC (59ºF to 86ºF) [See USP Controlled Room Temperature.] Protect from moisture. Store in original package until use. (b) (4) "
3.	As currently presented, the 2.5 grams strength product utilizes the abbreviation 'g' which is inconsistent with *Section 3 Dosage Forms and Strengths* of the PI.	Inconsistent strength presentation may lead to confusion and medication errors.	To provide clarity and minimize the potential for misinterpretation and medication errors we recommend replacing the abbreviation 'g' with its intended meaning "grams."
Sachet Label(s)			
1.	As currently presented, the expiration date and lot number appear more prominent than other important information (e.g., proprietary name, established name, strength, dosage form, and route of administration) on the Principal Display Panel (PDP).	The proprietary name, established name, strength, dosage form, and route of administration), among other critical elements, are product information that should appear as the most prominent information on the PDP. For more information see "Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to	We recommend you revise the PDP to bring prominence to the proprietary name, established name, strength, dosage form and route of administration. For example: Increase the font size of the proprietary name, established name, strength, dosage form and route of administration. Take into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

Table 3. Identified Issues and Recommendations for Galephar Pharmaceutical Research Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		Minimized Medication Errors."[c]	Additionally, rearrange the manufacturer name to appear on the bottom right or left corner of the PDP of the sachet label to allow prominence to important product information.
2.	As currently presented the "Rx Only" statement is missing.	The "Rx Only" statement is required on the drug label in accordance with Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act.	Add the "Rx Only" statement to the sachet label. Ensure the "Rx only" statement is not more prominent than critical information presented on the label (e.g., proprietary name, established name, strength, dosage form and route of administration).
3.	As currently presented, the usual dose statement is missing.	The usual dose statement is required per 21 CFR 201.55.	Add the usual dose statement "Dosage: See Prescribing Information for complete dosing instructions," similar to how it is stated on the carton labeling.
4.	As currently presented, there is inadequate differentiation between the 500 mg and 2.5 grams sachets.	Lack of differentiation between strengths may contribute to product selection errors leading to underdose or overdose medication errors.	We recommend adequate differentiation between the 500 mg and 2.5 grams strengths. You may consider using different colors, boxing, or some other means to provide adequate differentiation between the strengths.

[c] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013 Available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors

Table 3. Identified Issues and Recommendations for Galephar Pharmaceutical Research Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
5.	As currently presented, the linear barcode is missing.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label.	Add the product's linear barcode to each individual sachet label as required per 21 CFR 201.25. Please note, the barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode. Additionally, the barcode should be placed in an area where it will not be damaged.
Carton Labeling			
1.	The product identifier is missing.	The Drug supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier. The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following: NDC: [insert NDC] Serial: [insert serial number]	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (July 2021).[d] If you determine the product identifier requirements apply to your product, we request you add a placeholder for the product identifier, including the 2-D matrix barcode, to the carton labeling. Additionally, we recommend you ensure there is sufficient white space

[d] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

Table 3. Identified Issues and Recommendations for Galephar Pharmaceutical Research Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		LOT: [insert lot number] EXP: [insert expiration date]	between the linear barcode and 2-D matrix barcode to allow barcode scanners the ability to correctly read each barcode.
2.	As currently presented, the net quantity statement between the 500 mg 10-count *versus* 20-count and 2.5 grams 10-count *versus* 20-count carton labeling lack differentiation.	Lack of differentiation between the 500 mg 10-count *versus* 20-count and 2.5 grams 10-count *versus* 20-count cartons can contribute to selection errors.	We recommend revising the net quantity statement to ensure there is sufficient differentiation between the 500 mg 10-count versus 20-count and 2.5 grams 10-count versus 20-count carton labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for Legubeti that Galephar Pharmaceutical Research Inc. submitted on October 7, 2022, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and Legubeti		
Product Name	Mucomyst	Legubeti
Initial Approval Date	September 14, 1962 (Withdrawal FR Effective March 13, 2009)	N/A
Active Ingredient	Acetylcysteine	Acetylcysteine lysine
Indication	Inhalation: indicated as adjuvant therapy for patients with abnormal, viscid, or inspissated mucous secretions in several pulmonary conditions. Orally: indicated as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potential hepatotoxic quantity of acetaminophen.	Antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen.
Route of Administration	Inhalation or oral	Oral
Dosage Form	solution	Powder for oral solution
Strength	10% and 20%	500 mg and 2.5 grams
Dose and Frequency		Pre-Treatment Assessment Following Acute Ingestion: Obtain a plasma or serum sample to assay for acetaminophen concentration at least 4 hours after ingestion.

Reference ID: 5114849

		If the time of acetaminophen ingestion is unknown: • Administer a loading dose of LEGUBETI immediately • Obtain an acetaminophen concentration to determine the need for continued treatment If the acetaminophen concentration cannot be obtained (or is unavailable or uninterpretable) within the 8-hour time interval after acetaminophen ingestion or there is clinical evidence of acetaminophen toxicity: • Administer a loading dose of LEGUBETI immediately and continue treatment for a total of 17 doses. If the patient presents more than 8 hours after ingestion and the time of acute acetaminophen ingestion is known: • Administer a loading dose of LEGUBETI immediately • Obtain acetaminophen concentration to determine need for continued treatment If the patient presents less than 8 hours after ingestion and the time of acute acetaminophen ingestion is known and the acetaminophen concentration is known: • Use the Rumack-Matthew nomogram to determine whether or not to initiate treatment with LEGUBETI Loading dose: 140 mg/kg Maintenance doses: 70 mg/kg repeated every 4 hours for a total of 17 doses.

Reference ID: 5114849

Table1: LEGUBETI Loading Dose

Dissolve LEGUBETI powder in 300 mL of diet cola or other diet soft drinks			
Body weight (Kg)	Actual Acetylcysteine Dose to be Administered (b) (4)	Number of LEGUBETI (b) (4) to Dissolve in diet cola or other diet soft drinks	
		2.5 grams (b) (4)	500 mg (b) (4)
100 or greater	15	6	0
90 to 99	14	5	3
80 to 89	13	5	1
70 to 79	11	4	2
60 to 69	10	4	0
Dissolve LEGUBETI powder in 150 mL of diet cola or other diet soft drinks			
50 to 59	8	3	1
40 to 49	7	2	4
30 to 39	6	2	2
20 to 29	4	1	3

*No specific studies have been conducted to evaluate the necessity of dose adjustments in patients weighing over 100 kg. Limited information is available regarding the dosing requirements of patients that weigh more than 100 kg.

Table 2: LEGUBETI Maintenance Dose kg and greater

Dissolve LEGUBETI powder in 300 mL of diet cola or other diet soft drinks			
Body weight (Kg)	Actual Acetylcysteine Dose to be administered (b) (4)	Number of LEGUBETI (b) (4) to Dissolve in diet cola or other diet soft drinks	
		2.5 grams (b) (4)	500 mg (b) (4)
100 or greater*	7.5	3	0
90 to 99	7	2	4
80 to 89	6.5	2	3
70 to 79	5.5	2	1
60 to 69	5	2	0
Dissolve LEGUBETI powder in 150 mL of diet cola or other diet soft drinks			
50 to 59	4	1	3
40 to 49	3.5	1	2
30 to 39	3	1	1
20 to 29	2	0	4

		*No specific studies have been conducted to evaluate the necessity of dose adjustments in patients weighi over 100 kg. Limited information is available regarding the dosing requirements of patients that weigh mo 100 kg. <u>For Patients weighing 1 to 19 kg</u> Dissolve two 2.5-gram LEGUBETI powder sachets in 100 mL of water to create a 50 mg/mL solution. Calculate the loading and maintenance doses using the patient's kilogram weight: <u>*Loading dose:*</u> Calculate the dose by multiplying the patient's kilogram weight by 140 mg/kg and dividing by the concentration of the solution (50 mg/mL). The result is the dose in mL for administration using an oral syringe. <u>*Maintenance dose:*</u> Calculate the dose by multiplying the patient's kilogram weight by 70 mg/kg and dividing by the concentration of the solution (50 mg/mL). The result is the dose in mL for administration using an oral syringe.
How Supplied	Mucomyst®-20: 20% acetylcysteine solution (200 mg acetylcysteine per mL). NDC 0087-0570-03 Cartons of three 10 mL vials, 1 plastic dropper NDC 0087-0570-09 Cartons of three 30 mL vials NDC 0087-0570-07 Cartons of twelve 4 mL vials Mucomyst®-10: 10% acetylcysteine solution (100 mg acetylcysteine per mL).	500 mg sachets printed with "Lot Number and Expiration Date" on one side. Each carton containing 10 or 20 sachets • NDC 66277-319-10: box of 10 sachets. • NDC 66277-290-20: box of 20 sachets. 2.5 grams sachets printed with "Lot Number and Expiration Date" on one side. Each carton containing 10 or 20 sachets • NDC 66277-320-10: box 10 sachets. • NDC 66277-291-20: box 20 sachets

	NDC 0087-0572-01 Cartons of three 10 mL vials, 1 plastic dropper NDC 0087-0572-02 Cartons of three 30 mL vials NDC 0087-0572-03 Cartons of twelve 4 mL vials	
Storage	Store unopened vials at controlled room temperature, 59°F to 86°F (15°C to 30°C). MUCOMYST does not contain an antimicrobial agent, and care must be taken to minimize contamination of the sterile solution. Dilutions of MUCOMYST should be used freshly prepared and utilized within one hour. If only a portion of the solution in a vial is used, store the remaining undiluted portion in a refrigerator and use within 96 hours.	Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature.] Protect from moisture. Store in original package until use. (b) (4)
Container Closure	Vial	Sachet

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 5, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, acetylcysteine, acetylcysteine lysine and 215040. Our search identified five (5) previous reviews[e,f,g,h,i], and we considered our previous recommendations to see if they are applicable for this current review. We determined that our previous recommendations are not applicable to this current review.

[e] Barlow, M. Label and Labeling Review for Cetylev (acetylcysteine) (NDA 207916/2-004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 28. RCM No.: 2018-63.

[f] Barlow, M. Label and Labeling Review for Cetylev (acetylcysteine) (NDA 207916/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUN 23. RCM No.: 2017-381.

[g] Barlow, M. Label and Labeling Review for Cetylev (acetylcysteine) (NDA 207916). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 DEC 18. RCM No.: 2015-747.

[h] Barlow, M. Label and Labeling Review for Cetylev (acetylcysteine) (NDA 207916). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JAN 07. RCM No.: 2015-747.

[i] Barlow, M. Label and Labeling Review for Cetylev (acetylcysteine) (NDA 207916). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JAN 28. RCM No.: 2015-747-1.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[j] along with postmarket medication error data, we reviewed the following Legubeti labels and labeling submitted by Galephar Pharmaceutical Research Inc..

- Sachet label(s) received on October 7, 2022
- Carton labeling received on October 7, 2022
- Prescribing Information (Image not shown) received on October 7, 2022, available from: \\CDSESUB1\EVSPROD\nda215040\0006\m1\us\114-labeling\draft\labeling\draft-labeling-text-ms-word.doc

F.2 Label and Labeling Images

Sachet labels

500 mg	2.5 grams

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

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

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/

SOFANIT N GETAHUN
01/24/2023 04:23:00 PM

VALERIE S VAUGHAN
01/25/2023 09:34:13 AM

M E M O R A N D U M

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

DATE: 11/14/2022

TO: Division of Hepatology and Nutrition (DHN)
Office of Immunology and Inflammation (OII)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 215040

The Office of Study Integrity and Surveillance (OSIS) received an inspection request consult from the Office of Immunology and Inflammation (OII), Division of Hepatology and Nutrition (DHN), on August 31, 2022, for the below site. The requested review goal date is April 5, 2023, and the PDUFA date is May 7, 2023.

OSIS declines to conduct an inspection for the site listed on the consult. The rationale for this decision is noted below.

Rationale

OSIS determined that the requested review due date of April 5, 2023 does not provide sufficient time for an inspection to be completed and for OSIS to provide a review to the review division.

We note that OSIS's inspection history for the site is listed below.

OSIS inspected the site in (b) (4). The inspection was conducted under the following submissions: (b) (4)

OSIS concluded that data from the reviewed study was reliable.

Site

Facility Type	Facility Name	Facility Address
Analytical		(b) (4)

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/s/

JAMES J LUMALCURI
11/14/2022 09:42:37 AM