NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	215040
Priority or Standard	Standard
Submit Date(s)	July 7, 2022
Received Date(s)	July 7, 2022
PDUFA Goal Date	May 7, 2023
Division/Office	Division of Hepatology and Nutrition
Review Completion Date	May 5, 2023
Established/Proper Name	acetylcysteine
(Proposed) Trade Name	LEGUBETI
Pharmacologic Class	Antidote for acetaminophen overdose
Code name	N/A
Applicant	Galephar Pharmaceutical Research Inc.
Dosage form, Strength	Powder for oral solution 500 mg and 2.5 g
Applicant proposed Dosing Regimen	The recommended loading dose of LEGUBETI is 140 mg/kg. Administer a first maintenance dose of 70 mg/kg 4 hours after the loading dose. Repeat 70 mg/kg maintenance dose every 4 hours for a total of 17 maintenance doses.
Applicant Proposed Indication(s)/Population(s)	Indicated as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen.
Applicant Proposed SNOMED CT Indication	295124009, Acetaminophen overdose (disorder)

Disease Term for each Proposed Indication	
Recommendation on Regulatory Action	Complete Response

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Abbreviations: CDRH, Center for Devices and Radiological Health; DARS, Division of Applied Regulatory Sciences; DEPI, Division of Epidemiology; DHOT, Division of Hematology Oncology Toxicology; DIIP, Division of Inflammation and Immune Pharmacology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; DPV, Division of Pharmacovigilance; DPMH, Division of Pediatrics and Maternal Health; OB, Office of Biostatistics; OHOP, Office of Hematology and Oncology Products; OPDP, Office of Prescription Drug Promotion; OPMA, Office of Pharmaceutical Manufacturing Assessment; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
APAP	N-acetyl-p-aminophenol; acetaminophen
AR	adverse reaction
BA	bioavailability
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ESRD	end-stage renal disease
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007

FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HUS	hemolytic uremic syndrome
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NAC	N-acetylcysteine
NAPQI	N-acetyl-p-benzoquinone imine
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PLR	Physician Labeling Rule
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome

PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
RS	Reference Standard
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Legubeti (acetylcysteine) for oral solution is proposed as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen. It is essential to initiate treatment as soon as possible after the overdose and, in any case, within 24 hrs of ingestion of acetaminophen.

Legubeti contains acetylcysteine lysine as the active ingredient and is a powder packaged in aluminum sachets in 500 mg and 2.5 g strengths.

The Applicant proposed to establish the safety and efficacy of Legubeti by relying on the FDA's previous findings of safety and efficacy of Mucomyst (acetylcysteine solution; NDA 13601). Legubeti is a new lysine salt form of acetylcysteine whereas Mucomyst is acetylcysteine free acid in 10% or 20% solution.

The proposed indication and the dosage regimen for adult and pediatric patients are the same as those of the listed drug (LD), Mucomyst. The proposed dosage regimen in adults and pediatric patients weighing > 1 kg is the loading dose of 140 mg/kg followed by a first maintenance dose of 70 mg/kg 4 hrs after the loading dose and repeated every 4 hrs for a total of 17 maintenance doses. The maximum loading and maintenance dose is 15 g and 7.5 g, respectively for patients weighing 100 kg or greater.

Legubeti should be dissolved to form a solution prior to administration. Legubeti is completely dissolved to form a solution in the proposed liquid for oral administration: water, pediatric electrolyte solution, and Diet Coke. A dosing syringe may be used to administer the oral solution to the pediatric patients. For the patient who is persistently unable to retain the orally administered acetylcysteine, Legubeti may be administered by nasoduodenal tube.

The Applicant proposed the product as Tradename (acetylcysteine lysine) powder for oral solution. However, consistent with the USP nomenclature, it should be Tradename (acetylcysteine) for oral solution. Refer to Section 10.1.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant proposes to establish the efficacy and safety of Legubeti by relying on FDA's previous findings of efficacy and safety of Mucomyst as an antidote for acetaminophen overdose. To justify the reliance of efficacy and safety on Mucomyst, the Applicant conducted a relative bioavailability study 2021-5140 to compare Legubeti and the acetylcysteine oral solution (ANDA 072547), the reference standard per the

Orange Book because Mucomyst has been discontinued not for the reason of safety or efficacy.

The relative bioavailability study showed the equivalent bioavailability after a single dose administration of 1 g acetylcysteine by Legubeti and the acetylcysteine solution. Because the dose of acetylcysteine can be as high as 15 g for patients weighing greater than 100 kg based on the proposed weight-based dosage regimen, and Legubeti contains a high amount of L-lysine as the counter ion in this new acetylcysteine salt, additional justification was used to support the comparable bioavailability at doses higher than 1 g. Legubeti is completely dissolved to a solution for entire dose range and there is no evidence of interference with oral absorption of acetylcysteine by dissociated lysine as of now. Therefore, the comparable systemic exposure between Legubeti and the acetylcysteine oral solution at doses for all body weight range can be supported by the available relative BA data and self-evident bioavailability for oral solution.

However, the review team concluded that the currently available data are insufficient to fully justify the reliance on the previous findings of safety and efficacy of the listed LD because of the lack of comparison of tolerability between Legubeti and the LD at the clinically relevant doses.

Acetylcysteine is known to have an unpleasant odor and taste because of its sulfur moiety and to improve the palatability, the approved acetylcysteine oral solution is recommended to be diluted in diet soda for oral administration. The Applicant proposed to dissolve Legubeti in diet soda to an oral solution as well. Nevertheless, it is unknown if the addition of L-lysine which has a bitter taste to acetylcysteine would not adversely affect the palatability and tolerability especially considering the high amount of L-lysine per acetylcysteine dose (i.e., 2.5 g acetylcysteine strength includes 2.24 g L-lysine) because there are no clinical data available at the clinically relevant doses. The relative BA study conducted at 1 g, which is a dose for pediatric patients weighing < 20 kg, does not address the concerns because patients weighing $\geq$ 20 kg will receive 2 g or greater up to 15 g based on the proposed body weight-based dose.

Given timely administration of acetylcysteine is essential to prevent or mitigate hepatotoxicity from acetaminophen overdose, an inability to tolerate the full dose regimen of the drug product places patients at increased risk of acetaminophen-induced toxicity and can lead to loss of efficacy.

The Agency communicated this concern in the 74-day letter and in response, the Applicant proposed to conduct a study to assess the tolerability and palatability of Legubeti at a higher dose in comparison to the acetylcysteine oral solution. However, the study results have not been submitted. Therefore, the currently available data are inadequate to establish the effectiveness and safety of Legubeti based on the reliance on the FDA's previous findings of efficacy and safety for the LD.

The results of proposed tolerability and palatability study at high dose(s) will be needed to fully justify the reliance on the LD. As such a Complete Response will be issued.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Legubeti (acetylcysteine lysine) is proposed as an antidote for acetaminophen overdose.

Acetaminophen (N-acetyl-p-aminophenol, APAP) is one of the most widely used pain relievers and has been available as an over-the-counter preparation in the United States since 1960. APAP is safe and effective at therapeutic doses, but hepatotoxicity can occur with acute ingestion of > 7.5 g to 10 g (~ 140 mg/kg). Severe liver injury may also rarely occur with repeated doses of > 3-4 g/day, especially in at-risk populations. APAP toxicity is the most common cause of acute liver failure (ALF) in the US and Europe.

Acetylcysteine (N-acetylcysteine; NAC) is the approved pharmacological treatment for APAP toxicity. NAC is an N-acetyl derivative of cysteine, a naturally occurring amino acid. NAC exerts its action in APAP toxicity by repleting glutathione stores by providing cysteine, binding to toxic metabolites (N-acetyl-p-benzoquinone imine), and scavenging free radicals, increasing oxygen delivery to tissues, increasing mitochondrial ATP production, altering microvascular tone, and thus increasing blood flow to the liver and other vital organs. The efficacy of treatment depends on the time interval from when APAP was ingested. NAC administration is most effective within 8 hours of APAP ingestion but may provide clinical benefit even when administration is delayed beyond eight hours. If NAC is started within 24 hours of APAP overdose, the mortality rate is 0.7%. Multiple NAC products have been approved for oral or intravenous administration.

The Applicant did not conduct controlled clinical trials of efficacy or safety with Legubeti. The Applicant relied on FDA's previous findings of efficacy for the listed drug (LD) Mucomyst® (acetylcysteine solution, USP, NDA 013601, currently discontinued not for a reason of safety or efficacy). To establish a scientific bridge to the LD, the Applicant conducted a relative bioavailability (BA) study 2021-5140, comparing its proposed product to the oral acetylcysteine solution (reference standard, ANDA 072547) after a single dose of 1000 mg acetylcysteine in healthy subjects under fasted conditions and demonstrated equivalent systemic exposure to acetylcysteine.

NAC has an unpleasant smell and taste, and vomiting is common with oral administration. Most common adverse reactions with orally administered NAC include nausea, vomiting, diarrhea, and other gastrointestinal symptoms. Other adverse reactions observed include rash, urticaria, and fever. Anaphylactoid reactions have also been document with oral NAC but are more common with IV NAC. Safety data from this BA study 2021-5140, published literature review, and analysis of databases of post-marketing safety reports in the United States, did not identify any new safety issues with oral NAC.

Because this is a new salt of NAC, in which the L-Lysine content is approximately 47.25% (w/w) of the API, there is concern regarding the effect of L-Lysine on tolerability and palatability of Legubeti. There are insufficient data regarding the tolerability and palatability of the proposed Legubeti doses. An inability to ingest the full dose regimen, either due to inadequate palatability or inadequate tolerability poses significant safety concerns: (1) inability to tolerate full dose NAC regimen or delay in ingestion of doses, may increase the risk of APAP hepatotoxicity; and (2), lack of data on the effect L-lysine will have on

gastrointestinal adverse reactions when compared to NAC, as increased risk of vomiting may increase the risk of aspiration in patients, especially in children and those with altered mental status.

In adults, the dose of L-lysine expected to be administered is approximately 8-13 times higher than the recommended daily intake from a regular diet over a three-day period. Although there are limited human data to support safety of a high dose for a short period, animal data were adequate to support the safety of high dose, short-term L-lysine administration.

For pediatric patients, the Applicant did not provide adequate information supporting the safety of lysine administration 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/day with loading dose treatment on the first day and 313 mg/kg/day after completion of the maintenance dose on the last day of treatment. This amount of lysine expected to be delivered with the proposed dosage of Legubeti exceeds the estimated daily intake of lysine in enterally fed term neonates of 130 mg/kg/day (Huang et al. 2011). This would still need to be addressed to inform the benefit risk assessment of this product in the pediatric population weighing down to 1 kg.

Because of the lack of data regarding the tolerability and palatability of acetylcysteine lysine at clinically relevant doses for most patients compared to the LD, the conclusion of comparable safety as well as efficacy cannot be made to justify a favorable benefit-risk profile like that of the LD. Therefore, the available data are not adequate to conclude a favorable benefit-risk for approval of Legubeti.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acetaminophen (N-acetyl-p-aminophenol, APAP) is one of the most widely used pain relievers in use. It has been in use since 1960. • APAP is safe and effective at therapeutic doses. • APAP toxicity – Hepatotoxicity can occur with acute ingestion of > 7.5 g to 10 g (~ 140 mg/kg), and rarely occur with repeated doses of > 3-4 g/day, especially in at-risk populations. – It is the most common cause of acute liver failure (ALF) in the US and Europe, and the most common indication for liver transplantation for ALF in the U.S. • APAP overdose is responsible for 56,000 emergency department visits, 2,600 hospitalizations, and 500 deaths per year in the United States.	Acetaminophen is a widely used pain reliever. Although safe in therapeutic doses, acute or chronic ingestion can lead to severe liver injury which may result in acute liver failure and death.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The Rumack-Mathew Nomogram can be used to assess the risk of hepatotoxicity and the need for starting NAC. Without treatment, about 58% of patients with acetaminophen levels above the Rumack-Matthew nomogram "treatment line" will develop hepatotoxicity and about 5-6% of patients will die. • If NAC is given within eight hours of APAP ingestion, serious APAP toxicity is unlikely. NAC can be administered orally or intravenously (IV), and a 21-hour IV and a 72-hour oral dosing protocol are more commonly used.	
Current Treatment Options	• N-acetylcysteine (NAC) is the only approved pharmacological treatment for acetaminophen toxicity. • Several products of NAC are available for oral use. Mucomyst, the listed drug (LD) for this NDA was approved in 1963 as an antidote for APAP toxicity in adult and pediatric patients. It has since been discontinued. Cetylev (acetylcysteine), an effervescent tablet was approved in 2016, but has also been discontinued. There are multiple generic products of NAC, which can be used orally. There is also an IV product of NAC, Acetadote (see Section 2.2 for more information) • Oral administration of NAC is complicated by the unpleasant taste and odor of NAC which affects tolerability and palatability of oral NAC products. Patients with APAP toxicity experience nausea and vomiting as presenting symptoms, which combined with the unpleasant taste and odor of NAC can aggravate vomiting and thus make oral NAC intolerable. Patients can also have increased risk of aspiration, especially in children and patients with altered mental status.	NAC has been used as an antidote for acetaminophen since 1963 and if given early after overdose of acetaminophen provides a benefit on decreasing the likelihood of severe liver injury as compared with no treatment. NAC products for IV administration and generic products of NAC for oral administration are available.
Benefit	• The Applicant did not conduct any controlled clinical trials of efficacy or safety. The Applicant relies on FDA's previous findings of efficacy for the listed drug (LD) Mucomyst. • To establish a scientific bridge to the LD, the Applicant conducted a relative bioavailability (BA) study 2021-5140, comparing Legubeti to the Acetylcysteine Oral Solution, the reference standard per the Orange Book, because Mucomyst	The Applicant relies on FDA's previous findings of efficacy in adult and pediatric patients for the listed drug (LD) Mucomyst. The comparable efficacy of Legubeti to the LD can be expected based on the comparable systemic exposure between two products.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	is currently discontinued, after a single dose of 1000 mg NAC in healthy subjects under fasted conditions. • The equivalent bioavailability was shown between Legubeti and the reference standard at 1000 mg. Because Legubeti is completely dissolved to form a solution prior to oral administration and no evidence of dissociated lysine would affect oral absorption of acetylcysteine, available data also support the comparable systemic exposure between Legubeti and the Acetylcysteine oral solution at doses for all body weight range. • Legubeti can be reconstituted in the age-appropriate volume of liquid for oral administration for pediatric patients. • However, there are no data to support lack of adverse effects of L-lysine on the tolerability and palatability of acetylcysteine at clinically relevant doses.	However, the currently available data are not sufficient to conclude the efficacy of Legubeti will be comparable with the LD due to uncertainty in the tolerability and palatability that can affect the efficacy of Legubeti.
Risk and Risk Management	• Most common adverse reactions with orally administered NAC include nausea, vomiting, diarrhea, and other gastrointestinal symptoms. Rash, urticaria and mild fever have also been observed. Risk of upper gastrointestinal hemorrhage is also included in the Warnings and Precautions section of the LD label. NAC has an unpleasant smell and taste, and vomiting is common with oral administration. • Safety data from the BA study 2021-5140, published literature review, and analysis of databases of post-marketing safety reports in the United States, did not identify any new safety issues with oral NAC. • In adults, the amount of L-lysine administered from Legubeti will be approximately 8-13 times higher than the recommended daily intake from a regular diet over a three-day period. The animal toxicology data, as well as supportive data for safety of L-lysine in humans at higher doses than that from a regular diet from published reports, provide a reasonable assurance of safety regarding the dose of L-lysine administered. • For pediatric patients, the maximum daily amount of L-lysine expected to be administered from Legubeti at the proposed dosage ranges is two to four times the daily estimated intake of lysine in enterally fed term neonates of 130	The Applicant relies on FDA's previous findings of safety in adult and pediatric patients for the listed drug (LD) Mucomyst based on the comparable systemic exposure to NAC. Nonclinical toxicology study and published studies provide a reasonable assurance of safety regarding the amount of L-lysine administered from Legubeti in general. However, the available data are insufficient to assure the safety of l-lysine in pediatric patients down to patients weighing 1 kg. The palatability and tolerability of Legubeti remains unknown because of the lack of data for Legubeti, a lysine salt form of NAC at the clinically relevant doses. The inability to ingest the full dose regimen in a timely manner, due to inadequate palatability or tolerability would pose increased risk of APAP hepatotoxicity. Decreased palatability or tolerability

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	mg/kg/day. However, the provided information is not sufficient to support the safety of lysine at the level in young pediatric patients down to 1 kg. • However, while both acetylcysteine and L-lysine have an unpleasant odor and/or taste, there are insufficient data to ensure the L-lysine salt form does not adversely affect the palatability and tolerability of NAC. • To address the tolerability and palatability concerns, the Applicant proposed a trial to assess the tolerability and palatability of acetylcysteine lysine powder for oral solution in adults. As of this review, the study results are not available.	could also increase risk of vomiting, and subsequent aspiration, especially in children and patients with altered mental status. Altered mentation is not uncommon in patients who sustain APAP overdose. The relative BA study conducted at 1 g acetylcysteine dose only cannot address the palatability and tolerability of Legubeti while the amount of L-lysine intake would be as high as 14 g for a 100 kg patient at dose of 15 g acetylcysteine. Therefore, the data are **not adequate** to establish the safety of Legubeti via reliance on the LD.

1.4. Patient Experience Data

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

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

	□	Observational survey studies designed to capture patient experience data	
	□	Other: (Please specify):	
X	**Patient experience data was not submitted as part of this application.**		

2. Therapeutic Context

2.1. Analysis of Condition

2.1.1. Acetaminophen

Acetaminophen (N-acetyl-p-aminophenol, APAP) is a non-opioid analgesic and antipyretic agent approved to treat pain and fever. It is one of the most widely used pain relievers with more than 25 billion doses sold yearly. Acetaminophen has been available as an over-the counter product in the United States since 1960. (FDA 2022)

APAP is available in capsules or tablets of 325 mg, 500 mg or 650 mg. Liquid formulations for children are available in concentrations of 160 mg/5 mL. Chewable tablets are also on the market with 160 mg of APAP in each tablet. In addition, APAP is frequently combined with decongestants, antihistamines, or other analgesics (such as oxycodone, hydrocodone, and codeine) in many approved products for over-the-counter use and prescription.

APAP is absorbed rapidly once ingested from the gastrointestinal tract and reaches therapeutic levels in 30 minutes to two hrs. It has an elimination half-life of two hrs but can be longer in patients with hepatic dysfunction.(Agrawal and Khazaeni 2023)

2.1.2. Acetaminophen (APAP) Toxicity

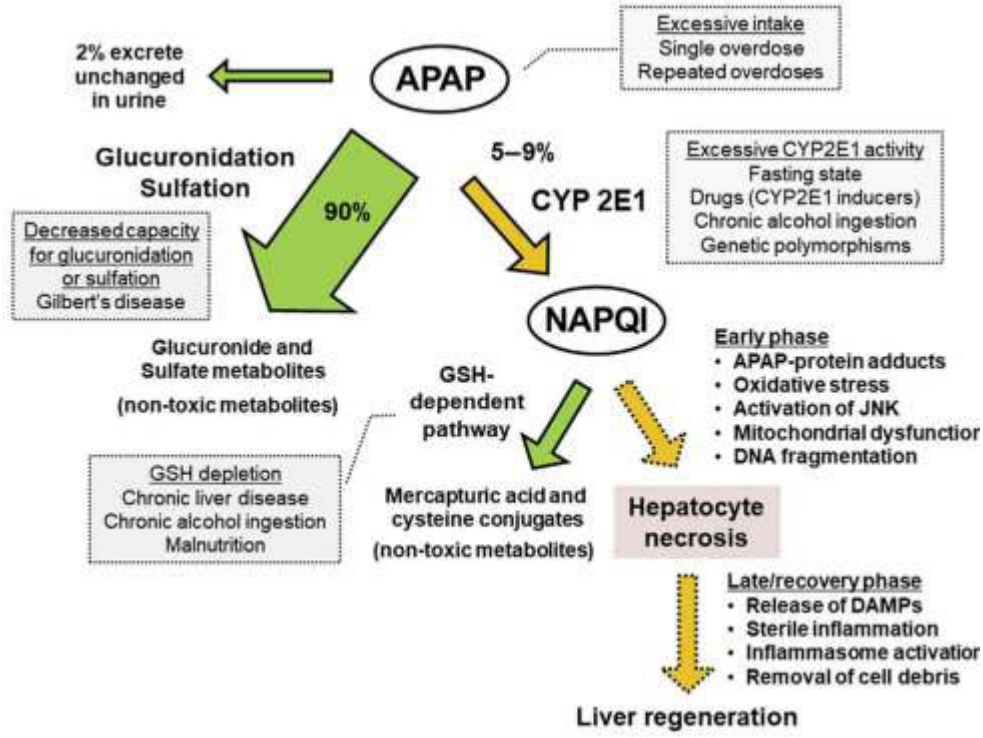
Hepatotoxicity can occur with acute ingestion of > 7.5 g to 10 g (~ 140 mg/kg). Severe liver injury may also rarely occur with repeated doses of > 3-4 g/day, especially in at-risk populations (e.g., those with alcohol use disorder, underlying liver disease, malnutrition). Because APAP is widely available and prescribed in combination products, intentional and accidental overdose events have resulted in APAP becoming the most common cause of acute liver failure (ALF) in the United States and Europe. Acetaminophen toxicity is the second most common indication for liver transplantation worldwide and the most common indication for liver transplantation in the United States. Acetaminophen overdose is responsible for 56,000 emergency department visits; 2,600 hospitalizations; and 500 deaths per year in the United States. Fifty percent of APAP-associated liver failure events are due to unintentional overdoses. (Lee et al. 2012; Agrawal and Khazaeni 2023)

Acetaminophen is largely metabolized into nontoxic glucuronide and sulfate metabolites which are secreted in urine (Figure 1). A small percentage of APAP is metabolized by the cytochrome P450 system to intermediate metabolites which can be toxic. One, N-acetyl-p-benzoquinone imine (NAPQI), is ordinarily rapidly conjugated to reduced glutathione (GSH), detoxified, and excreted.

However, if the GSH conjugation pathway is overwhelmed, or if GSH levels are low, NAPQI accumulates and forms APAP protein adducts on mitochondrial proteins, affecting components of the electron transport chain (e.g., ATP synthase and glutathione peroxidase), which leads to increased generation of reactive oxygen species

(e.g., superoxide). Superoxide combines with nitric oxide to increase oxidative stress leading to release of intermembrane proteins. These intermembrane proteins lead to DNA fragmentation and cell necrosis. (Larson 2007; NIDDK 2012; Bunchorntavakul and Reddy 2018; Ramachandran and Jaeschke 2018)

Figure 1. Mechanism of APAP Toxicity



Source: (Bunchorntavakul and Reddy 2018)

The clinical course of APAP toxicity is divided into four stages, based on time after ingestion (Agrawal and Khazaeni 2023):

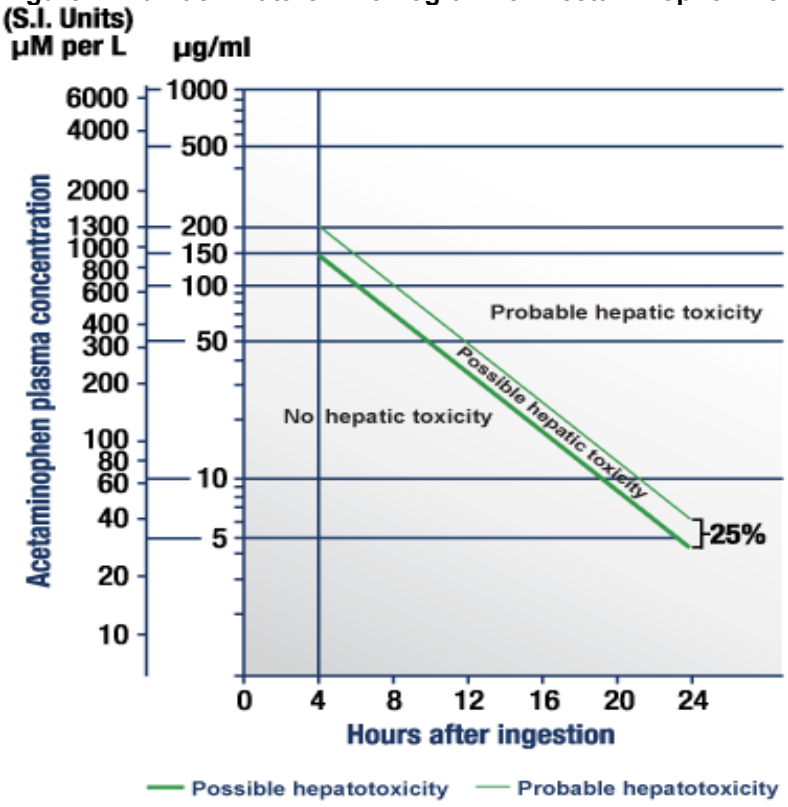
- First stage (½ to 24 hrs): the patient may be asymptomatic, or have nausea, vomiting, diaphoresis, pallor, lethargy, or malaise.
- Second stage (18 to 72 hrs): the patient may have vomiting with abdominal pain (right upper quadrant), hepatomegaly, and hypotension. Hepatic and renal injury become apparent.
- Third stage (72 to 96 hrs): marked elevation in hepatic enzymes, elevated ammonia, and bleeding. There are signs of severe hepatotoxicity such as coagulopathy and encephalopathy, and acute renal failure. Death most commonly occurs during this stage.
- Fourth stage (four days to 3 weeks): patients who survive the third stage enter a recovery phase.

Diagnosis rests on serum levels of APAP. Other laboratory testing includes assessment of transaminases, and coagulation profile. Co-ingestion with other agents (e.g., opiates,

benzodiazepines, and other agents which may affect mental status) may occur, therefore evaluation usually includes a urine drug screen, ECG, and a metabolic panel.

The treatment of APAP poisoning depends on when APAP was ingested. Gastrointestinal decontamination can be attempted if the patient presents within one hour of ingestion. All patients with high levels of APAP, as determined by the Rumack-Matthew Nomogram (Figure 2) need hospital admission and treatment with N-acetyl cysteine (NAC). (Rumack and Matthew 1975)

Figure 2: Rumack-Matthew Nomogram for Acetaminophen Poisoning



Source: (Rumack and Matthew 1975)

2.2. Analysis of Current Treatment Options

N-acetylcysteine (NAC) is the only approved pharmacological treatment for acetaminophen toxicity with multiple products available for oral and intravenous administration. Table 1 lists current and discontinued NDAs for acetylcysteine.

Table 1. Current and Discontinued Acetylcysteine NDAs

Drug	Indication	Reviewer Comment
Mucomyst* NDA 013601 approved 09/14/1963 oral solution	Antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen Adjuvant therapy for patients with abnormal, viscid, or inspissated mucous secretions in various pulmonary conditions.	Discontinued on 10/03/2007 Federal Register determination that product was not discontinued or withdrawn for safety or effectiveness reasons.(FDA 2023b) Multiple generic versions are on the market.
Acetadote NDA 021539 approved 01/23/2004 intravenous injection	Antidote for acetaminophen overdose indicated to prevent or lessen hepatic injury after ingestion of a potentially hepatotoxic quantity of acetaminophen in patients with an acute ingestion or from repeated supratherapeutic ingestion (RSI)	Multiple generic versions.
Cetylev NDA 207916 approved 01/29/2016 effervescent tablet	Antidote for acetaminophen overdose indicated to prevent or lessen hepatic injury after ingestion of a potentially hepatotoxic quantity of acetaminophen in patients with acute ingestion or from repeated supratherapeutic ingestion	Discontinued as of 03/04/2022 (87 FR 5828, February 2, 20200)(FDA 2023c) Drug is no longer marketed. No generic versions.

Source: Reviewer generated from Drugs@FDA (FDA 2023a)
*Listed drug for this application
Abbreviations: NDA, new drug application; RSI, repeated supratherapeutic ingestion

Serious toxicity due to APAP is unlikely if NAC is given within eight hrs post-APAP ingestion. Such patients generally do not develop hepatic failure or die. Most deaths from hepatic failure occur within the first week following overdose. Patients who recover generally do well and do not develop chronic liver dysfunction. (Algren 2008)

NAC is the only available medical therapy for APAP overdose to prevent or treat hepatic failure. Although APAP can be cleared by hemodialysis, there is no role for hemodialysis as a treatment for APAP overdose given the availability of NAC. Hemodialysis however may play a role in APAP overdose to address the complications of severe APAP toxicity, such as renal failure and lactic acidosis. Liver transplant may be required in some patients who develop acute liver failure due to APAP toxicity.

NAC can be administered orally or intravenously (IV) for APAP toxicity. The FDA approved regimens are a 21-hour IV protocol and a 72-hour (17 dose) oral dosing protocol. Off-label simplified IV protocols are used but there are insufficient data to recommend one protocol over another. The Rumack-Mathew Nomogram can be used to assess the risk of hepatotoxicity in acute single ingestions of APAP, and the need for starting NAC.(Rumack and Matthew 1975) Without NAC treatment, about 58% of patients with acetaminophen levels above the Rumack-Matthew nomogram (Figure 2) “treatment line” develop hepatotoxicity; approximately five to six percent of patients will die. When acetylcysteine is started within 0 to 24 hrs of overdose the mortality rate is reduced to 0.7%. (Hodgman and Garrard 2012; Chiew et al. 2018)

2.2.1. Mechanism of Action of N-Acetylcysteine in Acetaminophen Toxicity

NAC is an N-acetyl derivative of cysteine, a naturally occurring amino acid. NAC exerts its action in APAP toxicity by several mechanisms. (Ershad et al. 2023) These include:

- Repleting glutathione stores by providing cysteine
- Binding to toxic metabolites (NAPQI), and scavenging free radicals
- Increasing oxygen delivery to tissues
- Increasing mitochondrial ATP production
- Altering microvascular tone, and thus increasing blood flow to the liver and other vital organs

2.2.2. Adverse Effects of N-Acetylcysteine

NAC has an unpleasant smell and taste, and vomiting is common with oral administration. Most common adverse reactions with orally administered NAC include nausea, vomiting, diarrhea, and other gastrointestinal symptoms. Rash, urticaria and mild fever have also been observed. Hypersensitivity or anaphylactoid reactions are more common with IV administration but have been also observed with oral dosing. Risk of upper gastrointestinal hemorrhage is also included in the Warnings and Precautions section of the label. Cerebral edema, uncal herniation, and death have been reported with erroneous dosing of IV NAC. Death due to anaphylactoid reactions has also been rarely reported. (Heard 2008; Arbor 2017; Spence et al. 2023)

Because vomiting is a common adverse reaction of oral NAC that limits adherence, IV NAC has largely replaced oral NAC, and is often considered first-line treatment, especially in patients with vomiting, those who have contraindications to oral administration, evidence for hepatic failure, or those who refuse oral administration. (Lee et al. 2011) However, the disadvantage with use of IV NAC is a higher incidence of hypersensitivity or anaphylactoid reactions.

Since oral NAC is no longer available in the United States, there is an unmet need for an oral formulation with improved oral palatability and tolerability.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Legubeti is not currently marketed in the U.S.

MUCOMYST (NDA 013601), the Listed Drug (LD), was FDA-approved on September 14, 1963, but was discontinued from the U.S. market on March 13, 2009, by the manufacture based on a business decision, and not for reasons of safety or efficacy.

3.2. Summary of Presubmission/Submission Regulatory Activity

- **May 18, 2016:** A Type B Pre-IND meeting for PIND 130190 was held to discuss the contents of an NDA submission utilizing the 505(b)(2) regulatory pathway. During this meeting, the Agency agreed that the Sponsor could submit a 505(b)(2) application as their proposed product would not be a "duplicate" of the LD. The Agency also stated that as the proposed product involved a new active ingredient and a new dosage form, a biowaiver could not be granted and the Sponsor would need to conduct a relative bioavailability (BA) study to bridge their proposed product to the LD. The Agency also requested that justification for lysine component of NAL would not affect the safety and efficacy of NAC should be provided. The Sponsor was also informed that the product represented a new salt which was considered a new active ingredient and would trigger the Pediatric Research Equity Act (PREA). The design of the relative BA study design was not discussed. Meeting Minutes were sent on May 19, 2016.
- **April 15, 2020:** Agreed-Initial Pediatric Study Plan letter was issued which provided for partial waiver for children below 1 kilogram.
- **July 14, 2021:** Request for Small Business Waiver was granted for NDA 215040.
- **July 7, 2022:** NDA 215040 was submitted via 505(b)(2) regulatory pathway.
- **September 9, 2022:** Filing Review Issues Identified Letter was issued.
- **September 22, 2022:** Denied the proprietary name request for (b) (4).
- **October 7, 2022:** Applicant submitted a second proposed proprietary name, **LEGUBETI.**
- **October 21, 2022:** Draft protocol was submitted to PIND 130190 for tolerability and palatability study to be conducted to support the pending NDA submission. The Applicant proposed this protocol to address concerns regarding palatability and tolerability raised in the Filing Review Issues Identified Letter dated September 9, 2022.
- **December 16, 2022:** General Advice Letter containing comments on the draft protocol submitted to PIND 130190 was issued.
- **December 29, 2022:** Proprietary name request for **LEGUBETI** was conditionally acceptable.
- **December 30, 2022:** The Applicant submitted responses to the Filing Review Issues Identified letter dated September 9, 2022.

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

4.1. Office of Study Integrity and Surveillance (OSIS)

The inspection of the clinical and analytical sites for the relative bioavailability study was requested to the Office of Study Integrity and Surveillance (OSIS). The OSIS declined to conduct an inspection for analytical site ((b) (4)) due to insufficient time for the completion of inspection. However, OSIS inspected the same site in (b) (4) (b) (4) under other applications[1] and deemed the data from the reviewed study reliable.

As of 03/10/2023, OSIS completed the inspection of the clinical site at Pharma Medica Research Inc. in Scarborough, Ontario, Canada, where no objectional conditions or practices were found during the inspection (NAI).[2]

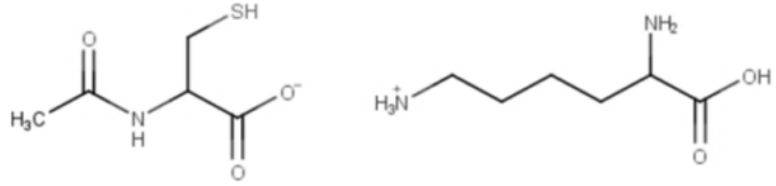
4.2. Product Quality

4.2.1. Drug Substance

The drug substance, acetylcysteine lysine has been developed as the active ingredient for drug product Legubeti (acetylcysteine) intended for prevention or lessening of hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen.

Acetylcysteine lysine is white to almost white powder with the Optical Rotation of 18° to 25°. It is freely soluble in water and insoluble in methanol, diethyl ether, and chloroform. It is hygroscopic and should protected from moisture. Acetylcysteine lysine is the lysine salt of acetylcysteine and has chemical name, (2R)-2-acetylamino-3-sulfanylpropanoic acid; (2S)-2,6-diaminohexanoic acid, molecular weight of 309.39 g/mol, molecular formula, C11H23N3O5S, and chemical structure below:

Figure 3. Structure of Acetylcysteine Lysine



Source: From the NDA

[1] DARRTS, NDA 215040, LUMALCURI, JAMES J, 11/14/2022 CONSULT REV-DSI-05 (Bioequivalence Establishment Inspection Report Review).

[2] DARRTS, NDA 215040, JAVIDNIA, MONICA, 03/10/2023, COR-DSIBIOEQ-05 (BIOEQ NAI Foreign).

Acetylcysteine lysine for this application is manufactured by Galephar Pharmaceutical Research, Inc. in accordance with the current Good Manufacturing Practices (cGMP). It is tested against a regulatory specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its proposed retest date of (b) (4) months. The proposed drug substance retest date is supported by the stability data submitted in the application.

4.2.2. Drug Product

The drug product, Legubeti (acetylcysteine) for oral solution, 500 mg and 2.5 g contains acetylcysteine lysine as the active ingredient and povidone (b) (4) as an inactive ingredient. This drug product is a powder packaged in aluminum sachets and should be dissolved in diet cola or water prior to administration. A dosing syringe may be used to administer the oral solution to the pediatric patients.

The 500 mg strength is composed of 948 mg N-acetylcysteine lysine equivalent to 500 mg of acetylcysteine and (b) (4) mg povidone (b) (4). The 2.5 g strength is composed of 4740 mg of N-acetylcysteine lysine equivalent to 2500 mg of acetylcysteine and (b) (4) mg of povidone (b) (4).

This drug product is manufactured Galephar Pharmaceutical Research, Inc. in accordance with the cGMP requirements. The final drug product is tested against regulatory specification that assures the identity, strength, purity, and quality of the drug product at release and throughout its proposed shelf-life 24 months. The proposed expiration dating period (shelf-life) of 24 months is supported by the stability data provided in the application.

4.2.3. The OPQ Recommendation

- The Applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, N-acetylcysteine lysine, and the drug product, Legubeti (acetylcysteine) for Oral Solution, 500 mg and 2.5 g.
- The Applicant's request for categorical exclusion from preparation of environmental assessment has been found adequate and is granted.
- The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.
- The CMC recommended changes in labeling as well as container and carton labels. The recommended change includes the dosage form to be "for oral solution" instead of "(b) (4)".
- The labeling negotiation will be deferred since this application will be given a complete response from the clinical perspective.

Therefore, from the OPQ perspective this NDA is not ready for approval in its current form until the CMC labeling deficiencies and recommendations are appropriately addressed as per 21 CFR 314.125(b)(6).

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Legubeti (acetylcysteine lysine) powder for oral solution is a new lysine salt of NAC indicated as an antidote to prevent or lessen hepatic injury which may occur following ingestion of a hepatotoxic or potentially hepatotoxic amount of acetaminophen. The proposed drug product (Legubeti [acetylcysteine] powder for oral solution) will be packaged in aluminum sachets, with acetylcysteine lysine (also known as nacystelyn or NAL) and Povidone (b) (4) as the ingredients. Acetylcysteine (free acid), which is often referred to as N-acetylcysteine or NAC, is an approved drug indicated to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen. The Applicant's NDA is mainly supported by reference to the Agency's previous findings of safety for the LD, Mucomyst, and available publications of nonclinical studies of acetylcysteine (free acid). In addition, the Applicant also submitted original reports of genotoxicity studies (standard battery) conducted with acetylcysteine lysine (nacystelyn). The LD is Mucomyst (NDA 013601), which has been discontinued from marketing. Mucomyst is a 10% or 20% solution of NAC for inhalation when used as a mucolytic agent. Both strengths are also indicated for oral administration in the treatment of acetaminophen overdose. The Agency did not request submission of nonclinical studies in previous communications under PIND 130190. The proposed labeling (sections 8.1 and 13.1) contains nonclinical data from publications. The same data is included in the labels for the listed drugs Mucomyst (NDA 013601) and/or Cetylev (NDA 207916). However, the Applicant has only designated Mucomyst for reliance on the Agency's findings of safety to support approval of their marketing application as a 505(b)(2) NDA.

To bridge Mucomyst solution for the Agency's prior findings of safety, the Applicant has conducted a clinical comparative bioavailability study. The Clinical Pharmacology team has determined that this study supports the comparable systemic exposure to the tested comparator product (acetylcysteine 20% oral solution). The proposed dosage for adult and pediatric patients is approximately 140 mg/kg for the loading dose and approximately 70 mg/kg for the maintenance dose, with the maintenance dose repeated every four hrs for a total of 17 doses. The dose unit (mg/kg) for the proposed dosing regimen is expressed as the acetylcysteine free acid equivalent. The proposed oral dose levels and the overall dosing regimen are identical to that of Mucomyst and other approved acetylcysteine products for oral administration with the same indication. However, Legubeti contains lysine as the counter ion in the active pharmaceutical ingredient, therefore large amounts of lysine will be delivered by the drug product when it is used in accordance with the dosing recommendations. Accordingly, the nonclinical evaluation of this marketing application is primarily focused on the safety assessment of lysine exposure from the drug product and the specified impurities in drug substance and drug product. Nacystelyn was negative in each of the submitted genotoxicity studies, as reviewed below.

5.2. Referenced NDAs, BLAs, DMFs

NDA 013601 and NDA 207916

5.3. Pharmacology

No studies were submitted.

5.4. ADME/PK

No studies were submitted.

5.5. Toxicology

Nonclinical toxicity studies of N-acetylcysteine (NAC), N-acetylcysteine lysine (NAL, nacystelyn), and lysine were submitted by the Applicant, as shown in the table below.

Table 2. Toxicology Studies of NAC, NAL, and Lysine Submitted by the Applicant

Study Type	NAC (N-Acetylcysteine)	NAL (N-Acetylcysteine Lysine; Nacystelyn)	Lysine
Acute Toxicity	X	X	
Repeat-dose Toxicity	X (Bonanomi and Gazzaniga 1980; Johnston et al. 1983)	X	X (Tsubuku et al. 2004)
Genotoxicity	X (Bonanomi and Gazzaniga 1980)	X (3 study reports)	
Carcinogenicity			
Reproductive and developmental	X (Bonanomi and Gazzaniga 1980; Johnston et al. 1983; Harada et al. 2003)		

Source: Table prepared by the nonclinical reviewer.

5.5.1. General Toxicology

General toxicology studies of acetylcysteine have been reported in publications. (Bonanomi and Gazzaniga 1980; Johnston et al. 1983)The findings in toxicity studies with acetylcysteine were not clinically significant. The Applicant also submitted toxicology studies conducted with nacystelyn, including an acute oral study in mice and rats and a 13-week oral study in rats. The findings in the nacystelyn toxicity studies do not raise any safety concern for the administration of nacystelyn in humans. However, both studies (unpublished reports dated 1985 and 1989) were conducted in an academic laboratory. Therefore, the accuracy and reliability of the data from these studies cannot be confirmed, and the data should not be used for safety assessment of

nacystelyn. Further, the Applicant's clinical bridging PK study with acetylcysteine 20% oral solution that supports comparable systemic exposure and the supporting toxicity study for L-lysine (reviewed below in section 5.5.5) provide an adequate assurance of safety for nacystelyn with the proposed dosing regimen in humans.

5.5.2. Genetic Toxicology

Acetylcysteine was negative in the Ames test. (Bonanomi and Gazzaniga 1980)

The Applicant submitted a standard battery of genotoxicity studies for nacystelyn (bacterial reverse mutation test, in vitro mouse lymphoma mutation assay, and in vivo micronucleus test in mice). These studies did not show any evidence of mutagenicity or clastogenicity, as summarized in the table below.

Table 3. Genotoxicity Studies of NAL (Nacystelyn)

Study	Positive/ Negative/ Equivocal	Notes
Ames (Study report 764638)	Negative	NAL was not mutagenic in *Salmonella typhimurium* or *Escherichia coli* (625, 1250, 2500, 5000 mcg/mL) in the absence or presence of S9 mix, when tested in ultra-pure water up to a predetermined maximum limit.
In vitro clastogenicity (Study report 764643)	Negative	NAL was not mutagenic in mouse lymphoma L5178Y cells (0, 625, 1000, 1250, 2000, 2500, 3000, 4000, 5000 mcg/mL) in the absence or presence of S9 mix.
In vivo micronucleus (Study report 764659)	Negative	NAL did not induce micronuclei in bone marrow cells in male or female mice when tested at a dose of 2000 mg/kg/day, given for 1-2 days

Source: Table prepared by the nonclinical reviewer.

5.5.3. Carcinogenicity

Carcinogenicity studies in animals have not been performed with acetylcysteine or nacystelyn. Since the duration of use for the proposed indication is three days, no carcinogenicity studies are needed to support the approval of Legubeti.

5.5.4. Reproductive and Developmental Toxicology

In a fertility study with acetylcysteine, rats were treated intravenously with 0, 100, 300, or 1000 mg/kg/day. (Harada et al. 2003) Dosing of male rats occurred from four weeks before mating to 22-25 days after mating. Female rats were dosed from two weeks before mating through gestation day 17. Acetylcysteine had no effects on mating or male fertility. However, intravenous administration of 1000 mg/kg/day (0.3 times the recommended human oral dose based on body surface area) produced 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). This study did not evaluate the reversibility of the effect on female fertility. The severe decrease in female fertility is notable because it occurred at a dose (Human Equivalent Dose = 161 mg/kg) that is substantially lower than the recommended dose for Legubeti (acetylcysteine free acid equivalent) for each day of treatment (approximately 560, 420, and 350 mg/kg on days 1, 2, and 3, respectively). Further, the use of intravenous dosing in the rat fertility study does not diminish the relevance of the study results with respect to possible fertility effects in female patients with acetaminophen overdose, where substantial drug absorption is clearly expected with oral administration of Legubeti and other acetylcysteine drug products. However, any risk of impaired fertility should be considered as acceptable, given that the indication can be a life-threatening condition.

In another fertility study, the effects of orally administered acetylcysteine were evaluated in male rats, with dosing performed for 15 weeks prior to mating and during the mating period. A slight, non-dose related reduction in fertility was observed at doses of 500 and 1000 mg/kg/day PO (0.1 and 0.3 times the maximum recommended dose for Legubeti [day 1], respectively, based on body surface area). (Bonanomi and Gazzaniga 1980)

Acetylcysteine produced no teratogenic effects in embryo-fetal development studies in rats at oral doses up to 2000 mg/kg/day (0.6 times the maximum recommended dose for Legubeti [day 1] based on body surface area) or in rabbits at oral doses up to 1000 mg/kg/day (0.6 times the maximum recommended dose for Legubeti [day 1] based on body surface area). Oral dosing with acetylcysteine in these studies was conducted during the period of organogenesis. (Bonanomi and Gazzaniga 1980)

No animal fertility or reproduction studies of nacystelyn were submitted.

5.5.5. Other Toxicity Studies

Lysine

Nacystelyn is a salt composed of N-acetylcysteine (MW = 163.19) and L-lysine (MW = 146.19) in a 1 to 1 molar ratio. Therefore, the recommended dosing regimen for nacystelyn will deliver high doses of lysine over the three-day treatment period. The calculated amounts of lysine that will be delivered in patients administered with Legubeti (acetylcysteine) in accordance with the weight-based dosing recommendations are shown in the tables below.

Table 4. Legubeti Loading Dose and Lysine Exposure

Body Weight (kg)	Acetylcysteine Equivalent (NAC) Dose (g)	Lysine Equivalent (L-lysine)* Dose (g)
100 or greater	15	13.44
90 to 99	14	12.54
80 to 89	13	11.64
70 to 79	11	9.85
60 to 69	10	8.96
50 to 59	8	7.17
40 to 49	7	6.27
30 to 39	6	5.37
20 to 29	4	3.58

Source: Table prepared by the nonclinical reviewer.
*The lysine dose is calculated based on the composition of nacystelyn as 52.75% NAC and 47.25% L-lysine.

Table 5. Legubeti Maintenance Dose and Lysine Exposure[a]

Body Weight (Kg)	Acetylcysteine Equivalent (NAC) Dose (g)	Lysine Equivalent (L-lysine)[b] Dose (g)
100 or greater	7.5	6.72
90 to 99	7	6.27
80 to 89	6.5	5.82
70 to 79	5.5	4.93
60 to 69	5	4.48
50 to 59	4	3.58
40 to 49	3.5	3.14
30 to 39	3	2.69
20 to 29	2	1.79

Source: Table prepared by the nonclinical reviewer.
[a]A total of 17 maintenance doses are administered at 4-hour intervals over 3 days.
[b]The lysine dose is calculated based on the composition of nacystelyn as 52.75% NAC and 47.25% L-lysine.

The recommended dosing of nacystelyn is expressed in the label as the NAC equivalent. The dosing regimen delivers a total of 1330 mg/kg given over a period of 72 hrs (three days), comprised of a loading dose of 140 mg/kg followed by administration of maintenance doses of 70 mg/kg starting four hrs after the loading dose and repeated every four hrs, for a total of 17 maintenance doses. Thus, the maximum dose to be administered in a single day is about 560 mg/kg NAC (140 mg/kg loading dose plus 420 mg/kg from six maintenance doses on day 1). It is noted that the actual maximum dose may be lower than 560 mg/kg, based on the patient's bodyweight. The resulting doses of lysine (approximate) on each day of nacystelyn administration are shown in the table below.

Table 6. Amount of Lysine Delivered with Administration of Legubeti (N-Acetylcysteine Lysine) Based on the Proposed Dosing Regimen

Component	Lysine Dose (mg/kg) Based on Proposed Dosing Regimen for Nacystelyn			
	Day 1	Day 2	Day 3	Cumulative Dose
L-lysine	502.6	376.2	313.5	~ 1192

Source: Table prepared by the nonclinical reviewer.
Notes: The lysine dose is calculated based on the composition of nacystelyn as 52.75% NAC and 47.25% L-lysine.

Thus, a safety assessment is needed for the high dose levels of lysine that will result from the administration of Legubeti (nacystelyn). Lysine can increase calcium absorption, therefore excessive doses can cause gallstones. (Bumpstead 2013) Increase in lysine intake has also been linked to hypercholesterolemia and renal complications. It also interacts with arginine and aminoglycoside antibiotics. (Mount Sinai 2023)

Lysine at 312 mg to 4 g daily has been used in clinical trials to prevent or treat herpes simplex infections, with higher dosages reserved for breakouts. (Drugs.com 2023) Studies of lysine toxicity in animals (mammals) and humans, and recommendations for safety of chronic dosage levels are well summarized in a publication by (Flodin 1997).

Tsubuku et al. evaluated the toxicity of L-lysine following oral administration for 90 days in male and female Wistar rats, age six weeks (pre-adolescent) at the start of treatment. (Tsubuku et al. 2004) L-lysine was mixed into a standard diet at concentrations of 1.25%, 2.5%, and 5.0% (w/w) for the treatment groups. The control group received a standard diet. The treatment period was followed by a five-week recovery period in which 6 rats/group were given a standard diet to examine the reversibility of any changes observed. The average intake of L-lysine (mg/kg/day) for the 1.25%, 2.50%, and 5.0% groups was 841.2 ± 29.3, 1677.4 ± 69.4, and 3356.6 ± 115.1, respectively, for males and 967.9 ± 46.5, 1971.2 ± 86.5 and 3986.3 ± 282.9, respectively, for females. There was no statistically significant difference in body weight between the lysine-treated rats and the control group. In urinalysis, a dose-dependent tendency for decreased pH occurred in both sexes treated with lysine, and chloride excretion was increased in a dose-dependent manner compared to controls at Week 5 and Week 13. Males that received the 5.0% lysine diet (~ 3356.6 ± 115.1 mg/kg/day) showed significantly higher urine volume (21.3 ± 8.1 mL/day as compared to 15.3 ± 4.8 mL/day in control males). This effect was reversible, as it was not observed at the end of the recovery period. For hematology, the most notable change was a significant increase in Hb (hemoglobin) in female rats that received 5.0% lysine diet (15.5 ± 0.6 g/dL as compared to 14.7 ± 0.6 g/dL in controls on Week 13). However, this increase was within the range of both the concurrent and historical control values observed in the testing facility. In addition, a significant decrease in serum chloride (mEq/L) was observed in males of all test article groups (controls, 111.9 ± 0.7; 1.25% group, 109.9 ± 1.1; 2.5% group, 110.3 ± 1.5; 5.0% group, 109.8 ± 1.3), and in females of the 5.0% L-lysine group (controls, 112.7 ± 1.2; 5.0% group, 110.1 ± 1.2). Additionally, a significant increase in total bilirubin (mg/dL) was observed in females in the 2.5% lysine diet group (0.11 ± 0.02 as compared to 0.09 ± 0.01 in controls), however no change in total bilirubin was observed in the 5.0% lysine diet group. The study authors concluded that the slight decrease in serum chloride was a compensatory response to the increase in ingested hydrochloride (L-lysine hydrochloride salt was used as the test article). This adaptive reaction was linked to a significant increase in daily chloride excretion at Weeks 5 and 13 of the treatment periods in both sexes. The authors hypothesized that the amount of chloride in urine was increased, and the urine pH was decreased due to the presence of hydrochloride. A slight increase in urine volume was found in females that received the 5.0% lysine diet, but this change was considered as an adaptive reaction to the large

increase in ingested chloride. The overall data indicated that renal function was not affected, based on urea nitrogen, creatinine, and the lack of histological abnormalities in kidneys. There were no significant treatment-related pathologies observed, with only a few minor changes that were independent of dose. Sporadic histopathologic alterations were observed in a small number of rats at the end of the treatment and recovery periods, but these changes were not related to treatment. Based on the totality of the data, the authors determined that the no-observed-adverse-effect level (NOAEL) for lysine was 5.0% w/w by dietary administration, which correlated with dose levels of 3.357 ± 0.115 g/kg/day in males and 3.986 ± 0.283 g/kg/day in females. We concur with the authors' conclusions for the NOAEL. The authors also concluded that the relatively high NOAEL is consistent with human observations that lysine is a safe and well-tolerated dietary substance for long-term use.

Conclusion on L-lysine safety

The 90-day oral toxicity study of L-lysine in rats, as summarized above, is useful for the safety assessment of lysine ingestion that occurs with the administration of nacystelyn. Use of the NOAEL in male rats (3357 mg/kg/day) provides the most conservative approach for safety assessment, since the NOAEL was higher in females. As shown in Table 6 above, the maximum lysine dose administered in a single day is 502.6 mg/kg (Day 1 of dosing with nacystelyn). The HED (Human Equivalent Dose) for the male rat NOAEL is 541.5 mg/kg/day, which is 1.08 times the maximum lysine daily dose in humans. The NOAEL for lysine in the 90-day rat toxicity study was identified at 5% in diet, which is generally considered to be the maximum level appropriate for testing in dietary toxicity studies. Therefore, we conclude that the 90-day oral (dietary) toxicity study in rats provides a reasonable assurance of safety for the oral exposure to lysine that occurs with the proposed dosing regimen for nacystelyn.

Comments on Impurities/Degradants of Concern

Drug Product Specifications

The specifications for drug substance and drug product are identical with respect to the specified impurities (identities and acceptance criteria). Therefore, the nonclinical review of the impurity acceptance criteria will be focused on the drug product. The proposed acceptance criteria for impurities ((b) (4)) in the drug product specifications are shown in Table 7 below. (b) (4)

Table 7. Acceptance Criteria for (b) (4) (Impurities) in Drug Product

Impurity	Acceptance Criterion
(b) (4)	(b) (4) NMT %
	NMT %
	NMT %
	NMT %
Max. unknown imp	NMT %
Total unknown imp	NMT %

Source: Copied from Applicant's submission.
Abbreviations: NMT, no more than

The observed levels of these impurities in the drug substance batches used to manufacture the clinical and stability batches of drug product are shown in Table 8 below (registration batches E3017, F0117, F0517 and F0419).

Table 8. Levels of Specified Impurities in Drug Substance

Impurities	Results			
	Lot E3017	Lot F0117	Lot F0517	Lot F0419
(b) (4)				(b) (4)
Max. unknown imp				
Total unknown imp				

Source: Copied from Applicant's submission.

The first step in the evaluation of impurity acceptance criteria usually involves the assessment of genotoxic potential, based on the recommendations in ICH M7(R1). (b) (4) (b) (4) herefore, the recommendations in ICH M7(R1) are not appropriate for the evaluation of the acceptance criteria for (b) (4) or its (b) (4). (b) (4) and (b) (4) may be controlled as ordinary (non-genotoxic) impurities and should be considered as qualified at the proposed acceptance criteria in accordance with ICH Q3B(R2) (see below for further details).

(b) (4) and (b) (4) were previously identified as (b) (4), as described below. Therefore, these impurities may be controlled as non-genotoxic impurities and should

be considered as qualified at the proposed acceptance criteria, in accordance with ICH Q3B(R2) (see below for further details).

The tables below show the maximum potential amounts of each specified impurity based on the proposed acceptance limits in the drug product and the proposed acetylcysteine doses (loading and maintenance) from nacystelyn administration, for each weight band.

Table 9. Legubeti Loading Dose and Exposure to Impurities

Body Weight (kg)	Acetylcysteine Equivalent Dose (g)	(b) (4) (g)	(g)	(g)	(g)	Total Impurities (g)
100 or greater	15					(b) (4)
90 to 99	14					
80 to 89	13					
70 to 79	11					
60 to 69	10					
50 to 59	8					
40 to 49	7					
30 to 39	6					
20 to 29	4					

Source: Table prepared by the nonclinical reviewer.
*Acceptance criterion = (b) (4)
**Acceptance criterion %

Table 10. Legubeti Maintenance Dose and Exposure to Impurities

Body Weight (kg)	Acetylcysteine Equivalent Dose (g)	(b) (4) (g)	(g)	(g)	(g)	Total Impurities (g)
100 or greater	7.5					(b) (4)
90 to 99	7					
80 to 89	6.5					
70 to 79	5.5					
60 to 69	5					
50 to 59	4					
40 to 49	3.5					
30 to 39	3					
20 to 29	2					

Source: Table prepared by the nonclinical reviewer.
*Acceptance criterion = (b) (4)
**Acceptance criterion %

Based on the proposed dosing regimen, the maximum dose of nacystelyn administered in a 24-hr period occurs on Day 1, therefore the maximum potential exposure to impurities also occurs on Day 1. The potential maximum exposures (doses) for each specified impurity on Day 1 are shown in the table below.

Table 11. Maximum Single-Day Dose of Legubeti and Exposure to Impurities (mg/kg)

Acetylcysteine Equivalent Dose (mg/kg)	(b) (4)				Total Impurities (mg/kg)
	(mg/kg)	(mg/kg)	(mg/kg)	(mg/kg)	
560					(b) (4)

Source: Table prepared by the nonclinical reviewer.
*Acceptance criterion = (b) (4)
**Acceptance criterion %

(b) (4)

Safety Assessment of the Impurities (b) (4) **and** (b) (4)

(b) (4)

(b) (4)

(b) (4). Based on the considerations described above, (b) (4) and (b) (4) are considered as qualified at the Applicant's proposed limit of ≤ (b) (4)% for each as individual impurities in the drug product.

Safety Assessment of the Impurity (b) (4)

(b) (4)

Therefore, based on the identification of (b) (4) (b) (4), this impurity is considered as qualified at the proposed limit of ≤ (b) (4)% in the drug product.

Safety Assessment of the Impurity (b) (4)

(b) (4)

Based on the identification of [redacted], this impurity is considered as qualified at the proposed limit of ≤ [redacted] percent in the drug product.

We note that none of the specified or unspecified impurities were detected in the product batches analyzed at the initiation of stability testing. Also, the batch data showed a trend of time-dependent accumulation for the specified impurities. Given the absence of detectable levels of impurities at the initial time-point of stability testing, it is reasonable to assume that all the unspecified impurities (controlled at ≤ [redacted] percent for total) are [redacted] Therefore, safety risk from the total content of unspecified degradants at the proposed limit of ≤ [redacted] percent may not be substantially different from the specified impurities, all of which are deemed as qualified. Therefore, from a nonclinical safety perspective, the proposed acceptance criteria for [redacted] including specified impurities, individual unspecified impurities, and total unspecified impurities, are acceptable.

Excipient Safety Assessment

Legubeti contains one excipient, which is Povidone (b) (4). The amount of API and Povidone (b) (4) in both strengths of drug product (sachets) is shown in the table below.

Table 12. Composition of Legubeti 0.5 g and 2.5 g Acetylcysteine Sachets

			Strength [Acetylcysteine Equivalent]			
			0.5 g NAC		2.5 g NAC	
Component	Quality Standard	Function	mg/sachet	% w/w	mg/sachet	% w/w
Nacystelyn (b) (4)	In-house	Active ingredient	948	(b) (4)	4740	(b) (4)
Povidone (b) (4)	USP (b) (4)					(b) (4)

Source: Table prepared by nonclinical reviewer

(b) (4)

Abbreviations: USP, United States Pharmacopeia

Povidone, also known as polyvinylpyrrolidone (PVP) or polyvidone, is a synthetic water-soluble polymer made from the monomer N-vinylpyrrolidone and is used (b) (4) in many pharmaceutical tablets and (b) (4) in eye drops. It is also used in many technical applications with various roles (b) (4). The best-known example of povidone formulations is povidone-iodine (Betadine), an important disinfectant.

Povidone (b) (4) has the molecular formula of $(C_6H_9NO)_n$ and appears as a white to slightly off-white powder. Povidone formulations are widely used in the pharmaceutical industry because of their ability to dissolve in both water and oil solvents. (b) (4)

Patients weighing 100 kg will consume 24 sachets (2.5 g strength) on day 1, based on the proposed dosing instructions (one loading dose + six maintenance doses). The resulting povidone dose on day 1 for these patients would be (b) (4) mg ((b) (4) mg/sachet). A search of the FDA Inactive Ingredient Database revealed that the highest daily amount of Povidone (b) (4) among approved drug product is (b) (4) mg. Therefore, the maximum intake of Povidone (b) (4) from Legubeti is only (b) (4)% higher than the maximum exposure among approved drugs for oral administration. Based on this consideration, we have no safety concerns for the use of Legubeti in adults, with respect to the amount of Povidone (b) (4).

However, Legubeti will be labeled for use in all ages, therefore we searched for oral drug products containing Povidone (b) (4) that are approved for use in infants. Based on our search results, we conclude that there is no safety concern for any age group. Our assessment is based on the availability of drugs approved for infants down to age 6 months, where the daily dose of povidone ((b) (4) mg for age 6 months) exceeds the povidone dose from Legubeti in neonates and infants.

6. Clinical Pharmacology

6.1. Executive Summary

The Applicant proposes N-Acetylcysteine Lysine (NAL), a lysine salt of N-Acetylcysteine (NAC) as an antidote for acetaminophen overdose. The proposed product is a powder for oral solution containing 500 mg and 2.5 g of NAC. The Applicant is pursuing a 505(b)(2) regulatory pathway relying on FDA's previous findings of safety and effectiveness of the LD, Mucomyst® (acetylcysteine) Solution (NDA 013601). The proposed dosing regimen is a loading dose of 140 mg/kg followed by a first maintenance dose of 70 mg/kg 4 hrs after the loading dose. Repeat 70 mg/kg maintenance dose every 4 hrs for a total of 17 maintenance doses. The proposed proprietary name for their product is Legubeti.

To establish the scientific bridge to the LD, the Applicant conducted a pivotal relative bioavailability (BA) study 2021-5140, comparing its proposed product to the LD, Mucomyst® after a single dose of 1000 mg NAC in healthy subjects under fasted conditions. Because Mucomyst is currently discontinued, a reference standard (RS), Acetylcysteine Solution, USP 20% (200 mg/mL, ANDA 072547) was used in the relative BA study as a comparator. The BA study 2021-5140 demonstrated comparable systemic exposure of acetylcysteine between the proposed Legubeti and the RS (refer to Section 13.3.2 for details). There were no significant adverse events reported such as vomiting during the study. The incidence rate of nausea was low (8.3%) and comparable for two drug products (refer to Section 13.3.2 below for details). No other clinical trials were conducted for the proposed product. The Applicant did not submit a biowaiver of the higher strength, 2.5 g.

This review focused on the adequacy of the clinical bridging between the proposed Legubeti and the LD. While the relative BA study was conducted at 1 g dose of NAC (2 x 500 mg sachets), the dosage can be as high as 15 g NAC (equals to 28.4 g of NAL containing 13.4 g of L-lysine) for patients weighing 100 kg or higher based on the proposed body weight-based dosage. During the review, two clinical pharmacology-related issues were identified:

- Can the relative BA study at the 1 g NAC dose ensure the comparable BA at all doses higher than 1 g NAC including the maximum proposed dose of 15 g NAC?
- Can lysine interfere with the PK of NAC at doses higher than 1 g NAC as the quantity of lysine intake proportionally increases with the acetylcysteine dose increase?

  Note: 1 g NAC equals to 1.89 g NAL. The amount of lysine intake is 0.89 g for 1 g NAC dose and can be as high as 13.44 g for 15 g NAC dose.

These issues were conveyed to the Applicant in the 74-day filing letter dated 09/09/2022, and in the response dated 12/30/2022, the Applicant submitted solubility testing data where the complete solubilization was confirmed for the entire dose range

up to 15 g NAC in the proposed liquid volume. The Applicant also stated that there was no lysine effect observed on the PK of acetylcysteine in the relative BA study at 1 g dose of NAC. In addition, as of now, there is no evidence of interference with oral absorption of acetylcysteine by dissociated lysine salt. As such although the pivotal BA study was conducted at 1 g dose of acetylcysteine, it supports the comparable exposure at higher doses than 1 g and up to maximum dose of 15 g NAC. Refer to the Biopharmaceutics Review for more comments.

Acetylcysteine is known to have an unpleasant odor which affect oral ingestion of acetylcysteine products. It is unknown whether the addition of L-lysine salt which also has an unpleasant taste, to acetylcysteine would adversely affect palatability and tolerability. The relative BA study conducted at 1 g dose of acetylcysteine does not address the concerns because the clinical doses for adult patients weighing > 60 kg are 10 g and greater and can be as high as 15 g for adult patients weighing 100 kg or higher.

Therefore, the PK bridging study in combination with the solubility data can support reliance of efficacy of acetylcysteine on the LD. However, the relative BA study conducted at 1 g acetylcysteine is not sufficient to justify the reliance on the LD for safety due to the unresolved tolerability/palatability issues that may prevent the timely dosing of the full doses and lead to suboptimal efficacy (see Section 8.2.6 for details). As a result, the clinical bridging is deemed **inadequate** due to the lack of tolerability/palatability data at the clinically relevant doses (refer to Section 6.2 below for additional comments).

Recommendation

The Office of Clinical Pharmacology has reviewed and found that the clinical bridge has not been adequately established between the proposed Legubeti and the LD, Mucomyst® (acetylcysteine) Solution to justify the reliance of FDA's findings of safety and efficacy of the LD.

Clinical and Bioanalytical Site Inspections

As of 11/14/2022, The Office of Study Integrity and Surveillance (OSIS) declined to conduct an inspection for analytical site ((b) (4)) as sufficient time was not given for an inspection to be completed and for OSIS to provide a review to the review division. However, OSIS inspected the same site in (b) (4) under other applications[3] and deemed the data from the reviewed study reliable. As of 03/10/2023, OSIS completed the inspection of the clinical site at Pharma Medica Research Inc. in

[3] DARRTS, NDA 215040, LUMALCURI, JAMES J, 11/14/2022 CONSULT REV-DSI-05 (Bioequivalence Establishment Inspection Report Review).

Scarborough, Ontario, Canada, where no objectional conditions or practices were found during the inspection (NAI).[4]

In the OSIS memorandum, there were comments about eligibility of Subject No. (b) (6) as the OSIS reviewer initially found Subject No. (b) (6) as being ineligible due to a record noting blood loss of >500 mL within 56 days prior to drug administration. The reviewer confirmed that Subject No. (b) (6) had a normal hemoglobin level at baseline. Therefore, from a clinical pharmacology standpoint, it would not significantly impact the study outcome of the relative BA study.

The key review findings with specific recommendations and comments are summarized below in Table 13:

Table 13. Summary of Clinical Pharmacology Review Issues and Comments

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	No clinical efficacy trials were conducted with Legubeti, and the Applicant is relying on FDA's previous findings of safety and effectiveness of the LD, Mucomyst®. The relative bioavailability study at 1 g dose (Study 2021-5140) in combination with the complete dissolution of Legubeti to a solution provides the pivotal evidence to support the comparable systemic exposure and the efficacy to the LD. Nevertheless because of the unresolved tolerability issue related to L-lysine component in Legubeti, which is not included in the LD formulation, the establishment of the clinical bridging for full reliance on the safety and efficacy of the LD cannot be concluded at this time. Additional tolerability data at more clinically relevant doses are needed to further support the clinical bridge.
Dosage regimen for adult and pediatric patients	The recommended dosage regimen in adult and pediatric patients weighing > 1 kg is the same as the dosage for the LD and is as follows: Loading dose: 140 mg/kg PO x 1 Maintenance doses: 70 mg/kg PO 4 hrs after loading dose and q4hours for a total of 17 doses Total dose: 1330 mg/kg PO over 72 hrs
Pharmacokinetics (PK)	Following oral administration of Legubeti 1 g (2 x 500 mg sachets), the peak concentration was attained in 0.50 hrs (median) and Cmax and AUC were 2170.74 ng/mL and 2615.07 hr*ng/mL, respectively. The half-life was 3.30 hrs.
Food effect	The food effect on PK of Legubeti was not evaluated. Per LD label, upon acetaminophen overdose, the stomach should be emptied promptly by lavage or by inducing emesis with syrup of ipecac.

[4] DARRTS, NDA 215040, JAVIDNIA, MONICA, 03/10/2023, COR-DSIBIOEQ-05 (BIOEQ NAI Foreign).

Review Issues	Recommendations and Comments
Formulations used in clinical trial	The to-be-marketed formulation of Legubeti was compared to the Acetylcysteine Solution, USP 20% (200 mg/mL, ANDA 072547, reference standard per the Orange Book,) in the relative BA study 2021-5140.

Source: Table generated by the clinical pharmacology reviewer from the submitted information.
Abbreviations: LD, low dose; PO, per oral; PK, pharmacokinetic; Cmax, maximum plasma concentration; AUC, area under the curve; USP, United States Pharmacopeia; BA, bioavailability

6.2. Summary of Clinical Pharmacology Assessment

Table 14. Summary of Clinical Pharmacology Findings

Variable	Description
Mechanism of action	Probably 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.
PK parameters	The Applicant calculated baseline corrected PK parameters of acetylcysteine following a single dose of 1000 mg of Legubeti (2 x 500 mg sachets) and 1000 mg (5 mL) of the RS, Acetylcysteine Solution, USP 20% (200 mg/mL, ANDA 072547) in healthy subjects under fasted conditions. The results are summarized in the table below:

Variable	Test Product	Reference Product
Mean AUC_{0-t} (CV%) (hr·ng/mL)	2615.07 (33.01)	2393.66 (38.74)
Mean $AUC_{0-\infty}$ (CV%) (hr·ng/mL)	2647.82 (32.63)	2426.85 (38.20)
Mean C_{max} (CV%) (ng/mL)	2170.74 (45.56)	2150.45 (48.66)
Median T_{max} (hr)	0.50	0.50
T_{half} (hr)	3.30	3.43

Note: The mean values of all PK parameter are comparable between the proposed Legubeti and the RS product.

Pharmacodynamics (PD)	The Applicant did not evaluate the PD.
Bioanalytical method	A high-performance liquid chromatography tandem mass spectrometric method was used to estimate acetylcysteine concentration in plasma. A full method validation report (b) (4)-1903-21 was submitted, and bioanalytical method was adequately validated. See Section 13.3.1 for details.

Source: Table generated by the clinical pharmacology reviewer from the submitted information.
Abbreviations: PK, pharmacokinetic; RS, reference standard; USP, United States Pharmacopeia; AUC0-t, area under the concentration-time curve from time 0 to last quantifiable concentration; CV, coefficient of variation; AUC0-∞, area under the concentration-time curve from time zero to infinity; Cmax, maximum plasma concentration; Tmax, time to maximum concentration; T_{half}, half-life; PD, pharmacodynamic

Clinical Bridge Established: (Inadequate)

It is noteworthy that in the PIND 130190, the Applicant requested a biowaiver of the proposed drug product as it was intended to pursue 505(b)(2) pathway. As the proposed product involves a new active ingredient (NAL vs NAC) and a new dosage form (powder vs solution) compared to the LD, Mucomyst® (acetylcysteine) Solution, the biowaiver request was denied and the Agency recommended to conduct a relative

BA study to bridge the proposed product to the LD for which the Applicant intends to rely on FDA's findings of safety and/or effectiveness.

In this NDA, to establish a clinical bridge, the Applicant conducted a pivotal relative BA Study 2021-5140 comparing its proposed drug, N-acetylcysteine Lysine (NAL) Powder for oral solution, 1000 mg (2 sachets of 500 mg) to 1000 mg (5 mL) of Acetylcysteine Solution, USP 20% (200 mg/mL, ANDA 072547) after a single dose in healthy subjects under fasted conditions (refer to Section 13.3.2 for details). The results of the relative BA study are summarized in the tables below:

Table 15. Statistical Analysis of Bioequivalence by the Applicant (With Baseline Correction)

Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting BA Study 2021-5140, N=24 (10 Males; 14 Females)							
Parameter	**Test**	**N**	**RS**	**N**	**Ratio**		**90% C.I.**
AUC_{0-t} (ng.hr/mL)	2481.01	24	2228.42	24	1.11	104.84	118.23
$AUC_{0-\infty}$ (ng.hr/mL)	2514.73	24	2263.94	24	1.11	104.70	117.85
C_{max} (ng/mL)	1967.56	24	1922.33	24	1.02	93.45	112.10

Source: CSR Study 2021-5140
*As acetylcysteine is a compound that can be endogenously present, a "baseline" was calculated by taking three pre-dose concentrations (-10, -2 and 0 hr).
Note: The baseline values are very low and refer to Section 13.3.2 for study results without baseline correction.
Abbreviations: BA, bioavailability; N, number of patients in treatment arm; RS, reference standard; CI, confidence interval; AUC0-t, area under the concentration-time curve from time 0 to last quantifiable concentration; AUC0-inf, area under the concentration-time curve from time 0 to infinity; Cmax, maximum plasma concentration

Table 16. Statistical Analysis of Bioequivalence by FDA (With Baseline Correction)

Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting BA Study 2021-5140, N=24 (10 Males; 14 Females)							
Parameter	**Test**	**N**	**RS**	**N**	**Ratio**		**90% C.I.**
AUC_{0-t} (ng.hr/mL)	2553.45	24	2308.47	24	1.11	104.07	117.56
$AUC_{0-\infty}$ (ng.hr/mL)	2592.64	24	2348.06	24	1.10	104.00	117.23
C_{max} (ng/mL)	1967.56	24	1922.33	24	1.02	93.45	112.10

Source: Table generated by the clinical pharmacology reviewer from the submitted information.
For reviewer's re-calculation, a "baseline" was also calculated by taking three pre-dose concentrations (-10, -2 and 0 hr). Refer to Section 13.3.2 for reviewer's calculation without baseline correction.
Abbreviations: BA, bioavailability; N, number of patients in treatment arm; RS, reference standard; CI, confidence interval; AUC0-t, area under the concentration-time curve from time 0 to last quantifiable concentration; AUC0-inf, area under the concentration-time curve from time 0 to infinity; Cmax, maximum plasma concentration

Table 17. Arithmetic Means (CV%) Pharmacokinetic Parameters (With Baseline Correction)

		Test				Reference				Ratio
Parameter	**Unit**	**Mean**	**CV%**	**Min**	**Max**	**Mean**	**CV%**	**Min**	**Max**	**(T/R)**
AUC_T	ng·hr/mL	2689.675	32.87	1414.39	4516.42	2477.824	38.66	1192.67	4253.86	1.09
AUC_{Inf}	ng·hr/mL	2726.095	32.29	1462.93	4545.90	2514.398	38.02	1211.02	4287.79	1.08
C_{MAX}	ng/mL	2170.738	45.56	985.34	4330.00	2150.448	48.66	779	4407.74	1.01
T_{MAX}*	hr	0.750	.	0.50	2	0.5	.	0.50	1.00	1.50
Ke	hr^{-1}	0.201	26.04	0.12	0.31	0.203	33.51	0.10	0.42	0.99
T_{HALF}	hr	3.700	27.91	2.22	5.63	3.785	33.45	1.64	6.93	0.98

Source: Table generated by the clinical pharmacology reviewer from the submitted information.
* Tmax values are presented as median
Abbreviations: CV, coefficient of variation; AUCT, area under the concentration-time curve at time t; AUCI, area under the concentration-time curve to infinity; Cmax, maximum plasma concentration; Tmax, time to maximum concentration; Ke, elimination constant; Thalf, half-life

Per the Applicant's calculation, the 90% confidence intervals (CIs) of the test/reference ratios for the geometric mean of AUCt, AUCinf and Cmax of baseline-corrected acetylcysteine fell within the BE limits of 80.00% to 125.00%, demonstrating comparable systemic exposure of the proposed drug product relative to the RS. The reviewer performed the statistical analysis using SAS Studio to verify the Applicant's PK and statistical results and found that the 90% CIs of all three PK parameters calculated by the reviewer agree with the Applicant's calculation and meet the BE criteria of 80.00-125.00% (see table above).

Although the relative BA study at 1 g dose of acetylcysteine demonstrated comparable systemic exposure of acetylcysteine between the proposed Legubeti and the RS, the following two clinical pharmacology-related issues were identified:

- Can the relative BA study at the 1 g NAC dose ensures the comparable BA at all doses higher than 1 g NAC including the maximum proposed dose of 15 g NAC?
- Can lysine interfere with PK of NAC at doses higher than 1 g NAC as the quantity of lysine intake proportionally increases with the acetylcysteine dose increase?

  Note: 1 g NAC equals to 1.89 g NAL. The amount of lysine intake is 0.89 g for 1 g NAC dose and can be as high as 13.44 g for 15 g NAC dose.

These concerns were conveyed to the Applicant in the 74-day filing letter dated 9/09/2022. In the response dated 12/30/2022, for the first issue, the Applicant provided solubility testing data that demonstrated a complete solubility of the highest dose 15 g Acetylcysteine Powder in relevant media (refer to Biopharmaceutics review for details). Therefore, the comparable BA observed at 1 g dose could be extrapolated to comparable BA at doses higher than 1 g and up to the maximum dose of 15 g.

As for the second concern whether lysine could interfere with PK of NAC at higher dose than 1 g, the Applicant did not provide any justification other than stating that there was no lysine effect observed on the PK of acetylcysteine in the relative BA study at 1 g NAC dose, which equals to 1.89 g NAL containing 0.89 g of lysine. Per reviewer's literature search, there is no information or literature available describing potential effects of lysine on the disposition of NAC. Lysine, an amino acid, is transported by an amino acid transporter in the GI tract. However, there is no evidence that acetylcysteine, a derivative of cysteine may be transported by the same transporter as lysine.

Therefore, based on the complete solubility of acetylcysteine lysine powder in relevant dosing solution and no evidence of interference with oral absorption of acetylcysteine by dissociated lysine salt, the reviewer is of the opinion that the PK bridging study can support the reliance of efficacy of acetylcysteine on the LD.

On the other hand, acetylcysteine is known to have an unpleasant odor which affect oral ingestion of acetylcysteine products. It is not known whether the addition of L-lysine to acetylcysteine would adversely affect the palatability and tolerability. As the clinical doses can be as high as 15 g for adult patients, the relative BA study conducted at one g dose of acetylcysteine does not address the palatability/tolerability concerns. Timely administration of acetylcysteine is essential to prevent or mitigate hepatotoxicity. An inability to tolerate the full dose regimen of Legubeti, places patients at increased risk of acetaminophen (APAP)-induced toxicity and can lead to a lower efficacy than the LD. Refer to Clinical Section 8.2.6 below for palatability/tolerability concerns.

Therefore, the PK based bridging study at one g dose is not sufficient to justify the reliance on the LD for safety due to the tolerability/palatability issues.

As a result, the clinical bridging between the proposed Legubeti and the LD is deemed **inadequate** due to the lack of tolerability data at the clinically relevant doses.

6.2.1. Pharmacology and Clinical Pharmacokinetics

Please refer to Section 13.3.2 for details of the pivotal relative BA study 2021-5140.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dosage regimen is a loading dose of 140 mg/kg followed by a first maintenance dose of 70 mg/kg 4 hrs after the loading dose. Repeat 70 mg/kg maintenance dose every four hrs for a total of 17 maintenance doses. The recommended dosage is consistent with the approved dosage for the LD. Of note, the LD, which is a 20% oral solution provides the weight-based doses by varying the product volume. On the other hand, the proposed dosage preparation is to prepare a fixed volume with varying drug amount.

Patients Weighing 20 kg and Greater

(Table 18 and Table 19) below provide the weight-based loading and maintenance doses, respectively, of Legubeti for patients weighing 20 kg and greater. For patients weighing 20 to 59 kg dissolve Legubeti powder in 150 mL of caffeine-free diet cola or other diet soft drink. For patients weighing 60 kg and greater dissolve Legubeti powder in 300 mL of caffeine-free diet cola or other diet soft drink.

NAC is commonly diluted in caffeine-free diet sodas to mask the smell and taste and to facilitate acceptance. The dosing vehicle of diet cola or other diet soft drinks is recommended for the LD per the labeling of Mucomyst.

Table 18. Proposed 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 (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.

Source: Copied from Applicant's submission.

Table 19. Proposed Legubeti Maintenance Dose

Dissolve LEGUBETI powder in **300 mL** of diet cola or other diet soft drinks			
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	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 weighing over 100 kg. Limited information is available regarding the dosing requirements of patients that weigh more than 100 kg.

Source: Copied from Applicant's submission.

Patients Weighing 1 to 19 kg

Dissolve two 2.5-gram Legubeti powder sachets in 100 mL of water to prepare 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.

The volume of the loading dose can be as low as 2.8 mL of 50 mg/mL solution for patients weighing 1 kg and 53.2 mL of 50 mg/mL for patients weighing 19 kg.

The volume of the maintenance dose can be as low as 1.4 mL of 50 mg/mL solution for patients weighing 1 kg and 26.6 mL of 50 mg/mL for patients weighing 19 kg.

Legubeti can be dissolved in pediatric electrolyte solution in addition to water and diet soda, and the total volume of liquid for dosing is considered acceptable for pediatric patients. The proposal to use water as a dosing vehicle for patients weighing 1 to 19 kg is deemed acceptable considering the complete solubilization of Legubeti in water. Refer to Section 9 Pediatrics for more comments on the total volume of solution to be administered to very young patients. Consistent with LD label, the proposed label proposes that if the patient is persistently unable to retain the orally administered

acetylcysteine, Legubeti may be administered by nasoduodenal tube. Because Legubeti can be dissolved to a neutral solution at the time of administration, the assessment of the compatibility with nasogastric tube material was deemed not necessary per Dr. Caroline Strasinger, the OPQ reviewer.

Therapeutic Individualization

The recommended pediatric dosing is the same as the adult dose and consistent with the labeled pediatric dose for the LD, which is deemed acceptable.

Consistently with the LD, Mucomyst label, no dosage adjustment for intrinsic or extrinsic factors are recommended.

Outstanding Issues

The tolerability at clinically relevant doses is needed to be addressed to further support the conclusion of the clinical bridging.

The Applicant referred to Cetylev, an effervescent tablet form of NAC. The Cetylev label is in the PLR format for the clinical pharmacology section. The Applicant did not specify Cetylev as a LD but stated to use its labeling as a template for PLR format of the Legubeti label. Cetylev was approved in 2016 via the 505(b)(2) pathway with Mucomyst as a LD. Nevertheless, because there is new clinical pharmacology information proposed to be included in the Legubeti label that can be found only in Cetylev labeling, but not in Mucomyst label, the Applicant needs to provide supportive data (e.g., published literature) for specific clinical pharmacology information that would be included in the Legubeti label that are not found in the Mucomyst label.

In addition, we will recommend the Applicant conduct a comprehensive literature review for available clinical pharmacology information in published literature. For example, per the reviewer's literature search, (Nolin et al. 2010) PK of NAC in patients with end-stage renal disease (ESRD) were reported in a published literature (Nolin et al. 2010). In the published study, ESRD patients were dosed with 600 or 1200 mg of sustained-release NAC orally every 12 hrs for 14 days. A doubling of the dose resulted in a two-fold increase in AUC of NAC in patients with ESRD. However, NAC clearance was reduced by 90% in ESRD, leading to a seven-fold greater AUC and 13-fold longer half-life compared with healthy control subject. The implications of such information related to Legubeti labeling and use should be further considered.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Following oral administration of Legubeti 1 g (2 x 500 mg sachets), the peak concentration was attained in 0.50 hrs (median) and Cmax and AUC were 2170.74 ng/mL and 2615.07 hr*ng/mL, respectively. The half-life was 3.30 hrs.

Elimination

Acetylcysteine (i.e., N-acetylcysteine) undergoes extensive first pass metabolism and is postulated to form cysteine and disulfides (N,N-diacetylcysteine and N-acetylcysteine). Cysteine is further metabolized to form glutathione and other metabolites.

After a single oral dose of [35S]-acetylcysteine 100 mg, between 13 to 38% of the total radioactivity administered was recovered in urine within 24 hrs. (Rodenstein et al. 1978) In a separate study, renal clearance was estimated to be approximately 30% of total body clearance.

Hepatic Impairment

Following a 600 mg intravenous dose of acetylcysteine to subjects with mild (Child Pugh Class A, n=1), moderate (Child-Pugh Class B, n=4) or severe (Child-Pugh Class C; n=4) hepatic impairment and six healthy matched controls, mean $T_{1/2}$ increased by 80%. Also, the mean clearance (CL) decreased by 30% and the systemic acetylcysteine exposure (mean AUC) increased 1.6-fold in subjects with hepatic impairment compared to subjects with normal hepatic function. However, these changes are not considered to be clinically meaningful. (Jones et al. 1997)

Renal Impairment

Hemodialysis may remove some of total acetylcysteine. (Hernandez et al. 2015)

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide pivotal evidence of effectiveness?

The Applicant intended to pursue a 505(b)(2) regulatory pathway that relies on FDA's previous findings of safety and effectiveness for the LD, Mucomyst®. To establish a clinical bridge between the proposed Legubeti label and the LD, the Applicant conducted a pivotal relative BA study 2021-5140 at one g dose of acetylcysteine, which demonstrated comparable BA between the Legubeti and LD (refer to Section 13.3.2 for details).

Based on the complete solubility of acetylcysteine lysine powder in relevant dosing solution and no evidence of interference with oral absorption of acetylcysteine by dissociated lysine, the comparable BA observed at the one g dose could be extrapolated to comparable BA at doses higher than one g and up to the maximum proposed dose of 15 g. Therefore, the PK bridging study can support the reliance of efficacy of acetylcysteine on the LD.

However, acetylcysteine is known to have an unpleasant odor which may affect patient tolerance of acetylcysteine products. It is not known whether the addition of L-lysine salt, which also has an unpleasant taste, to acetylcysteine would adversely affect the palatability and tolerability (refer to Clinical Section 8.2.6 below for details). As the clinical doses can be as high as 15 g for adult patients, the relative BA study conducted

at a much lower dose of one g acetylcysteine is not sufficient to justify the reliance on the LD for safety due to the tolerability/palatability issues.

Therefore, the clinical bridge between the proposed Legubeti and the LD, Mucomyst® (acetylcysteine) Solution is deemed **inadequate** due to the lack of tolerability/palatability data at the clinically relevant doses.

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

The proposed dosing regimen is same as the LD, Mucomyst®: Administer a loading dose of 140 mg/kg followed by a first maintenance dose of 70 mg/kg four hrs after the loading dose. Repeat 70 mg/kg maintenance dose every four hrs for a total of 17 maintenance doses.

The proposed drug is also indicated for pediatric patients weighing greater than 1 kg and the recommended pediatric dosing is the same as the adult dose and consistent with the labeled pediatric dose for the LD. Therefore, the proposed dosing regimen is appropriate.

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

No dosage adjustment is recommended based on intrinsic patient factors, renal, or hepatic impairment. This is consistent with the LD labeling and there are no new studies conducted with Legubeti.

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

No food-effect study was conducted for the current NDA. Per the LD label, the stomach should be emptied promptly by lavage or by inducing emesis with syrup of ipecac following an overdose with acetaminophen. Consistent with the LD label, the proposed label does not specify any information about meal/food.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant did not conduct any controlled clinical trials of efficacy or safety. To establish a scientific bridge to the LD, the Applicant conducted a relative bioavailability (BA) study, 2021-5140, comparing the proposed acetylcysteine lysine product to the LD, after a single dose of one g in healthy subjects under fasted conditions. This BA study is described in Section 6 and Section 13.3.2.

7.2. Review Strategy

The Applicant relies on FDA's previous findings of efficacy for the LD) Mucomyst® (acetylcysteine solution, USP, NDA 013601; Apothecon Inc div Bristol Myers Squibb), and has not conducted any clinical efficacy studies in the target population.

Establishment of safety of Legubeti relies on the following sources:

- FDA's previous findings of safety for the LD Mucomyst.
- Safety data from the BA study 2021-5140.
- Safety information from published literature of the LD
- Safety information from the FDA Adverse Event Reporting System (FAERS) database for the LD.
- Safety information from the published literature regarding high dose lysine ingestion

Notably, Legubeti contains approximately 47.25% of L-lysine. This raises the question whether the presence of L-lysine in Legubeti will affect the safety profile established for NAC. The Applicant stated in their submission that study 2021-5140 showed bioequivalence of Legubeti from a PK perspective. In addition, nonclinical safety data (refer to section 5.5.5) suggest that the presence of lysine will not alter the safety profile of Legubeti.

However, the Division asked the Applicant to provide a rationale for use of L-lysine as a salt and justify the excess exposure to L-Lysine. In addition, the Applicant was asked to submit a thorough review of published literature, including original publications regarding the safety of the proposed dosing of lysine in all age groups as well as specific populations in the 74-day letter dated September 9, 2022. The Applicant was also asked to provide data concerning how addition of L-lysine would affect tolerability and palatability of Legubeti, since both lysine and acetylcysteine have an unpleasant taste, and acetylcysteine has an unpleasant odor. Therefore, both L-lysine and acetylcysteine may affect the palatability of oral ingestion.

The Applicant provided responses to these questions in their response to the 74-day letter dated December 30, 2022. Literature evaluating the safety of high dose L-Lysine ingestion was submitted and is reviewed below. To address palatability and tolerability

concerns already noted, the Applicant proposed a palatability and tolerability study. The protocol is an open-label single dose study comparing palatability of n-acetylcysteine with Legubeti. This protocol was submitted to the PIND. An advice letter with FDA's comments regarding deficiencies in the protocol was sent to the Applicant on December 16, 2022. At the time of this review, the Applicant had not initiated this trial, and stated it was having issues procuring the LD to be used as the comparator for the proposed study. Therefore, at the close of the review cycle there were no data to offer assurances that Legubeti would be tolerated by patients who present with APAP overdose. Hence, it is still unclear whether an effective dose of the product would achieve systemic levels adequate to serve as an antidote for acetaminophen overdose.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The Applicant did not conduct any controlled clinical trials of efficacy or safety. The Applicant relies on FDA's previous findings of efficacy for the reference listed drug (RLD) Mucomyst® (acetylcysteine solution, USP, NDA 013601; Apothecon Inc div Bristol Myers Squibb).

To establish a scientific bridge to the LD, the Applicant conducted a relative bioavailability (BA) study 2021-5140, comparing its proposed product to the LD, Mucomyst after a single dose of 1000 mg in healthy subjects under fasted conditions. Although study 2021-5140 does not inform efficacy, pertinent details as related to this section are mentioned here. Full details and conclusions regarding this BA study are described in Section 6 and 13.3.2**.**

8.1.1. A Single-Dose, Bioequivalence Study of Two Formulations of Acetylcysteine 1000 mg Under Fasting Conditions (Study 2021-5140)

Trial Design

This was an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover, bioequivalence study.

Study Objectives

Primary

Evaluate the bioequivalence between N-Acetylcysteine Lysine powder for oral administration, 0.5 g, and Acetylcysteine Solution, USP 20% (200 mg/mL) after a single dose in healthy subjects under fasted conditions.

Secondary

Evaluate the safety and tolerability of the study treatments.

Study Population

Healthy, non-smoking adults, with a body mass index ≥19 and ≤30 kg/m^2. A total of 24 subjects were enrolled and completed the study.

8.1.2. Study Results

Compliance With Good Clinical Practices

The Applicant stated in the NDA clinical study report for study 2021-5140 that the trial was performed in compliance with the Declaration of Helsinki, ICH Guidelines for Good Clinical Practice.

Financial Disclosure

The Applicant submitted a list of investigators (NDA 215040 Module 1.3.4 and 16.1.4) and FDA form 3454 certifying that all investigators had no disclosable financial interests or arrangements as defined in 21 CFR 54.2 (a, b, and f) that could affect the outcome of the trial. As a result, no financial disclosures were submitted for any investigator in this NDA. Refer also to Appendix 13.2.

Patient Disposition

All 24 subjects completed the study.

Protocol Violations/Deviations

There were no protocol violations/deviations that had a significant impact on study results.

Table of Demographic Characteristics

Table 20 displays the demographic information for the study population. Of the 24 enrolled subjects, 58% were female, and subjects had a median age of 48 years with most subjects between 41 and 64 years. The median body mass index (BMI) was 26.5 kg/m^2 with the highest BMI of 30 kg/m^2. A majority (approximately 63%) of the population was White, 21% were Black or African American, and 13% identified as Asian. Two-thirds of the population were not of Hispanic or Latino ethnicity.

Table 20. Demographic Characteristics in Study 2021-5140

Characteristic	Safety Dataset N=24
Sex, n (%)	
Female	14(58.3)
Male	10(41.7)
Age (years)	
Mean (SD)	46.8 (10.3)
Median (range)	48 (27-68)
Age Group, n (%)	
18-40	7 (29.2%)
41-64	15 (62.5%)
65-75	2 (8.3%)
>75	0 (0.0%)
Weight (kg)	
Mean (SD)	73.9 (10.1)
Median (range)	72.5 (58.6-96.9)
Height (cm)	
Mean (SD)	167.8(9.3)
Median (range)	169.1(153.5-186.1)
BMI (kg/m²)	
Mean (SD)	26.2 (2.7)
Median (range)	26.5(21-30)
Race, n(%)	
Asian	3 (12.5%)
Black or African American	5 (20.8%)
Multi-Racial	1 (4.2%)
White	15 (62.5%)
Ethnicity, n (%)	
Hispanic or Latino	8 (33.3%)
Not Hispanic or Latino	16 (66.7%)

Source: modified from Table 11-1 in Applicant submitted report for study 2021-5140 (module 5.3.1.2)
Abbreviations: BMI, body mass index; N, number of subjects included in each dataset; n, number of subjects in respective categories; SD, standard deviation

8.2. Review of Safety

8.2.1. Safety Review Approach

The clinical review of safety for Legubeti focuses on FDA's previous findings of safety for the LD Mucomyst, safety data from the BA study 2021-5140, information from published literature, and information from the FDA Adverse Event Reporting System (FAERS) database for the LD.

8.2.2. Review of the Safety Database

Overall Exposure

All 24 subjects who completed the BA study received a single, one g of acetylcysteine in each period.

Adequacy of the Safety Database:

Assessment of safety for Legubeti relies on FDA's previous findings on safety for the LD, Mucomyst. Data from this single dose trial may be supportive, but is insufficient to establish safety of Legubeti for the following reasons:

- This was a single dose study and Legubeti is prescribed as a loading dose followed by a maintenance dose every four hrs for up to a total of 17 doses, in needed. This study does not address repeat-dose safety of Legubeti.
- The dose tested in this study was small (one g) compared to much higher doses that can potentially be administered for treatment of APAP-toxicity. A subject weighing 100 kg would need a loading dose of 14g. Therefore, it is possible that the safety data for higher doses is different from what is reported in this BA study.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The quality of the overall submission met the requirement for clinical safety assessment. There are no issues with data integrity that precluded the analysis and conclusions.

Categorization of Adverse Events

The process for recording, coding, and categorizing adverse events (AEs) and safety analyses were reasonable and appropriate.

Routine Clinical Tests

Overall, laboratory and scheduled visit safety assessments were reasonable and adequate in this study.

8.2.4. Safety Results

Deaths

There were no deaths reported in the BA study.

Serious Adverse Events

There were no serious adverse events (SAEs) reported in the BA study.

Dropouts and/or Discontinuations Due to Adverse Effects

No subjects discontinued from the study due to AEs.

Treatment Emergent Adverse Events and Adverse Reactions

Table 21 summarizes the incidence and frequency of all Treatment-Emergent Adverse Events (TEAEs) by preferred term (PT), system organ class (SOC) for each treatment that occurred in the study.

Table 21. Summary of All Treatment-Emergent Adverse Events(TEAEs) by System Organ Class and Preferred Term for Each Treatment

	Reported Incidence* by Treatment Group n (%)		
System Organ Class Preferred Term	**N-Acetylcysteine Lysine N=24**	**Acetylcysteine Solution N=24**	**Total N=24**
Subjects with TEAEs†	6(25.0)	6(25.0)	9(37.5)
Gastrointestinal disorders	2 (8.3)	2 (8.3)	3(12.5)
Nausea	2 (8.3)	2 (8.3)	3(12.5)
General disorders and administration site conditions	2 (8.3)	1 (4.2)	3 (12.5)
Catheter site related reaction	1 (4.2)	1 (4.2)	2 (8.3)
Vessel puncture site reaction	1 (4.2)	0(0)	1 (4.2)
Nervous system disorders	5 (20.8)	5 (20.8)	7 (29.2)
Dizziness	1 (4.2)	1 (4.2)	2 (8.3)
Headache	5 (20.8)	5 (20.8)	7 (29.2)

Source: modified by Reviewer from Table 12-2 in Applicant submitted report for study 2021-5140 (module 5.3.1.2)
*Subjects having 2 or more adverse events under the same treatment are counted only once within a category.
†The same subject may appear in different categories and treatments.
Adverse event terms are classified according to MedDRA Version 24.1 and sorted alphabetically by SOC and PT.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects dosed; n, number of subjects in respective categories; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Overall, 19 TEAEs affecting nine subjects (37.5% of subjects dosed) were reported during the conduct of this study. All TEAEs were mild in severity. No episodes of vomiting were reported during this study. The AE with the highest incidence was headache followed by nausea and then dizziness.

Concomitant Medications

The only concomitant drug given during this study was acetaminophen to treat headache affecting two subjects (8.3% of the subjects dosed). The Applicant states that use of acetaminophen had no significant impact upon the integrity of the trial.

Laboratory Finding

Hematology, biochemistry, and urinalysis tests were conducted at the end-of-study. Liver function laboratory tests were conducted at end of the second period check-in. Outside of urinary abnormalities in two subjects, with one of these most likely consistent with a urinary tract infection, no clinically significant abnormalities were reported.

Vital Signs

Vitals signs were normal. Abnormalities noted were minor and not clinically significant.

Electrocardiograms (ECGs)

Although the Applicant reports that no clinically significant abnormalities on ECG were noted, three subjects had left axis deviation (LAD), first degree atrioventricular block with sinus bradycardia, and severe sinus bradycardia one-hour post-dose.

8.2.5. N-Acetylcysteine Safety from Published Literature

The Applicant relies on FDA's previous findings of safety for the LD, Mucomyst®. The Applicant has not conducted any clinical studies with Legubeti in the target population. Safety findings from the BA study conducted by the Applicant to establish a bridge to the LD have been discussed above. This section will discuss the findings regarding NAC safety from published literature. Given that NDA 215040 is a 505(b)(2) application, the Division requested the Division of Epidemiology (DEPI) to evaluate published literature and post-marketing reports with marketed NAC products to identify relevant safety data. A summary of the DEPI review (Weissfeld, 2023) and NAC safety is discussed below.

Safety of Oral NAC for Acetaminophen Poisoning

In a study of 1329 patients started on oral NAC (standard 72-hour regimen) for APAP poisoning, vomiting and diarrhea occurred frequently. Overall, approximately 36% of patients treated with NAC had vomiting and 31% had diarrhea. Oral NAC was considered as the principal cause for diarrhea and a contributing cause for vomiting (Table 22).(Miller and Rumack 1983)

Table 22. Patients With Acetaminophen Overdose with Vomiting and Diarrhea After Oral N-Acetylcysteine Treatment

		Patients With Vomiting		Patients With Diarrhea	
Doses of NAC	**N**	**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: adapted from Applicant submitted summary of clinical safety in module 2.7.4 which uses data from the Rumack study (Miller and Rumack 1983)
Abbreviations: N, number of subjects; n, number of subjects in respective categories

Anaphylactoid reactions have been reported after oral NAC. In a case report a 25-year-old man treated with oral NAC for APAP poisoning developed angioedema.(Mroz et al. 1997) In a retrospective review, 2.1% of the 145 patients who received oral NAC reported anaphylactoid reactions (bronchospasm, pruritus, flushing, urticaria, other rash, chest tightness, and hypotension). This was less than the 5.9% (18/306) reported in patients who received IV NAC.(Bebarta et al. 2010) In another systematic review, nausea occurred more frequently in patients treated with oral NAC, and anaphylactoid reactions occurred more frequently in patients receiving IV NAC. (Chiew et al. 2018)

Safety of Intravenous NAC for Acetaminophen Poisoning

In contrast to side effects noted with oral NAC administration, anaphylactoid reactions, including cutaneous symptoms (urticaria, pruritus, facial flushing, angioedema) and systemic symptoms (wheezing, dyspnea, and hypotension), are more common with IV NAC administration. Other adverse reactions noted with IV NAC administration include nausea and vomiting. An increase in international normalized ratio (INR) has been associated with initiation of IV NAC. (Sandilands and Bateman 2009)

Electrocardiographic Changes

The Applicant mentions ECG abnormalities secondary to NAC administration in their summary of clinical safety (module 2.7.4). Specifically the Applicant quotes a publication by Miller and Rumack (Miller and Rumack 1983). In this article, the authors report that around 90% of these electrocardiographic (ECG) abnormalities were trivial (minor repolarization changes) with T-wave flattening being the most common abnormality encountered. Non-trivial changes consisted of arrhythmias other than sinus arrhythmias: premature ventricular contractions, right or left bundle branch block, first-degree AV block with a PR interval longer than 0.27 seconds, second- or third-degree AV blocks, T-wave inversion, ST-segment depression and elevation, and evidence of infarction and ventricular hypertrophy. However, the distribution of these non-trivial ECG changes in unclear. It is possible, these non-trivial changes occurred in patients who were quite ill. Cardiac arrythmias and other abnormalities were reported in over 90% of patients in one series of 106 patients with fulminant hepatic failure.(Weston et al. 1976)

Miller and Rumack also state that in NAC-treated patients a statistical analysis revealed a stronger association of ECG abnormalities with the estimated risk of developing hepatotoxicity based on nomogram extrapolated blood levels of APAP than with the number of NAC doses used in treatment. Based on analysis of a subsample of the data by a consultant cardiologist, they concluded that NAC did not aggravate, but may have decreased the incidence of ECG changes in patients with APAP overdose. Moreover, these ECG changes have not been previously included in NAC labelling, except for tachycardia in the Acetadote label. (Am Regent 1995; Arbor 2017; Cumberland 2019)

Other Adverse Events (AEs)

Other AEs observed in patients treated with NAC, excluding gastrointestinal AEs and ECG changes, include (in order of frequency, in ≥ 0.5% of patients) headache, grogginess, fever, increased blood pressure, hypotension, lethargy, rash, and chest pain (Table 23).

Table 23. Prevalence of Adverse Events (Excluding Gastrointestinal AEs and ECG Changes) in APAP Overdose Patients Treated with One or More Oral Doses of NAC

Body System	Preferred Term	NAC
Blood and lymphatic system disorders	Bleeding	1 (0.1%)
Nervous system disorders	Grogginess	30 (2.3%)
	Lethargy	9 (0.7%)
	Coma	4 (0.3%)
	Confusion	4 (0.3%)
	Drowsiness	3 (0.2%)
Vascular disorders	Increased blood pressure	13 (1.0%)
	Hypotension	9 (0.7%)
Respiratory, thoracic, and mediastinal disorders	Shortness of breath	3 (0.2%)
	Difficulty breathing	1 (0.1%)
	Asthma	1 (0.1%)
Gastrointestinal disorders	Bleeding in stool	3 (0.2%)
	Hematemesis	2 (0.2%)
	Other	2 (0.2)
Body as a whole	Headache	32 (2.5%)
	Fever	21 (1.6%)
	Chest pain	6 (0.5%)
	Chest discomfort	4 (0.3%)
	Sternal pain	2 (0.2%)
Skin and subcutaneous tissue disorders	Rash	7 (0.5%)
	Itching	4 (0.3%)
	Hives	2 (0.2%)

Source: Sponsor submitted summary of clinical safety in module 2.7.4, which is adapted from Miller and Rumack (Miller and Rumack 1983)

The Applicant submitted additional safety data in the summary of clinical safety.

Safety data on hepatic and renal impairment is discussed under clinical pharmacology, Section 6. (Jones et al. 1997; Nolin et al. 2010; Hernandez et al. 2015)

The Applicant also states that there are limited data investigating the relationship of race and safety with use of NAC. Studies published in Chinese and Malaysian patients have similar safety data as described above. (Chan and Critchley 1994; Zyoud et al. 2010)

In subjects with end-stage renal disease, NAC clearance is reduced by 90% with significant increases in AUC (seven-fold increase), with a 13-fold longer half-life in healthy subjects. (Nolin et al. 2010) Additionally, the PK of NAC is significantly altered by hemodialysis, but not by venovenous hemofiltration. (Hernandez et al. 2015)

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no abuse potential. No withdrawal symptoms or rebound effects occur with cessation of NAC.

Cases of accidental NAC overdose have been reported. These overdoses arise from calculation errors made by healthcare providers prior to and during dosing of IV NAC.

Spence et al. report a case of a 15-year-old female who received a non-intentional six-fold overdose of IV NAC for APAP toxicity due to a prescribing error. (Spence et al. 2023) She developed a headache within two hrs after the infusion which progressed to seizure. Imaging demonstrated cerebral edema and transforaminal herniation of the cerebellar tonsils. After an electroencephalogram showing electrocerebral silence, and a diffusible radionuclide test showing lack of intracranial blood flow and uptake, brain death was confirmed. The authors also submit a table summarizing seven case reports of NAC infusion overdose. NAC overdose ranged from four-fold to 11.8-fold the therapeutic dose. Four cases had seizures (three with status epilepticus), and cerebral edema with uncal herniation: three patients died, and the fourth suffered severe neurological injury. One patient developed status epilepticus and required hospitalization. Two cases developed hemolytic uremic syndrome (HUS), and only one survived (one case of HUS cited in the Mahmoudi, et. al., case report below), and lastly one case had mild hemolysis and recovered fully (case report below, Srinivasan et al.)

Mahmoudi et al report a case of overdose in a 23-year-old female who received a 100 g dose of NAC IV instead of 10 g and developed agitation, nausea, vomiting, dyspnea, tachypnea, hypotension, drowsiness, and periorbital edema. She had a decreased level of consciousness with hypotension and tachypnea. Imaging showed cerebral edema. She gradually developed respiratory depression, metabolic acidosis, respiratory alkalosis, oliguria leading to acute renal failure, hemolysis, and thrombocytopenia. She died 12 days later due to HUS. (Mahmoudi et al. 2015)

Srinivasan et al. describe a 20-year-old woman who was administered eight times the approved dosage of NAC IV. She did not exhibit any significant signs and symptoms but did develop hemolysis and elevated bilirubin. She did not experience any significant adverse effects, survived the hospital admission, and was discharged home. (Srinivasan et al. 2015)

Elms et al. report a case of NAC overdose in a 53-year-old male who received ten-fold higher dose of NAC IV due to a formulation error. Shortly after initiating the NAC infusion, the patient developed periorbital edema, skin rash, and hypotension. He developed ST elevation in the inferior leads on his ECG. This evolved into an inferior myocardial infarction by ECG with elevated cardiac enzymes. Despite aggressive support, the patient died approximately 17 hrs after initiation of IV NAC due to a fatal myocardial infarction. (Elms et al. 2011)

The cases listed are not an exhaustive list but are demonstrative of the common presentations of unintentional IV NAC overdose due to healthcare provider errors. More cases of NAC overdose were found in the DPV-I review by Kangas, 2023. Notably,

overdose cases due to oral NAC were not identified by this reviewer and the DPV-I review.

Summary of Safety of Acetylcysteine

Safety data from the BA study in which a single, one g dose of NAC was tested in 24 subjects in an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover, study did not demonstrate any significant or overarching safety concerns. No deaths or SAEs were reported, nor any subjects discontinued the study due to AEs. All TEAEs were mild in severity, and most comment AEs were headache, nausea, and dizziness.

However, this was a single dose study which examined a very small dose (one g) in adults. A patient with APAP toxicity would likely need to receive much higher loading and maintenance doses (for example a 100 kg subject would need a loading dose of 14g and a maintenance dose of 7g). Therefore, data from the BA study may not be reflective of safety when therapeutic doses are administered, or in patients who have more severe APAP-related liver injury based on nomogram dosing.

The Applicant reports that three subjects had left axis deviation (LAD), first degree atrioventricular block with sinus bradycardia, and severe sinus bradycardia one-hour post-dose in the BA study. LAD can be a normal variation. (Kashou et al. 2023) First degree AV block could be due to increased vagal tone in younger patients.(Oldroyd et al. 2023) Sinus bradycardia is an incidental finding in many healthy adults and is common in athletes and during sleep. (Hafeez and Grossman 2023) It is also possible these ECG findings are due to a yet undiagnosed underlying condition. The Applicant also reported the potential for ECG changes associated with NAC use based on review of published literature; however, it is not clear whether the ECG changes are due to NAC or due to consequences of hepatic failure due to APAP toxicity. The most common ECG changes reported were repolarization events. Given the lack of follow-up data on the events, the limited number of cases in the BA study; and inconsistencies in the published literature, these ECG changes do not warrant changes to the current label for NAC, or the proposed label for Legubeti.

From published literature, the most common AEs secondary to administration of oral NAC are vomiting and diarrhea. Although not as common in IV administration, anaphylactoid reactions (angioedema, bronchospasm, pruritus, flushing, urticaria, other rash, chest tightness, and hypotension) have been reported with oral NAC. Other, less common AEs, include headache, grogginess, fever, increased blood pressure, hypotension, lethargy, rash, and chest pain. Some of these AEs (gastrointestinal AEs and anaphylactoid reactions) have been documented in Acetylcysteine and Cetylev labels. The latter two can be administered orally, although Cetylev has been discontinued.

There are limited data, but it is possible that subjects who have either renal or hepatic impairment may be at an increased risk of AEs due to NAC. At present, there is insufficient evidence to suggest modifications to NAC dosing in patients who have either renal or hepatic impairment.

There are multiple cases in the literature of IV NAC overdoses secondary to formulation errors. Symptoms and signs after NAC overdose include headaches, agitation, nausea, vomiting, dyspnea, tachypnea, hypotension, drowsiness, periorbital edema, seizures (including status epilepticus), cerebral edema, uncal herniation, hemolysis, hemolytic uremic syndrome, acute renal failure, myocardial infarction, and death. These events were reported exclusively with IV NAC infusions. It is not known whether similar events could occur due as result of NAC overdose with oral NAC formulations. Overdose is only mentioned in the Acetadote label and not in the generic NAC label.

8.2.6. Analysis of Submission-Specific Safety Issues

8.2.6.1. L-Lysine Safety

L-lysine is primarily available in the United States as a dietary supplement 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). Legubeti consists of one molecule of L-lysine and one molecule of acetylcysteine. The molecular weight of acetylcysteine is 163.19 and that of lysine is 146.19 for an approximate molar ratio of 53:47. Therefore, about 47.25% of each dose of Legubeti is comprised of L-lysine (Table 24).

Table 24. Maximum Amounts of NAC and L-Lysine That Would Be Administered from Legubeti

	Amount as Per Approved Dosing Schedule (mg/kg/d)			
Component	**Day 1**	**Day 2**	**Day 3**	**Total 3-day Dose**
N-Acetylcysteine	560	420	350	1330
L-Lysine	502.6	376.2	313.5	~ 1192

Source: Applicant provided summary of clinical safety in module 2.7.4
Notes: The dose of lysine administered is calculated based on the composition of NAL as 52.75% NAC and 47.25% l-lysine

The dietary reference intake (DRI) for adults of L-lysine, for example, is 38 mg/kg/d (Table 25). Based on the amount of L-lysine in the dosing schedule (Table 24), an adult would receive approximately eight to 13 times the DRI of L-lysine per day over the course of treatment. (Institute of Medicine 2005)) The BA study only tested a small dose of Legubeti (one g), which would not be adequate to assess the effect of L-lysine on safety.

Table 25. Dietary Reference Intake for L-Lysine

Age, Gender, or Group	Lysine DRI*
>19y and adults	38 mg /kg/d
0-6 months	107 mg/kg/d
7-12 months, boys, and girls	89 mg/kg/d
1-3 years, boys, and girls	58 mg/kg/d
4-8 years boys and girls	46 mg/kg/d
9-13 years, boys	46 mg/kg/d
9-13 years, girls	43 mg/kg/d
14-18 years, boys	43 mg/kg/d
14-18 years, girls	40 mg/kg/d
Pregnancy, all ages	51 mg/kg/d
Lactation, all ages	52 mg/kg/d

Source: Reviewer generated from the Institute of Medicine report, 2005 (Institute of Medicine 2005)
Abbreviations: DRI, Dietary Reference Intake

The Applicant states that L-Lysine will not alter the safety profile of Legubeti, based upon the results of a 13-week repeat dose study conducted in rats (see Section 5 for more details). No deaths, treatment-related clinical signs, or organ toxicity were observed at the maximum dose of 2300mg/kg.

The rationale for use of L-lysine as the amino acid salt (compared to other amino acids or other biological molecules) was not initially provided in the NDA submission. The Applicant was asked to provide a rationale for use of L-lysine as the amino acid salt and submit a thorough review of published literature, including copies of publications, regarding the safety of the proposed dosing of L-lysine in all age groups including pediatric and geriatric patients and specific populations in the 74-day letter.

The Applicant response is summarized below:

- Justification of addition of L-Lysine:

(b) (4)

(b) (4)

The Applicant's justification for using L-lysine as a salt is acceptable, but concerns regarding use of high-dose L-lysine remain as the BA study did not test high doses of Legubeti.

Evidence for safety of L-lysine:

Fourteen articles submitted by the Applicant in support of L-lysine safety were reviewed. Refer to Section 13.1 for full citation.

- Most of the articles submitted by the Applicant were reviews (Flodin 1997; Singh et al. 2011; Mailoo and Rampes 2017; Hayamizu et al. 2020).
- Articles by Griffith et al. and Wass et al. (Griffith et al. 1987; Wass et al. 2011), included controlled trials in which oral L-lysine was used to treat Herpes simplex virus (HSV) infection and schizophrenia respectively. In their response to the Division's 74-day letter, the Applicant notes that an L-lysine dose of 40 g/day was well- tolerated in congestive heart failure, but refers to the Wass et al. paper instead of the correct paper by Rubin et al. (Rubin et al. 1960)
- The article by Lo et al. (Lo et al. 1996) is a case report of a 44-year-old woman who developed Fanconi's syndrome in association with long-term (five-year) oral ingestion of L-lysine.
- Gabardi et al. (Gabardi et al. 2007) published a review article on dietary supplement–induced renal dysfunction, but the authors refer to the article by Lo JC, et. al., for L-lysine related renal dysfunction.
- Article by Racusen et al. (Racusen et al. 1985) is an animal study, and is not relevant to the clinical section of the review.
- De Rosa et al. and Ooi et al. address the use of NAC in human immunodeficiency virus (HIV) infection and treatment of psychiatric disorders respectively. These reports are not relevant to the safety review of L-lysine. (De Rosa et al. 2000; Ooi et al. 2018)
- Tome and Bos, and Payne et al., (Tomé and Bos 2007; Payne et al. 2018), address only L-Lysine requirements, not safety or toxicity.
- Article by Cynober et al. consists of discussions and findings of the Tenth Amino Acid Assessment Workshop (held in November 2019 in Tokyo)' which suggested a no observed adverse effect levels (NOAELs) for methionine, histidine, and lysine in healthy adults. (Cynober et al. 2020)

In addition, the Applicant submitted a package insert for LysaKare, a product approved in Europe but not in the US as supportive information for lysine safety but did not submit

post-marketing safety data or relevant articles documenting safety of LysaKare. LysaKare is approved in Europe as an infusion of 25 g of L-arginine and 25 g of L-lysine, intended to protect the kidneys from radiation damage due to radioactive lutetium (177Lu) oxodotreotide. As LysaKare also contains L-arginine, which is an antagonist of L-lysine, it is possible that adverse effects of LysaKare listed in the packaging (nausea and vomiting) could be due to L-arginine, or possibly related to IV administration. (Laboratoire Bioluz 2019)

The Applicant was also asked to provide literature on L-lysine safety in special populations:

- **Elderly:** The Applicant refers to the review of Hayamizu et al. (Hayamizu et al. 2020) to characterize safety of L-lysine in the elderly population (age > 65 years old). In the 71 articles included in this review, three were conducted specifically in the elderly analyzing doses at 1.2g/day, 1.5g/day and 1.9g/day. There was no description of AEs in the article in the elderly population. In summary, there are limited data concerning the safety of L-lysine in elderly patients.
- **Renal Impairment:** L-lysine has not been specifically studied in patients with renal impairment.
  - The Applicant submitted a case report of a 44-yr-old woman who developed Fanconi syndrome and tubulointerstitial nephritis after consuming 3 g/day L-lysine for five years, which then progressed to chronic renal failure.(Lo et al. 1996)
  - They also state that LysaKare, which is indicated for reduction of renal radiation exposure during peptide-receptor radionuclide therapy (PRRT) with lutetium (^{177}Lu) oxodotreotide in adults, carries a warning that it should not be administered in patients with creatinine clearance <30 mL/min. LysaKare is approved in the European Union and contains both 25 g each of L-arginine and L-lysine. It is administered intravenously (IV) over a four-hour period. (Laboratoire Bioluz 2019)
  - Lastly the Applicant states that infusion of L-lysine leads to nearly complete inhibition of renal tubular protein reabsorption, but no renal abnormalities have been reported with oral L-lysine. This statement is based on review by Singh et al. (Singh et al. 2011) but in this review, Singh et al. do not ascribe a source for their assertion.
- **Hepatic impairment:** The Applicant states the use of L-lysine has not been studied in patients with severe hepatic impairment.
- **Pregnancy and Breastfeeding:** The Applicant states that there are limited data in the literature for the safety of L-lysine in pregnancy and that a maximum safe dose for nursing women has not been established. This is discussed further in the pregnancy and lactation section of the review.

There is a paucity of well-conducted trials that assess safety of L-lysine when given in high doses. It is difficult to compare studies as they comprise different disease

conditions, different populations (adults with disease, healthy adults, pediatric age groups), various dose ranges and regimens (single dose to multiple doses), and different durations of therapy (days to years). Doses as high as 40 g orally and 41.3 g intravenously have been studied and the most common side effects noted were gastrointestinal tract symptoms, such as nausea, vomiting, abdominal pain or cramps, and diarrhea. (Flodin 1997; Singh et al. 2011; Mailoo and Rampes 2017; Hayamizu et al. 2020) A no observed adverse effect level (NOAEL) for supplemental lysine at 6.0 g/day has been proposed. (Cynober et al. 2020) (Cynober et al. 2020)This NOAEL was confirmed by (Hayamizu et al. 2020) in their systematic review. However, Legubeti will deliver substantially higher dose of L-Lysine for APAP toxicity.

There are limited data to assess safety of L-lysine in specific populations. It is possible that L-lysine may affect the kidneys, as it has been shown to inhibit renal tubular protein reabsorption nearly completely in high doses given IV.(Mogensen and Sølling 1977; Flodin 1997) Given chronically, even in low doses, there may be concern for renal adverse events.(Lo et al. 1996) In this case report, Lo et al., report a 44-year-old woman developed Fanconi syndrome and tubulointerstitial nephritis after consuming 3 g daily of Lysine for 5 years for HSV prophylaxis. Potential kidney toxicity of L-lysine is more important in the elderly as they are more likely to have decreased renal and other organ function compared to younger age groups.

However, no kidney malformations or dysfunction has been reported in hereditary hyperlysinemia (where there is increase in lysine levels). (Houten et al. 2013; OMIM 2020) Moreover L-lysine appears to be safe at dietary intake levels.

Even though L-lysine is an essential amino acid and is available as a food additive and food supplement, and according to 21CFR172.320, L-lysine can be safely used as a food additive for direct addition to food for human consumption, there is limited data on high dose supplementation or dosing. (21 CFR 172.320 2023) And as discussed above, the data that is available in other disease states may not fully inform its use in treatment of APAP toxicity. Therefore, the safety of L-lysine cannot be assumed in the context of its use for APAP toxicity, even if it is deemed safe as a food additive and supplement based upon the clinical data provided

Also, exposure reported in most of the studies is much lower than the proposed Legubeti dosing. Legubeti is dosed by weight, so comparisons with studies which do not use weight-based dosing may not be valid.

In summary, even though the Applicant’s justification of using L-lysine as a salt is acceptable and L-lysine has been shown to be safe in other disease conditions, there are limited data regarding safety of high-dose oral administration of L-lysine, and no data on the effects of L-Lysine on tolerability and palatability of Legubeti at the labeled dose (see below).

<u>Tolerability and Palatability of Legubeti</u>

There are insufficient data regarding the tolerability of the proposed Legubeti doses. There are no data on the effect of L-lysine on palatability of NAL as both L-lysine

(Schiffman and Dackis 1975) and NAC (Greene et al. 2016) have an unpleasant taste, and NAC has an unpleasant odor that may affect the palatability of oral ingestion. An inability to ingest the full dose regimen, either due to inadequate palatability or inadequate tolerability, poses the following safety concerns:

- Inadequate treatment of acetaminophen (APAP)-induced toxicity

  Timely administration of acetylcysteine is required to prevent or mitigate hepatotoxicity. An inability to tolerate the full dose regimen of the drug product places patients at increased risk of APAP-induced toxicity.

- Risk of aspiration

  Nausea and vomiting are the most common adverse reactions of NAC and there are no data to assess what effect the addition of lysine will have on gastrointestinal adverse reactions when compared with NAC. Pediatric patients and patients with altered mental status are at increased risk of aspiration with vomiting. Altered mental status can occur in the setting of APAP overdose, either because of liver injury or because of concurrent ingestion of drug products and toxins that affect mental status. (Schmidt and Dalhoff 2002)

These concerns were conveyed to the Applicant in the 74-day letter. To address this potential safety concern, the Applicant has proposed a palatability and tolerability trial, to evaluate the tolerability and palatability of acetylcysteine lysine powder for oral solution in healthy subjects.

An advice letter with Agency comments regarding the protocol was sent to the Applicant on December 16, 2022. As of writing this review, the Applicant has not initiated the palatability and tolerability trial, and it is unclear when the results of this trial will be available for review. The Division's concerns regarding the effect of L-lysine on tolerability and palatability of Legubeti as discussed above, and the inability of the Applicant to provide data on tolerability and palatability in a timely manner, is a significant safety issue.

8.2.7. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Due to its antioxidant properties, acetylcysteine may affect cancer biomarkers by inhibiting their presence, or for treatment of cancer. (Estensen et al. 1999; Van Schooten et al. 2002; Kwon 2021) However, use of acetylcysteine did not have any effect on survival, event free survival, or second primary tumors in subjects with head and neck cancer, or with lung cancer. (van Zandwijk et al. 2000) Acetylcysteine may reduce cancer treatment-related adverse reactions. (Lin et al. 2006; Al-Tonbary et al. 2009; Moslehi et al. 2014) No reports linking NAC to increased risk of carcinogenicity or tumor development were identified in the literature.

Human Reproduction and Pregnancy

Given that NDA 215040 is a 505(b)(2) application that relies on the Agency's previous findings of safety for a LD (i.e., Mucomyst), the Division requested the Division of Pediatric and Maternal Health (DPMH) evaluate published literature and post-marketing reports with marketed NAC products to identify relevant safety data for maternal health related sections of labeling. A summary of the review is discussed below. Refer to the DPMH complete review for additional details (Kratz 2023).

Pregnancy

There are limited data regarding the use of NAC during pregnancy to treat APAP overdose. Even though NAC crosses the placenta, DPMH review of 124 published cases from case reports, case series, and a prospective pilot study, revealed no increased risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In addition, withholding NAC treatment for acetaminophen overdose in pregnancy increases the probability of fetal demise.(Riggs et al. 1989) 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 did not recommend any additional post-marketing pregnancy safety studies.

Lactation

There are no human data available regarding the presence of NAC in human milk, or its effect on the breast fed infant or on milk production. DPMH did not recommend the Applicant conduct a clinical lactation study.

Fertility

No data were found on the effects of NAC on fertility.

Pediatrics and Assessment of Effects on Growth

See DPMH (pediatrics) review for more detail in Section 9.

8.2.8. Safety in the Post-market Setting

Safety Concerns Identified Through Postmarketing Experience

Given that NDA 215040 is a 505(b)(2) application that relies on the Agency's previous findings of safety for the LD (i.e., Mucomyst), the Division requested the Division of Pharmacovigilance I (DPV-I) to evaluate post-marketing reports with marketed LD products to identify AEs relevant to the review. Refer to the DPV-I complete review for additional details. The findings of the review (Kangas 2023) are discussed briefly here.

DPV-I performed a high-level analysis of FAERS reports and medical literature and compared product labeling between NAC products and Legubeti to identify AEs of interest with NAC or L-lysine for further review.

- Oral NAC:

  DPV-I identified the following AEs of interest with oral NAC: severe rash, hypersensitivity including pruritis and angioedema, drug induced liver injury (DILI), and serum sickness-like reactions.

- Oral Lysine:

  DPV-I also identified the AE of interest of Fanconi's syndrome with L-lysine use (previously described in the review c.f. Section 8.2.6.1)

Although outside the scope of this review, DPV-I review identified two potential safety signals specific to the IV formulation of NAC:

- DPV identified a case of cardiac arrest following anaphylaxis associated with FDA approved dosages of IV NAC. 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. DPV suggested continued monitoring of this event.
- DPV 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. (b) (4)

In conclusion, the DPV-I reviews did not identify any new post-marketing safety issues with oral NAC warranting changes to the current oral NAC product labeling or the proposed Legubeti product labeling. They did not identify any safety signals with lysine that would impact the proposed Legubeti product labeling. (b) (4)

8.2.9. Integrated Assessment of Safety

The Applicant relies on FDA's previous findings of safety for the LD, Mucomyst, and has not conducted any clinical studies with Legubeti in the target population. To establish a scientific bridge to the LD, the Applicant conducted a relative bioavailability (BA) study 2021-5140, comparing its proposed product to the LD, Mucomyst after a single dose of 1000 mg in healthy subjects under fasted conditions.

NAC has been in use since 1963 for APAP toxicity. Safety data from this BA study, published literature review, findings of safety and efficacy of the LD, and analysis of databases of post-marketing safety reports in the United States, did not identify any new safety issues with oral NAC. Specifically, the most common AEs secondary to

administration of oral NAC are gastrointestinal. Anaphylactoid reactions have been reported with oral NAC, but these are not as common as with IV administration.

However, because this is a new salt of NAC with L-lysine, there is concern regarding use of high dose Legubeti, especially how L-Lysine will impact patient tolerability and palatability. There are insufficient data regarding the tolerability and palatability of the proposed Legubeti doses. As discussed above the inability to ingest the full dose regimen, either due to inadequate palatability or inadequate tolerability poses significant safety concerns: (1) inadequate treatment of APAP toxicity due to inability to tolerate full dose regimen, can delay timely administration of NAC which can increase risk of hepatotoxicity; and, (2,) given that nausea and emesis are most common adverse reactions of NAC, absence of data for the effect of L-lysine on gastrointestinal AEs compared to NAC alone, may increase risk of aspiration in patients. Risk of aspiration is higher in children, those with altered mental status, and the elderly.

In addition to the risks discussed above, L-lysine may have an adverse effect on kidney function, although the clinical relevance for short term use in the intended use population is unknown.

To address the tolerability and palatability concerns, the Applicant proposed a trial to assess the tolerability and palatability of acetylcysteine lysine powder for oral solution in adults. The Applicant submitted the protocol for this trial to the PIND.

At the conclusion of ten-month review cycle, the Applicant has not submitted to Agency the results of the palatability and tolerability study. It is unclear when the results of this study will be available for review. The Division considers the lack of available data a significant safety issue.

8.3. Conclusions and Recommendations

Due to the lack of data concerning palatability and tolerability the Division cannot conclude that Legubeti has a favorable benefit-risk profile. Therefore, the clinical review team has concluded Legubeti should not be approved as a 505(b)(2) new drug to be an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen. This conclusion is based on the lack of data regarding the effect of L-lysine on tolerability and palatability of Legubeti.

9. Pediatrics

The proposed product, Legubeti (acetylcysteine lysine powder for oral solution) is subject to the Pediatric Research Equity Act (PREA) 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 Applicant is proposing the same weight-based dosage for adult and pediatric patients.

The Applicant is relying on FDA's previous findings of efficacy and safety for Mucomyst (acetylcysteine solution) NDA 013601 as the LD. Mucomyst labeling is not in the Physician Labeling Rule (PLR) format. However, FDA approved another acetylcysteine product, Cetylev effervescent tablets for oral solution (500 mg and 2.5 g), under NDA 207916 for the same indication in January 2016. Cetylev labeling is in PLR format. Both Mucomyst and Cetylev have been discontinued from marketing for reasons other than safety and efficacy.

An Agreed iPSP issued April 15, 2020, contains a plan to request a partial waiver in patients weighing less than 1 kg. In this iPSP, FDA agreed that, if the Applicant was able to establish a bridge to the LD, then Legubeti would be deemed fully assessed in pediatric patients. This approach to drug development is consistent with the amount and type of pivotal data required for the 2016 approval of Cetylev. However, because Cetylev had Orphan Drug Designation (ODD) and was, therefore exempt from PREA requirements, FDA did not have the authority to require additional studies for pediatric patients such as palatability assessments. Because Legubeti does not have ODD and is subject to PREA, FDA may require additional safety assessments from the Applicant, if needed, to ensure adequate pediatric use information is obtained.

FDA held a Filing Meeting on August 24, 2022, at which time 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 on (1), the volume of water needed to fully reconstitute the drug prior to administration; and (2), whether that volume of free water would exceed daily free water limits for the youngest and lowest weight patients. These concerns were stated in the Filing Communication Letter dated September 9, 2022. Additionally, DPMH asked the Applicant to provide evidence supporting the safety of the total amount of lysine delivered with the loading, and 16 maintenance weight-based doses to patients down to 1 kg of body weight. Finally, the Division conveyed to the Applicant throughout the review cycle that both Mucomyst and Cetylev were discontinued because of preferential use of the injectable dosage form. Therefore, DPMH concurred with the Clinical review team regarding the lack of data supporting the 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.

In a response to the Filing Communication dated December 30, 2022, 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. The Applicant stated the results demonstrate that Legubeti powder dissolves very rapidly (minutes) in water, pediatric electrolyte solution, Diet Coke, and NaCl 0.9 %. The Applicant stated these findings demonstrate 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 nine ml of water. This represents the capacity of water to dissolve amounts of Legubeti of nine to 18 times more than the required quantity 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, pediatric electrolyte solution, or normal saline.

This 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 Mucomyst, 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).

Regarding the safety of the proposed dosing of lysine in pediatric patients, the Applicant submitted publications to support the claim that the L-lysine dose is safe. However, the publications submitted by the Applicant failed to provide adequate evidence to support the safety of administering such maximum doses of L-Lysine to patients down to 1 kg. The Applicant acknowledged that safety information pertinent to ingestion of very high daily oral doses is limited and submitted seven publications to support the use of higher doses of oral L-Lysine. One publication was a nonclinical study conducted in rats. (Racusen et al. 1985) Two publications were randomized clinical trials (RCT) conducted in adults, (Griffith et al. 1987; Wass et al. 2011).One publication was a systematic literature review, (Hayamizu et al. 2020). One publication was a consensus paper (Cynober et al. 2020). The remaining two publications were general reviews (Flodin 1997; Singh et al. 2011)). The systematic literature review (Hayamizu et al. 2020) on the safety of oral L-Lysine supplementation as part of a regular diet included 71 publications, several of which described undernourished pediatric patients receiving lysine fortified supplements at lysine doses more than 25-fold lower than the proposed weight-based Legubeti dose.

One pediatric publication (Angeles-Agdeppa et al. 2011) included in the systematic literature review, 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 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 mcg 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.

This reviewer was unable to identify any publications describing the effects of L-Lysine in pediatric patients. The only product identified through a search in the Orange Book for products containing lysine as a salt is the 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 two doses of 5 mg/kg each after 24 and 48 hrs. Each mL contains 17.1 mg/mL ibuprofen L-Lysine (including 7.1 mg of L-Lysine). (Recordati 2021) Assessment of the safety of the L-Lysine salt component of ibuprofen was derived from a 13-week toxicity study in which L-Lysine was fed to rats at concentrations of 5% of their diet which apparently showed no adverse effects. The NDA for NeoProfen did not contain information about the pediatric safety of the L-Lysine component of NeoProfen while a clinical trial was conducted with ibuprofen L-lysine in premature neonates.[5]

In response to request for further assessment of tolerability and palatability in pediatric patients, the Applicant stated that it was its understanding that once it establishes a bridge between acetylcysteine lysine (NAL) and the reference LD acetylcysteine (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, like the LD labeling for pediatric patients who cannot swallow or ingest the dose, Legubeti may be given via a nasogastric or nasoduodenal feeding tube. However, the use of NGTs in pediatric patients can present independent challenges related to NGT placement and retention. Patients often do not tolerate their presence and younger pediatric patients have been known to pull the tubes out which requires repeated attempts to replace them. 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 potentially heighten the risk of hepatic injury in pediatric patients with APAP overdose if the full dosage regimen is unable to be ingested, either due to inadequate palatability, inadequate tolerability, or delayed administration. (b) (4) and submitted a protocol proposing to evaluate the tolerability of NAL at the highest loading dose in a parallel-group, crossover palatability, and tolerability study relative to a 11 g dose of NAC solution (American Reagent) following caffeine free, Diet Coke, in healthy adult

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

subjects only. If the Applicant could prove its hypothesis with the adult palatability study (b) (4) then it may be reasonable not to duplicate the efforts in the pediatric population.

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 one (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.

(b) (4) 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, Legubeti, has acceptable palatability, the Applicant will also need to provide adequate data that the product would be tolerated by pediatric patients when given orally.

Even if the adult palatability trial can demonstrate that Legubeti has acceptable palatability, a major deficiency in this application that would still need to be addressed to inform the benefit risk assessment of this product in the pediatric population would be the safety of the lysine component. The maximum daily amount of L-lysine expected to be administered with Legubeti at the proposed dosage will range from 502.6 mg/kg/day including the loading dose on the first day to 313 mg/kg/day after completion of the maintenance doses on the last day of treatment. This amount of lysine expected to be delivered with the proposed dosage of Legubeti exceeds the estimated daily intake of lysine in enterally fed term neonates of 130 mg/kg/day as estimated by Huang et al. 2011. The Applicant did not provide adequate information supporting the safety of lysine administration at these levels to pediatric patients weighing down to 1 kg.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Prescribing Information

General

Labeling negotiations have been deferred as the application will receive a complete response (CR) from the review division.

In this review, a summary of the Division's labeling recommendations and edits in the Legubeti (acetylcysteine) labeling are included. These edits are made to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of Legubeti.

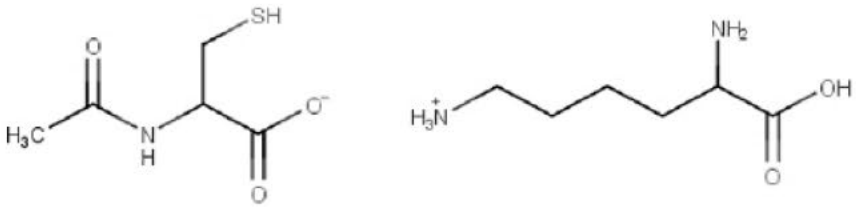
Table 26 (see below) provides a summary and rationale of the proposed changes to the Full Prescribing Information (FPI) from the Applicant-proposed label submitted on 02/09/2023. Further discussion and negotiation with the Applicant will be needed upon resubmission.

Table 26. FDA Recommendations for the Prescribing Information

Section	Section Title	Summary of Significant Labeling Changes
1	Indications and usage	This section was revised for clarity and according to principles described in the guidance for industry: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (March 2010). In summary, revisions were made to include proposed addition(s) that clarify the specific target population. This added information further clarifies (b) (4) Therefore, under Section 1, we recommended the following language: (b) (4)
2	Dosage and Administration	This section was revised for clarity and according to principles described in the guidance for industry: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (March 2010). In summary, revisions were made to subsection 2.3. (b) (4) To mitigate the risk for dosing errors, the total amount of drug product needed to prepare the solution were also updated throughout this section. Moreover, 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.

Section	Section Title	Summary of Significant Labeling Changes
3	Dosage forms and strengths	This section was revised for clarity and according to principles described in the USP Chapters <7> and the draft guidance for industry *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products – Content and Format* (January 2018). In summary, revisions were made to clarify the proper dosage form terminology. In the case of a powder that is reconstituted to make an oral solution, the appropriate terminology would be “for oral solution”. Moreover, important packaging information that facilitates prescribing, include following items were recommended to be listed in the following order: (1) dosage form, (2) strength(s), (3) identifying characteristics, and (4) limited packaging information. The revised statement is as follows: For oral solution: 500 mg acetylcysteine white powder in (b) (4) printed with “Lot Number and Expiration Date” on one side 2.5 grams acetylcysteine white powder in (b) (4) printed with “Lot Number and Expiration Date” on one side
4	Contraindications	No changes were recommended in this section at this time.
5	Warnings and precautions	This section was omitted and not included as part of the PI submitted for review.
6	Adverse reactions	No changes were recommended in this section at this time.
7	Drug interactions	This section was omitted and not included as part of the PI submitted for review.

Section	Section Title	Summary of Significant Labeling Changes
8	Use in specific populations	In summary, revisions have been made as shown below: 8.1 Pregnancy and 8.2 Lactation – These sections have been revised to be consistent with revised *draft guidance for industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (July 2020). Data about the use of N-acetylcysteine (NAC) during pregnancy to treat acetaminophen overdose are limited. Among 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. Therefore, the Risk Summary and Clinical Considerations summaries in Section 8.1 have been updated to highlight that " (b) (4) [redacted] We also recommended the addition of a statement to indicate that acetylcysteine lysine (active ingredient) was not tested in animal reproduction studies. Section 8.5 Geriatric Use – We recommended the removal of (b) (4) [redacted] The below statement was deleted: (b) (4) [redacted]
10	Overdosage	This section was omitted and not included as part of the PI submitted for review.

Section	Section Title	Summary of Significant Labeling Changes
11	Description	This section was revised for clarity and according to principles described in the USP Chapters <7>, the USP Salt Policy, the equivalency statement per the guidance for industry: *Naming of Drug Products Containing Salt Drug Substances* (June 2015), and the MAPP 5021.1 the Naming of Drug Products Containing Salt Drug Substances (December 2017). The section was revised to include the following information (see below): LEGUBETI (acetylcysteine) for oral solution is an antidote for acetaminophen overdose. (b) (4) (b) (4) with the molecular formula C11H23N3O5S, a molecular weight of 309.39, and has the following structural formula:  LEGUBETI contains 500 mg and 2.5 g of acetylcysteine (equivalent to 948 mg and 4740 mg of acetylcysteine lysine, respectively) and the inactive ingredient povidone.
12	Clinical pharmacology	No changes were made to this section at this time and were deferred as the application will receive a complete response (CR).
13	Nonclinical toxicology	Statements were added to this section to indicate that acetylcysteine lysine (active ingredient) was not tested in carcinogenicity or fertility studies.
14	Clinical studies	This section was omitted and not included as part of the PI submitted for review.
15	References	This section was omitted and not included as part of the PI submitted for review.

Section	Section Title	Summary of Significant Labeling Changes
16	How supplied/ storage and handing	This section was revised for clarity and according to principles described in the USP Chapters <7> and the draft guidance for industry *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products – Content and Format* (January 2018). In summary, revisions were made to clarify the proper dosage form terminology. In the case of a powder that is reconstituted to make an oral solution, the appropriate terminology would be “for oral solution”. Additionally, appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, imprinting, and other characteristics as applicable (e.g., flavor, size) and National Drug Code (NDC) number(s) were updated. Updates to the storage conditions instructions were updated where applicable, using the USP storage range rather than storage at a single temperature.
17	Patient counseling information	This section has been revised in accordance with The Guidance for Industry *Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (December 2014). We recommended the removal of the FDA-approved patient labeling statement as none were submitted for review. In summary, the below statement has been deleted. ~~Advise the patient to read the FDA-approved patient labeling (Patient Information).~~

Source: Table prepared by the Associate Director for labeling from the Division of Hepatology and Nutrition (DHN).
Abbreviations: CR, complete response; NDC, National Drug Code; PI, prescribing information; USP, United States Pharmacopeia

11. Division Director (Clinical) Comments

See review below.

12. Office Director (or Designated Signatory Authority) Comments

I concur with the recommendation of the review team to take a Complete Response action for NDA 215040 for Legubeti as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen.

NDA 215040 was submitted as a 505(b)(2) application for the treatment of acetaminophen toxicity which can occur when intentional or accidental high dose acetaminophen is ingested. Acetaminophen overdose can result in severe liver injury and possible acute liver failure (ALF). Acetaminophen is the most common drug-related liver injury in the U.S.; and, as such is a leading indication for drug-toxicity-related ALF and need for liver transplantation. The Applicant stated that it relied on the safety and effectiveness of the LD Mucomyst (acetylcysteine solution) approved under NDA013601. During the review by the 505(b)(2) committee, questions arose concerning how the Applicant also used the Cetylev (NDA207916) label, which is discussed below.

In clinical practice, N-acetylcysteine (NAC) is administered via the parenteral route because the oral formulation of the LD is poorly tolerated by patients due to its unpleasant taste and odor. NDA 0130601 was discontinued not for reasons related to safety or efficacy; rather its withdrawal was the result of limited use in clinical practice due to its poor oral tolerance in the emergency setting which necessitates the antidote to be administered via the parenteral route.

As reviewers note, since the LD was not in Physician Labeling Rule (PLR) format, the Applicant cited the Cetylev (NDA207916) label as a reference to comply with the PLR. However, following review by the 505(b)(2) Committee, the Applicant was found to be deficient in citing key original published manuscripts in the public domain to support information that it borrowed from the Cetylev label. This regulatory deficiency is not related to PLR formatting. References included as supportive of this NDA submitted by the Applicant did not include all necessary original published studies to support what the Applicant borrowed beyond PLR formatting from the Cetylev label. In the next cycle the Applicant will need to correct this deficiency by including additional original published studies to support any information that was present in the Cetylev label, but not present in the Mucomyst label.

The Applicant initiated development of NAL via a PIND (IND 130190) meeting request held on March 21, 2016, by the Division of Gastroenterology and Inborn Errors Products (DGIEP). (b) (4) The Agency commented that an in vivo relative bioavailability study would be needed to establish a bridge because a new active ingredient (L-lysine) and a new dosage form

was proposed. The Agency advised that the justification that the lysine portion of the NAL molecule would not affect the safety or efficacy of NAC should be provided. Following the meeting with DGIEP, the Applicant did not file an active IND, nor did it request a pre-NDA meeting, as was advised in the final meeting minutes of May 19, 2016. Because the Applicant intended to market its product for both children and adults, an iPSP was submitted and final agreement between the Agency and the Applicant for its iPSP was reached on April 15, 2020.

The Agency filed the application on September 9, 2022, but FDA identified several issues the Applicant would need to address across all disciplines. Although most of these issues were adequately addressed during the review cycle, several key review issues remain unresolved at the close of the ten-month review cycle. The primary issue remaining for the review team was the uncertainty as to whether patients could tolerate up to 15 g of NAL given that previous oral formulations of NAC were poorly tolerated due to the unpleasant taste and odor and given that L-lysine also has an unpleasant taste.

Because the Applicant did not maintain an active IND in the United States, it proposed [redacted] (b) (4) At this time the Agency has not received data concerning palatability, [redacted] (b) (4), or a [redacted] (b) (4) to assess patient tolerability and palatability that DCOA could review.

The Applicant provided data to support the comparable bioavailability including solubility data between Legubeti and the LD. These data provided evidence that NAL was soluble in the range of loading and maintenance dosages that would be used in both pediatric and adult populations in age-appropriate volume of liquid. However, the foul odor and taste led to poor tolerability and rendered oral formulations of NAC to fall out of favor for use. While the Applicant's rationale of its formulation of NAL was to improve palatability and tolerability, no data were submitted to support the claim and without such data which would ultimately support the effectiveness of NAL, NDA 215040 cannot be approved at this time. Moreover, the Applicant will need to demonstrate palatability in adults first before considering use in the pediatric population. If the Applicant is unable to demonstrate that its product, NAL, is palatable and tolerable, the Applicant will need to provide adequate data that the product would also be tolerated by pediatric patients when given orally.

Also, the safety of lysine in the pediatric population needs to be better supported because there are a paucity of published data describing the safety of lysine in this population. The Applicant also did not provide adequate information supporting the safety of administering the proposed maximum doses of L-Lysine down to children weighing one kg.

Given that the parenteral route for use of NAC in treating acetaminophen toxicity is preferred and there are available generic formulations of NAC for oral administration,

there is currently not an unmet medical need to introduce a new oral formulation of NAC. Although the Applicant has hypothesized NAL would be better tolerated than the LD because of the creation of the lysine salt, the Applicant did not provide original data to support its hypothesis for safe and effective use in both adults and children. Poor tolerance would likely lead to lower effectiveness of NAC compared to parenteral administration because it is possible that poorly tolerated oral antidote will lead to lower systemic NAL concentrations, and therefore reduce the product's efficacy in preventing or mitigating APAP-induced liver injury. Conceivably, increased nausea and vomiting could lead to choking and possible aspiration in both adults and the pediatric population. In conclusion, the benefit-risk assessment of NDA 215040 does not favor an overall benefit for marketing, and a complete response (CR) will be issued.

13. Appendices

13.1. References

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Code of Federal Regulations

21 CFR 172.320, 2023, Title 21 Chapter I Food and Drug Administration Department of Health and Human Services Subchapter B Part 172 Food Additives Permitted for Direct

Addition to Food for Human Consumption Subpart D Special Dietary and Nutritional Additives Sec 172.320 Amino Acids, accessed, 2023, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=172.320.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 2021-5140

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 5		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. OCP Appendices (Technical Documents Supporting OCP Recommendations)

13.3.1. Summary of Bioanalytical Method Validation

In this NDA, the Sponsor submitted bioanalytical method validation report ((b) (4) -1903-21) and bioanalysis report (BSAP-2021-5140). Acetylcysteine in human plasma was quantified using a validated LC-MS/MS method. The method validation results are summarized in Table 27 below. The bioanalytical method was adequately validated and met the acceptance criteria suggested in the FDA *Bioanalytical Method Validation Guidance* (May 2018).

Table 27. Summary of LC-MS/MS Method Validation Results

Item	Results
Analyte(s)	Acetylcysteine derivative (N-Acetyl-S-(p-methoxyphenacyl)cysteine)
Internal standard(s)	N-acetyl-S-(p-methoxy phenacyl) cysteine $^{13}CD_3$
Biological matrix	Human Plasma
Anticoagulant	K_2EDTA
Volume (mL)	0.0500
Methodology	LC-MS/MS
Calibration range (ng/mL)	5.00-5000
Intra-day precision (%)	
LLOQ QC 5.00 ng /mL	10.9 - 19.6
QC A 15.0 ng /mL	3.8 - 8.3
QC B 2500 ng /mL	0.8 - 9.1
QC C 4000 ng /mL	0.5 - 6.5
Intra-day accuracy (%)	
LLOQ QC 5.00 ng /mL	82.6 - 119.4
QC A 15.0 ng /mL	98.0 - 109.3
QC B 2500 ng /mL	99.2 - 102.4
QC C 4000 ng /mL	100.3 - 103.5
Inter-day precision (%)	
LLOQ QC 5.00 ng /mL	18.4
QC A 15.0 ng /mL	6.8
QC B 2500 ng /mL	4.4
QC C 4000 ng /mL	3.2

Inter-day accuracy (%)	
LLOQ QC 5.00 ng /mL	96.2
QC A 15.0 ng /mL	100.7
QC B 2500 ng /mL	101.6
QC C 4000 ng /mL	102.0
Coefficient of determination (r^2)	≥ 0.9910
Stability in biological matrix	
Freeze-thaw at -25 ± 10 °C	Demonstrated for 3 cycles
Short term at room temperature Bench-top	Demonstrated for 20.00 hours
Short term refrigerated at 5 ± 3 °C	Demonstrated for 20.75 hours
Bench-top stability in fresh whole blood	Demonstrated for 2.00 hours at room temperature
	Demonstrated for 2.00 hours in an ice-water bath
Stability of processed samples	
Autosampler at approximately 5 °C	Demonstrated for 89.00 hours
Room temperature	Demonstrated for 2.25 hours
Stability in solutions	
Short term stock solution at room temperature	Demonstrated for 17.75 hours
Working solution at room temperature	Demonstrated for 22.00 hours
Recovery (%)	
Analyte	93.2 - 94.8
Internal standard	98.1 - 100.0

Dilution integrity factor 2 – QC 2D 8000 ng /mL	
Precision (%)	1.4
Accuracy (%)	99.1
Dilution integrity factor 5 – QC 5D 20000 ng /mL	
Precision (%)	2.3
Accuracy (%)	99.0
Selectivity – blank matrices (8)	No interference
Injection carry-over	No interference
Matrix effect	
Precision (%)	2.3 - 4.5
Accuracy (%)	99.5 - 100.7
Matrix factor	
QC A mean	0.992
QC A precision (%)	1.8
QC C mean	0.991
QC C precision (%)	0.9
Hemolyzed QC samples experiment	
Precision (%)	1.8 - 5.5
Accuracy (%)	99.3 - 100.8
Lipemic QC samples experiment	
Precision (%)	1.8 - 3.3
Accuracy (%)	99.8 - 100.7
Specificity – concomitant medications (19)	No interference
Specificity – hormonal contraceptives (13)	No interference
Evaluation in the presence of concomitant medications	
Precision (%)	1.3 - 5.8
% Difference	-0.3 to 6.0
Evaluation in the presence of hormonal contraceptives	
Precision (%)	1.4 - 4.6
% Difference	2.5 to 10.0
Batch size determination	275 samples

Source: (b) (4)-1903-21 Validation Report
Abbreviations: LLOQ, lower limit of quantification; QC, quality control

13.3.2. In Vivo BA Study 2021-5140

To establish a scientific bridge to the LD, the Sponsor conducted a pivotal relative bioavailability (BA) Study 2021-5140 comparing a single dose of 1000 mg (2 sachets of 500 mg) of the proposed drug, N-acetylcysteine Lysine (NAL) Powder for oral solution to 1000 mg (5 mL) of Acetylcysteine Solution, USP 20% (200 mg/mL, ANDA 072547) in healthy subjects under fasted conditions.

Note: Per the Orange Book, the LD, Mucomyst® (acetylcysteine) Solution (NDA 013601) is currently discontinued not due to safety or efficacy reasons. Its reference standard (RS), Acetylcysteine Solution, USP 20% (200 mg/mL, ANDA 072547) was used for the BA study.

Title of Study:

A single-dose, bioequivalence study of two formulations of acetylcysteine 1000 mg under fasting conditions.

Study Design:

An open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover study in healthy subjects

Number of Subjects:

A total of 24 healthy subjects (14 Females; 10 males) were enrolled and completed the study

Drug Product:

- Test product: N-acetylcysteine Lysine (NAL) Powder for oral solution, 500 mg
- Reference product: Acetylcysteine Solution, USP 20% (200 mg/mL, ANDA 072547)

Dose:

- Test product: A single dose of 1000 mg (2 sachets of 500 mg) of N-acetylcysteine Lysine (NAL)
- Reference product: A single dose of 1000 mg (5 mL) of Acetylcysteine Solution, USP 20% (200 mg/mL)

Sampling Schedule/Washout Period:

PK blood samples were collected prior to dosing, -10, -2, and 0-hour, and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, and 12 hrs, post-dose, totaling 17 samples in each period. The washout period was 7 days.

Safety:

An assessment of safety was based primarily on the incidence, frequency, and severity of adverse events (AEs).

Findings:

- The product-specific guidance for a generic product of Acetylcysteine Effervescent Tablets also recommends a single-dose, two-way crossover study. Based on the half-life of acetylcysteine (i.e., ~3.5 hr) identified from the current BA study, the PK blood sampling time points up to 12 hr post dose and washout period of 7 days seem reasonable. Therefore, the study design of current BA study is deemed adequate for its objective.
- There was no dropout during the study as all 24 subjects who were enrolled (10 males; 14 females) completed the study.
- The administration of the study drug (a single 1 g dose) was generally well-tolerated by the healthy subjects. A total of 19 TEAEs affecting 9 subjects (37.5% of subjects dosed) were reported during the conduct of this study. All TEAEs were mild in severity and no SAE or death were reported. There were no significant adverse events reported such as vomiting during the study. The incidence rate of nausea was low (8.3%) and comparable for two drug products (refer to Table 33 below).
- The Applicant reported protocol deviations in vital signs measurement and electrocardiogram monitoring being measured late. The reviewer considers these deviations minor and there would be no significant impact on the integrity of the study outcome.
- All clinical samples from the pivotal BA Study 2021-5140 were analyzed within the established long-term stability period (55 days at -25 ± 10 °C).
- Among six analytical runs, there was one rejected run (ID: 5140-CR05-JAN2722-RS) for incurred sample reanalysis (ISR) due to extraction error as internal standard was added to CO-BLK2, CO-BLK2 and BLK. Samples were re-extracted in a repeat run (ID: 5140-CR05-RE-JAN2822-RS) and got accepted. The reviewer considers the Applicant's handling acceptable. There were no other analytical repeats.
- There was no reinjected nor manually reintegrated samples reported in the study.
- A total of 90 (11.03%) out of 816 study samples were reassayed for ISR. The ISR sample size of 90 is in line with the SOP for ISR (at least 10% of the first 1000 samples). The ISR is deemed acceptable as 80 ISR samples (88.9%) met the acceptance criteria (the % difference between the original and repeat values should be within ±20.0% for 67% of the total incurred samples analyzed).
- Per Applicant's calculation, the 90% CIs of the test to reference ratios of the geometric means for AUCt, AUCinf, and Cmax of plasma baseline-adjusted acetylcysteine were within the acceptable BE criteria of 80.00 – 125.00%, demonstrating comparable exposure of the proposed drug product relative to the LD (refer to table of PK results below). The clinical pharmacology reviewer repeated the analysis and reached the same conclusion (See Section 6.2 for details).
- However, the clinical bridge between the proposed Legubeti and the LD, Mucomyst® (acetylcysteine) Solution is deemed **inadequate** due to the lack of

tolerability/palatability data at the clinically relevant doses (see Section 6.2 for detailed comments).

Table 28. Summary of Study Results Based on Plasma Measured Acetylcysteine Levels (Without Baseline Correction)

Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
AUC_t	**A**	24	2620.30 (33)	2486.76	**A vs B**	111.56	105.04 - 118.49	12
*(hr*ng/mL)*	**B**	24	2394.80 (39)	2229.04				
AUC_{inf}	**A**	24	2655.06 (33)	2522.71	**A vs B**	111.43	105.02 - 118.22	12
*(hr*ng/mL)*	**B**	24	2427.82 (38)	2263.99				
C_{max}	**A**	24	2171.17 (46)	1968.07	**A vs B**	102.38	93.47 - 112.13	19
(ng/mL)	**B**	24	2150.54 (49)	1922.37				

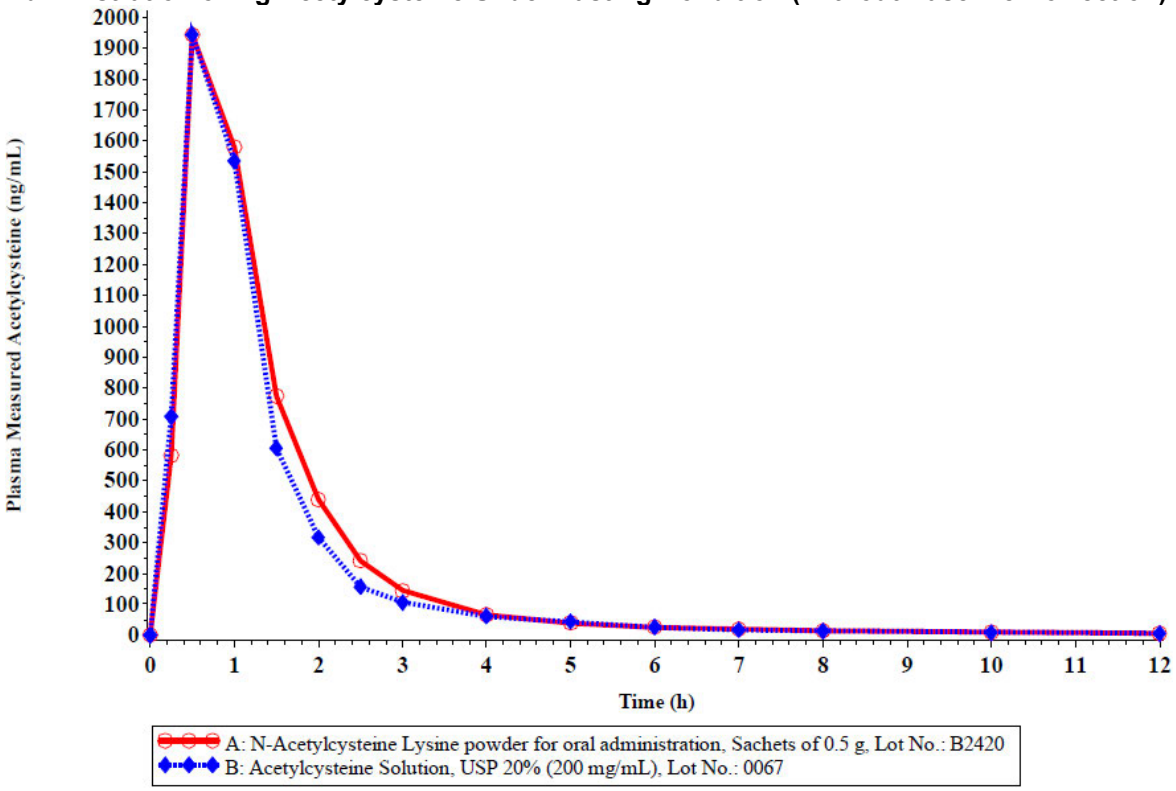
Treatment A (Test): N-Acetylcysteine Lysine powder for oral administration, Sachets of 0.5 g, Lot No.: B2420 (Galephar Pharmaceutical Research Inc., Puerto Rico)

Treatment B (Reference): Acetylcysteine Solution, USP 20% (200 mg/mL), Lot No.: 0067 (American Regent, Inc., USA)

Source: CSR 2021-5140

Abbreviations: AUCinf, area under the concentration-time curve at time infinity; AUCt, area under the concentration-time curve, at time t; Cmax, maximum plasma concentration; CV, coefficient of variation; n, number of subjects in respective group; trt, treatment

Figure 5. Mean Plasma Concentration-Time Profile for Acetylcysteine After Single Dose Administration of 1 g Acetylcysteine Under Fasting Condition (Without Baseline Correction)



Source: CSR 2021-5140

Table 29. Statistical Analysis of Bioequivalence by the Applicant (Without Baseline Correction)

	Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
	Fasting BA Study 2021-5140, N=24 (10 Males; 14 Females)						
Parameter	**Test**	**N**	**RS**	**N**	**Ratio**		**90% C.I.**
AUC_{0-t} (ng·hr/mL)	2486.76	24	2229.04	24	1.12	105.04	118.49
$AUC_{0-\infty}$ (ng·hr/mL)	2522.71	24	2263.99	24	1.11	105.02	118.22
C_{max} (ng/mL)	1968.07	24	1922.37	24	1.02	93.47	112.13

Source: CSR 2021-5140

Abbreviations: AUC0-inf, area under the concentration-time curve from time 0 to infinity; AUC0-t, area under the concentration-time curve from time 0 to last quantifiable concentration; BA, bioavailability; CI, confidence interval; Cmax, maximum plasma concentration; N, number of subjects in respective group; RS, reference standard

Table 30. Statistical Analysis of Bioequivalence by FDA (Without Baseline Correction)

	Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
	Fasting BA Study 2021-5140, N=24 (10 males; 14 females)						
Parameter	**Test**	**N**	**RS**	**N**	**Ratio**		**90% C.I.**
AUC_{0-t} (ng.hr/mL)	2559.18	24	2309.07	24	1.11	104.27	117.81
$AUC_{0-\infty}$ (ng.hr/mL)	2602.44	24	2349.03	24	1.11	104.34	117.64
C_{max} (ng/mL)	1968.07	24	1922.37	24	1.02	93.47	112.13

Source: Reviewer's table

**Only baseline-unadjusted raw datasets were submitted. For reviewer's recalculation using SAS, only one pre-dose sampling point at 0 hr was included while excluding two other pre-dose sampling points at -10 and -2 hr.

Abbreviations: AUC0-inf, area under the concentration-time curve from time 0 to infinity; AUC0-t, area under the concentration-time curve from time 0 to last quantifiable concentration; BA, bioavailability; CI, confidence interval; Cmax, maximum plasma concentration; N, number of subjects in respective group; RS, reference standard

Table 31. Summary of PK of Acetylcysteine Following a Single Dose Administration of 1 gm Acetylcysteine under Fasting Conditions (With Baseline Correction)

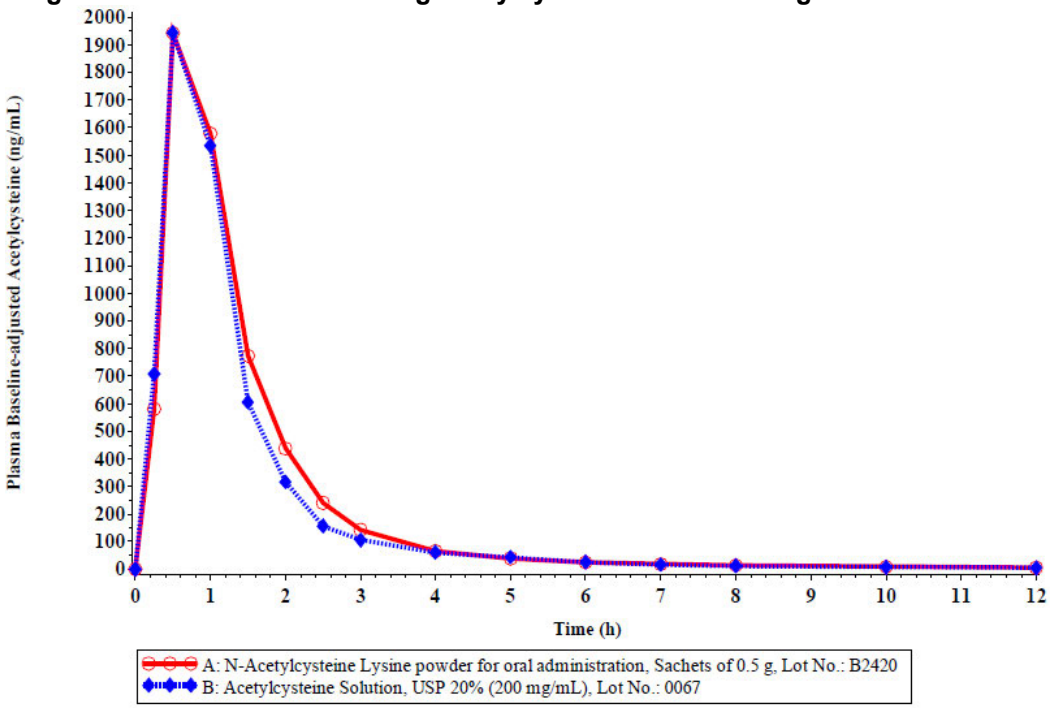
Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
AUC_t	**A**	24	2615.07 (33)	2481.01	**A vs B**	111.33	104.84 - 118.23	12
*(hr*ng/mL)*	**B**	24	2393.66 (39)	2228.42				
AUC_{inf}	**A**	24	2647.82 (33)	2514.73	**A vs B**	111.08	104.70 - 117.85	12
*(hr*ng/mL)*	**B**	24	2426.85 (38)	2263.94				
C_{max}	**A**	24	2170.74 (46)	1967.56	**A vs B**	102.35	93.45 - 112.10	19
(ng/mL)	**B**	24	2150.45 (49)	1922.33				

Treatment A (Test)	N-Acetylcysteine Lysine powder for oral administration, Sachets of 0.5 g, Lot No.: B2420 (Galephar Pharmaceutical Research Inc., Puerto Rico)
Treatment B (Reference)	Acetylcysteine Solution, USP 20% (200 mg/mL), Lot No.: 0067 (American Regent, Inc., USA)

Source: CSR 2021-5140

Abbreviations: AUCinf, area under the concentration-time curve at time infinity; AUCt, area under the concentration-time curve, at time t; Cmax, maximum plasma concentration; CV, coefficient of variation; n, number of subjects in respective group; trt, treatment.

Figure 6. Mean Baseline Adjusted Plasma Concentration-Time Profile for Acetylcysteine After Single Dose Administration of 1 g Acetylcysteine Under Fasting Condition



Source: CSR 2021-5140

Table 32. Descriptive Statistics for Plasma Baseline-Adjusted Acetylcysteine Pharmacokinetic Parameters

Parameter	*Trt*	*GeoMean*	*ArithMean*	*SD*	*CV%*	*Median*	*Minimum*	*Maximum*	*N*
AUC_t	A	2481.01	2615.07	863.11	33.01	2487.82	1363.30	4391.77	24
*(hr*ng/mL)*	B	2228.42	2393.66	927.40	38.74	2135.25	1119.62	4085.14	24
AUC_{inf}	A	2514.73	2647.82	864.06	32.63	2531.70	1390.28	4428.44	24
*(hr*ng/mL)*	B	2263.94	2426.85	926.99	38.20	2170.59	1142.75	4116.69	24
AUC_t/AUC_{inf}	A	98.66	98.66	0.64	0.65	98.81	97.01	99.48	24
(%)	B	98.43	98.43	0.65	0.66	98.54	97.12	99.33	24
C_{max}	A	1967.56	2170.74	988.89	45.56	1894.04	985.34	4330.00	24
(ng/mL)	B	1922.33	2150.45	1046.36	48.66	1815.00	779.00	4407.74	24
T_{max}	A	0.71	0.77	0.36	46.77	0.50	0.50	2.00	24
(hr)	B	0.67	0.71	0.25	35.55	0.50	0.50	1.00	24
T_{half}	A	3.20	3.30	0.83	25.09	3.17	2.17	4.81	24
(hr)	B	3.33	3.43	0.87	25.23	3.52	2.07	5.52	24
K_{el}	A	0.2166	0.2229	0.0539	24.17	0.2184	0.1440	0.3197	24
(1/hr)	B	0.2080	0.2142	0.0525	24.53	0.1972	0.1255	0.3345	24
TLIN	A	5.73	5.96	1.66	27.79	6.00	4.00	8.03	24
(hr)	B	5.93	6.13	1.52	24.73	6.50	3.00	8.13	24
R^2	A	0.9624	0.9632	0.0380	3.94	0.9729	0.8732	1.0000	24
	B	0.9727	0.9731	0.0291	2.99	0.9800	0.8778	0.9997	24
Ct	A	6.58	6.75	1.45	21.49	6.94	3.55	9.78	24
(ng/mL)	B	6.74	6.83	1.13	16.51	6.78	5.17	8.57	24
LQCT	A	11.75	11.77	0.68	5.82	12.00	10.00	12.22	24
(hr)	B	11.28	11.34	1.13	9.98	12.00	8.00	12.05	24

Source: CSR 2021-5140

Abbreviations: AUCinf, area under the concentration-time curve at time infinity; AUCt, area under the concentration-time curve, at time t; Cmax, maximum plasma concentration; Ct, last measurable concentration value of LQCT (this value was used for the extrapolation to infinity); CV, coefficient of variation; K_{el}, constant; LQCT, time for the last quantifiable concentration; N, number of subjects in respective group; R^2 , coefficient of determination for regression analysis; SD, standard deviation; Thalf, half-life; TLIN, start time for linear regression; Tmax, time to maximum concentration; trt, treatment

Table 33. Summary of All Treatment-Emergent Adverse Events by System Organ Class and Preferred Term for Each Treatment

	Reported Incidence by Treatment Group n (%)			Reported Frequency by Treatment Group no. (%)		
System Organ Class Preferred Term	A N = 24	B N = 24	Total N = 24	A No. = 10	B No. = 9	Total No. = 19
Subjects with TEAEs	**6 (25.0%)**	**6 (25.0%)**	**9 (37.5%)**	**N/A**	**N/A**	**N/A**
Subjects with No TEAEs	18 (75%)	18 (75%)	15 (62.5%)	N/A	N/A	N/A
Gastrointestinal disorders	**2 (8.3%)**	**2 (8.3%)**	**3 (12.5%)**	**2 (20.0%)**	**2 (22.2%)**	**4 (21.1%)**
Nausea	2 (8.3%)	2 (8.3%)	3 (12.5%)	2 (20.0%)	2 (22.2%)	4 (21.1%)
General disorders and administration site conditions	**2 (8.3%)**	**1 (4.2%)**	**3 (12.5%)**	**2 (20.0%)**	**1 (11.1%)**	**3 (15.8%)**
Catheter site related reaction	1 (4.2%)	1 (4.2%)	2 (8.3%)	1 (10.0%)	1 (11.1%)	2 (10.5%)
Vessel puncture site reaction	1 (4.2%)	0 (0%)	1 (4.2%)	1 (10.0%)	0 (0%)	1 (5.3%)
Nervous system disorders	**5 (20.8%)**	**5 (20.8%)**	**7 (29.2%)**	**6 (60.0%)**	**6 (66.7%)**	**12 (63.2%)**
Dizziness	1 (4.2%)	1 (4.2%)	2 (8.3%)	1 (10.0%)	1 (11.1%)	2 (10.5%)
Headache	5 (20.8%)	5 (20.8%)	7 (29.2%)	5 (50.0%)	5 (55.6%)	10 (52.6%)

Source: CSR 2021-5140
Abbreviations: N, number of subjects; n, number of subjects in respective groups; TEAE, treatment emergent adverse events

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Ashish Dhawan	OND/OII/DHN	Section: 2, 7, 8	**Select one:** _x_ Authored ___ Approved
	Signature: Ashish Dhawan -S Digitally signed by Ashish Dhawan -S Date: 2023.05.03 15:22:10 -04'00'			
Clinical Team Leader	George Makar	OND/OII/DHN	Section: 2, 7, 8	**Select one:** ___ Authored _x_ Approved
	Signature: George A. Makar -S Digitally signed by George A. Makar -S Date: 2023.05.03 15:26:18 -04'00'			
Division Director (Acting) Signatory (Clinical)	Frank Anania	OND/OII/DHN	**Authored:** Section: 12 **Approved:** All sections	**Select one:** **x** Authored _x_ Approved
	Signature: Frank A. Anania -S Digitally signed by Frank A. Anania -S Date: 2023.05.03 15:45:25 -04'00'			
Regulatory Affairs Project Manager	Chinedu Ebonine	OND/ORO/OII/DHN	Section: 3	**Select one:** _x_ Authored ___ Approved
	Signature: Chinedu Ebonine -S Digitally signed by Chinedu Ebonine -S Date: 2023.05.03 15:52:02 -04'00'			

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Regulatory Affairs Chief, Project Management Staff	Ayanna Augustus Bryant	OND/ORO/OII/DHN	Sections: 3.1, 3.2	**Select one:** __ Authored _X_ Approved
	Signature: Ayanna Augustus -S Digitally signed by Ayanna Augustus -S Date: 2023.05.03 15:16:53 -04'00'			

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
OPQ, Application Technical Lead (ATL)	Hamid Shafiei	CDER/OPQ/ONDP/DNDPII/NDPB4	Sections: 4.2	**Select one:** _X_ Authored _X_ Approved
	Signature:	Hamid Shafiei -S Digitally signed by Hamid Shafiei -S Date: 2023.05.01 10:20:56 -04'00'		

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Rosalyn Jurjus	OND/OII/DPT-II	Sections: 5	**Select one:** _X_ Authored ___ Approved
	Signature: Rosalyn A. Jurjus -S Digitally signed by Rosalyn A. Jurjus -S Date: 2023.04.26 10:13:46 -04'00'			
Nonclinical Supervisor	David Joseph	OND/OII/DPT-II	Sections: 5	**Select one:** ___ Authored _X_ Approved
	Signature: David B. Joseph -S Digitally signed by David B. Joseph -S Date: 2023.04.26 10:55:45 -04'00'			

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Sung-Yong (Mark) Hwang	OTS/OCP/DIIP	Sections: 6, 13.3	**Select one:** _X_ Authored ___ Approved
	Signature: Sung-yong Hwang -S Digitally signed by Sung-yong Hwang -S Date: 2023.05.03 15:39:58 -04'00'			
Clinical Pharmacology Team Leader, CDTL	Insook Kim	OTS/OCP/DIIP	**Authored:** Sections: 1, 6, 13.3 **Approved:** Sections 1-11, 13.3	**Select one:** _x_ Authored _X_ Approved
	Signature: Insook Kim -S Digitally signed by Insook Kim -S Date: 2023.05.03 16:18:15 -04'00'			

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
DPMH Reviewer	Ndidi Nwokorie	CDER/OND/ORDPURM/DPMH	Sections: 9	**Select one:** _X_ Authored ___ Approved
	Signature: Ndidi N. Nwokorie -S Digitally signed by Ndidi N. Nwokorie -S Date: 2023.05.03 11:24:04 -04'00'			
DPMH Team Leader	Mona Khurana	CDER/OND/ORDPURM/DPMH	Sections: 9	**Select one:** ___ Authored _X_ Approved
	Signature: Mona Khurana -S Digitally signed by Mona Khurana -S Date: 2023.05.03 14:33:47 -04'00'			

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Associate Director of Labeling	Stephen Chang	OND/ORO/OII/DHN	Sections: 10	**Select one:** _X_ Authored ___ Approved
	Signature: Stephen H. Chang -S Digitally signed by Stephen H. Chang -S Date: 2023.05.01 10:43:37 -04'00'			

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/

INSOOK KIM
05/04/2023 05:01:05 PM

FRANK A ANANIA
05/04/2023 05:14:36 PM

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CETYLEV® safely and effectively. See full prescribing information for CETYLEV.

CETYLEV (acetylcysteine) effervescent tablets for oral solution
Initial U.S. Approval: 1963

----------INDICATIONS AND USAGE----------
CETYLEV is an antidote for acetaminophen overdose indicated to prevent or lessen hepatic injury after ingestion of a potentially hepatotoxic quantity of acetaminophen in patients with acute ingestion or from repeated supratherapeutic ingestion. (1)

----------DOSAGE AND ADMINISTRATION----------
Pre-Treatment Assessment Following Acute Ingestion (2.1):
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 CETYLEV 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 CETYLEV 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 CETYLEV 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 (Figure 1) to determine whether or not to initiate treatment with CETYLEV (2.2)

Nomogram for Estimating Potential for Hepatotoxicity from Acute Acetaminophen Ingestion (2.2):

- See the Full Prescribing Information for instructions on how to use the nomogram to determine the need for loading and maintenance dosing.

Recommended Adult and Pediatric Dosage (2.3):

- CETYLEV is for oral administration only; not for nebulization or intratracheal instillation
- Loading dose: 140 mg/kg
- Maintenance doses: 70 mg/kg repeated every 4 hours for a total of 17 doses.
- See Full Prescribing Information for weight-based dosage and preparation and administration instructions.

Repeated Supratherapeutic Acetaminophen Ingestion (2.4):

- Obtain acetaminophen concentration and other laboratory tests to guide treatment; Rumack-Matthew nomogram does not apply.

----------DOSAGE FORMS AND STRENGTHS----------
Effervescent tablets: 500 mg and 2.5 grams (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Reactions, Including Urticaria: Discontinue CETYLEV unless deemed essential to patient management and the reactions can be otherwise controlled (5.1)
- Risk of Upper Gastrointestinal Hemorrhage: Consider the risk/benefit for patients at risk of hemorrhage (e.g., those with esophageal varices, peptic ulcers, etc.) versus the risk of developing hepatic toxicity, and treat with CETYLEV accordingly.(5.2)

----------ADVERSE REACTIONS----------
Most common adverse reactions are nausea and vomiting, other gastrointestinal symptoms, and rash with or without fever. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Arbor Pharmaceuticals LLC at 1- 866-516-4950 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION and Patient Information.

Revised: 04/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CETYLEV is indicated to prevent or lessen hepatic injury after ingestion of a potentially hepatotoxic quantity of acetaminophen in patients with acute ingestion or from repeated supratherapeutic ingestion (RSI).

2 DOSAGE AND ADMINISTRATION

2.1 Pretreatment Assessment and Testing Following Acute Acetaminophen Ingestion

The following recommendations are related to acute acetaminophen ingestion. For recommendations related to repeated supratherapeutic exposure see *Dosage and Administration (2.4)*.

1. Assess the history and timing of acetaminophen ingestion as an overdose.
    - The reported history of the quantity of acetaminophen ingested as an overdose is often inaccurate and is not a reliable guide to therapy.

2. Obtain the following laboratory tests to monitor hepatic and renal function and electrolyte and fluid balance: aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, international normalized ratio (INR), creatinine, blood urea nitrogen (BUN), blood glucose, and electrolytes.

3. Obtain a plasma or serum sample to assay for acetaminophen concentration at least 4 hours after ingestion. Acetaminophen concentrations obtained earlier than 4 hours post-ingestion may be misleading as they may not represent maximum acetaminophen concentrations.

4. If the time of acute acetaminophen ingestion is unknown:
    - Administer a loading dose of CETYLEV immediately *[see Dosage and Administration (2.3, 2.4)]*.
    - Obtain an acetaminophen concentration to determine need for continued treatment *[see Dosage and Administration (2.2)]*

5. 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 CETYLEV immediately and continue treatment for a total of 17 doses *[see Dosage and Administration (2.3)]*.

6. If the patient presents more than 8 hours after ingestion and the time of acute acetaminophen ingestion is known:
    - Administer a loading dose of CETYLEV immediately *[see Dosage and Administration (2.3)]*.
    - Obtain acetaminophen concentration to determine need for continued treatment *[see Dosage and Administration (2.2)]*.

7. 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 (Figure 1) to determine whether or not to initiate treatment

with CETYLEV *[see Dosage and Administration (2.2)]*

2.2 Nomogram for Estimating Potential for Hepatotoxicity from Acute Acetaminophen Ingestion and Need for CETYLEV Treatment

If the timing of the acute acetaminophen ingestion is known and the results of the acetaminophen assay are available within 8 hours:

- Refer to the Rumack-Matthew nomogram (see Figure 1) to determine whether or not to initiate treatment with CETYLEV.
- Initiation of CETYLEV depends on the acetaminophen concentration and also the clinical presentation of the patient.

The nomogram may underestimate the hepatotoxicity risk in patients with chronic alcoholism, malnutrition, or CYP2E1 enzyme inducing drugs (e.g., isoniazid), and consideration should be given to treating these patients even if the acetaminophen concentrations are in the nontoxic range.

Loading Dose

For patients whose acetaminophen concentrations are at or above the "possible" toxicity line (dotted line in nomogram):

- Administer a loading dose of CETYLEV *[see Dosage and Administration (2.3)]*.

For patients with an acute overdose due to an extended-release acetaminophen, if the acetaminophen concentration at 4 hours post ingestion is below the possible toxicity line then obtain a second sample for acetaminophen concentration 8 to 10 hours after the acute ingestion. If the second value is at or above the "possible" toxicity line (dotted line in nomogram):

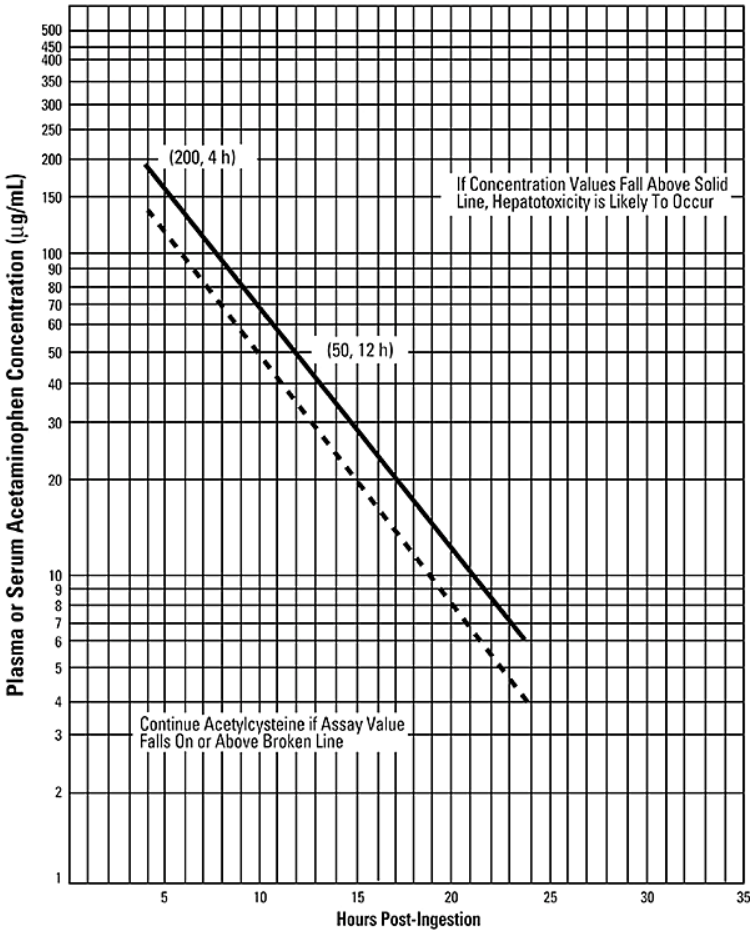
- Administer a loading dose of CETYLEV *[see Dosage and Administration (2.3)]*.

For patients whose values are below the "possible" toxicity line, but time of ingestion was unknown or sample was obtained less than 4 hours after ingestion:

- Administer a loading dose of CETYLEV *[see Dosage and Administration (2.3)]*.

For patients whose values are below the "possible" toxicity line and time of ingestion is known and the sample was obtained more than 4 hours after ingestion, do not administer CETYLEV because there is minimal risk of hepatotoxicity.

Figure 1 Rumack-Matthew Nomogram for Estimating Potential for Hepatotoxicity from Acetaminophen Poisoning – Plasma or Serum Acetaminophen Concentration versus Time (hours) Post-acetaminophen Ingestion (Adapted from Rumack and Matthew, Pediatrics 1975; 55:871−876.)



Maintenance Dose

Determine need for continued treatment with CETYLEV after the loading dose. Choose ONE of the following based on the acetaminophen concentration:

The acetaminophen concentration is above the possible toxicity line according to the nomogram (see Figure 1):

- Continue CETYLEV treatment with the maintenance dose for 17 doses *[see Dosage and Administration (2.3)]*.
- Monitor hepatic and renal function and electrolytes throughout treatment.

The acetaminophen concentration could not be obtained:

- Continue CETYLEV treatment with the maintenance dose for 17 doses *[see Dosage and Administration (2.3)]*.
- Monitor hepatic and renal function and electrolytes throughout treatment.

For patients whose acetaminophen concentration is below the "possible" toxicity line (see Figure 1) and time of ingestion is known and the sample was obtained more than 4 hours after ingestion:

- Discontinue CETYLEV.

The acetaminophen concentration was in the non-toxic range, but time of ingestion was unknown or less than 4 hours:

- Obtain a second sample for acetaminophen concentration and consider the patient's clinical

status to decide whether or not to continue CETYLEV treatment.

- If there is any uncertainty as to patient's risk of developing hepatotoxicity, it is recommended to administer a complete treatment course under medical observation with appropriate monitoring..

Continued Therapy After Completion of Loading and Maintenance Doses

In cases of suspected massive overdose, or with concomitant ingestion of other substances, or in patients with preexisting liver disease; the absorption and/or the half-life of acetaminophen may be prolonged. In such cases, consideration should be given to the need for continued treatment with CETYLEV beyond a total of 17 maintenance doses.

Acetaminophen levels and ALT/AST and INR should be checked after the last maintenance dose. If acetaminophen levels are still detectable, or if the ALT/AST are still increasing or the INR remains elevated; the maintenance doses should be continued and the treating physician should contact a US regional poison center at 1-800-222-1222, or alternatively, a "special health professional assistance line for acetaminophen overdose" at 1-800-525-6115 for assistance with dosing recommendations.

2.3 Recommended Dosage and Preparation and Administration Instructions in Adults and Pediatrics for Acute Acetaminophen Ingestion

- CETYLEV is for oral administration only; not for nebulization or intratracheal instillation.
- After appropriate preparation and dilution, CETYLEV is interchangeable with 20% acetylcysteine solution, when given at the same acetylcysteine dosage.
- Adults and Pediatrics: The recommended loading dose of CETYLEV is 140 mg/kg. Administer a first maintenance dose of 70 mg/kg 4 hours after the loading dose. Repeat 70 mg/kg maintenance dose every 4 hours for a total of 17 maintenance doses.

Preparation and Administration Instructions

- Dissolve the appropriate number of 2.5 gram and/or 500 mg CETYLEV effervescent tablets in the volume of water indicated in dosing tables and text below, based upon patient weight.
- Once the tablets are dissolved, administer the oral solution immediately.
- Solutions should be freshly prepared for each dose and utilized within 2 hours.
- If the patient vomits an oral dose of CETYLEV within 1 hour of administration, repeat that dose.
- If the patient is persistently unable to retain the orally administered acetylcysteine, CETYLEV may be administered by nasoduodenal tube. An intravenous formulation of acetylcysteine may also be considered.

Patients Weighing 20 kg and Greater

Tables 1 and 2 provide the weight-based loading and maintenance doses, respectively, of CETYLEV for patients weighing 20 kg and greater. For patients weighing 20 to 59 kg dissolve CETYLEV tablets in 150 mL of water. For patients weighing 60 kg and greater dissolve CETYLEV tablets in 300 mL of water.

Table 1: CETYLEV Loading Dose

Dissolve CETYLEV Tablets **in 300 mL of Water**			
Body weight (Kg)	Actual Acetylcysteine Dose to be Administered (grams)	Number of CETYLEV Tablets to Dissolve in Water	
		2.5 gram tablets	500 mg tablets
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 CETYLEV Tablets **in 150 mL of Water**			
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: CETYLEV Maintenance Dose

Dissolve CETYLEV Tablets **in 300 mL of Water**			
Body weight (Kg)	Actual Acetylcysteine Dose to be Administered (grams)	Number of CETYLEV Tablets to Dissolve in Water	
		2.5 gram tablets	500 mg tablets
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 CETYLEV Tablets **in 150 mL of Water**			
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 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 two 2.5 gram CETYLEV effervescent tablets 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.

2.4 Recommendations for Repeated Supratherapeutic Acetaminophen Ingestion

Repeated supratherapeutic acetaminophen ingestion (RSI) is an ingestion of acetaminophen at dosages higher than those recommended for extended periods of time. The risk of hepatotoxicity and the recommendations for treatment of acute acetaminophen ingestion (i.e., the Rumack-Matthew nomogram) do not apply to patients with RSI. Therefore, obtain the following information to guide CETYLEV treatment for RSI.

- Acetaminophen serum or plasma concentrations. A reported history of the quantity of acetaminophen ingested is often inaccurate and is not a reliable guide to therapy.
- Laboratory tests to monitor hepatic and renal function and electrolyte and fluid balance: AST, ALT, bilirubin, INR, creatinine, BUN, blood glucose, and electrolytes.

For specific CETYLEV dosage and administration information in patients with RSI, consider contacting your regional poison center at 1-800-222-1222, or alternatively, a special health professional assistance line for acetaminophen overdose at 1-800-525-6115.

3 DOSAGE FORMS AND STRENGTHS

CETYLEV effervescent tablets are supplied as white, round, flat tablets with a lemon mint flavor in the following dosage strengths:

- 500 mg tablets debossed with "I" on one side.
- 2.5 gram tablets debossed with "O" on one side.

CETYLEV tablets contain the inactive ingredient sodium bicarbonate which may be clinically relevant in some patients *[see Use in Specific Populations (8.6), Description (11)]*.

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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited published case reports and case series on acetylcysteine use during pregnancy are insufficient to inform a drug-associated risk of birth defects and miscarriage. However, there are clinical considerations *[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]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. 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

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.

Data

Animal Data

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.

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 development and health benefits of breastfeeding should be considered along with the mother's clinical need for CETYLEV and any potential adverse effects on the breastfed infant from CETYLEV or from the underlying maternal condition.

8.4 Pediatric Use

Pediatric approval, including dosing, is not based on adequate and well-controlled clinical studies. Pediatric dosing recommendations are based on clinical experience *[see Dosage and Administration (2.3)]*.

8.5 Geriatric Use

Clinical studies of acetylcysteine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience with acetylcysteine has not identified differences in the responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

8.6 Patients Sensitive to High Sodium Intake

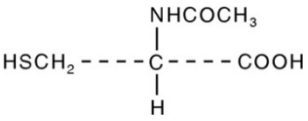
CETYLEV tablets contain sodium. Consider the total sodium content from dietary and non-dietary sources in patients who may be sensitive to excess sodium intake, such as those with congestive heart failure, hypertension, or renal impairment.

At the recommended dosage an average sized adult (60 kg) may receive a total of 7 grams of sodium (304.3 mEq) on the first day of treatment, 5.3 grams of sodium (230.4 mEq) on the second day of treatment, and 4.4 grams of sodium (191.3 mEq) on the third day of treatment.

If sodium intake is a concern, please refer to Table 3 for the amount of sodium in each tablet *[see Description (11)]* and to Tables 1 and 2 for the recommended dosage in adults and pediatrics based on body weight in order to calculate the amount of sodium administered to an individual patient *[see Dosage and Administration (2.3)]*.

11 DESCRIPTION

Acetylcysteine is an antidote for the treatment of acetaminophen overdose. It is the N-acetyl derivative of the naturally-occurring amino acid, cysteine. Acetylcysteine is a white crystalline powder that is freely soluble in water, alcohol, practically insoluble in chloroform and in ether with the molecular formula $C_5H_9NO_3S$, a molecular weight of 163.2, and chemical name of N-acetyl-L-cysteine. Acetylcysteine has the following structural formula:



CETYLEV (acetylcysteine) effervescent tablets for oral solution contain 500 mg or 2.5 grams of acetylcysteine. The following are inactive ingredients: sodium bicarbonate, maltodextrin, lemon flavor, sucralose, peppermint flavor, and edetate disodium.

The amount of sodium in each tablet of CETYLEV is shown in Table 3.

Table 3: Amount of Sodium Per CETYLEV Tablet

Tablet Strength	Sodium Bicarbonate (mg)*	Sodium (mg)	Sodium (mEq)
500 mg	320 mg	88 mg	3.8 mEq
2.5 grams	1600 mg	438 mg	19 mEq

*inactive ingredient

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Acetylcysteine has been shown to reduce the extent of liver injury following acetaminophen overdose. Acetaminophen doses of 150 mg/kg or greater have been associated with hepatotoxicity. Acetylcysteine probably protects the liver by maintaining or restoring the glutathione levels, or by acting as an alternate substrate for conjugation with, and thus detoxification of, the reactive metabolite of acetaminophen.

12.3 Pharmacokinetics

Absorption
After administration of a single oral dose of 11 grams of CETYLEV (dissolved in 300 mL of water) to 29 healthy adult subjects, the mean C_{max} (CV%) was 26.5 (29) mcg/mL and mean (CV) AUC_{inf} was 186 (29) hr•mcg/mL. The median (range) time to reach C_{max} (T_{max}) was 2 (1 to 3.5) hours.

Distribution
The steady-state volume of distribution (V_d) following administration of an intravenous dose of acetylcysteine was 0.47 liter/kg. The protein binding for acetylcysteine ranges from 66% to 87 %.

Elimination
Metabolism
Acetylcysteine (i.e., *N*-acetylcysteine) undergoes extensive first pass metabolism and is postulated to form cysteine and disulfides (N,N-diacetylcysteine and *N*-acetylcysteine). Cysteine is further metabolized to form glutathione and other metabolites.

Excretion
After a single oral dose of [^{35}S]-acetylcysteine 100 mg, between 13 to 38% of the total radioactivity administered was recovered in urine within 24 hours. In a separate study, renal clearance was estimated to be approximately 30% of total body clearance.

In healthy subjects given a single oral dose of 11 grams of CETYLEV, the mean (CV%) terminal plasma half-life ($T_{1/2}$) was 18.1 (22%) hours.

Specific Populations
Hepatic Impairment
Following a 600 mg intravenous dose of acetylcysteine to subjects with mild (Child Pugh Class A, n=1), moderate (Child-Pugh Class B, n=4) or severe (Child-Pugh Class C; n=4) hepatic impairment and 6 healthy matched controls, mean $T_{1/2}$ increased by 80%. Also, the mean CL decreased by 30% and the systemic acetylcysteine exposure (mean AUC) increased 1.6-fold in subjects with hepatic impairment compared to subjects with normal hepatic function. These changes are not considered to be clinically meaningful.

Renal Impairment

Hemodialysis may remove some of total acetylcysteine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Carcinogenicity studies in laboratory animals have not been performed with acetylcysteine.

Mutagenesis
Acetylcysteine was negative in the Ames test.

Impairment of Fertility
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.

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).

16 HOW SUPPLIED/STORAGE AND HANDLING

CETYLEV effervescent tablets are supplied as white, round, flat tablets with a lemon mint smell packaged in 2-count peelable foil blister packs in the following dosage strengths:

- 500 mg tablets debossed with “I” on one side; Each carton containing 2-count blister packs (24338-700-02)
  - NDC 24338-700-10: 10 pack carton containing 20 tablets
- 2.5 gram tablets debossed with “O” on one side; Each carton containing 2-count blister packs (24338-725-02)
  - NDC 24338-725-10: 10 pack carton containing 20 tablets

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 tablets in original blister package until use.

Dilutions of acetylcysteine should be used freshly prepared and utilized within two hours.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions
Advise patients that hypersensitivity reactions, including generalized urticaria may occur and to report any signs or symptoms to their healthcare provider immediately *[see Warnings and Precautions (5.1)]*.

Manufactured for:

Atlanta, GA 30328

Made in Switzerland by Alpex Pharma SA.

CET-PI-02
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