

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207916Orig1s000

PHARMACOLOGY REVIEW(S)

**ADDENDUM TO PHARMACOLOGY/TOXICOLOGY REVIEW OF
NDA 207,916 DATED 11/19/2015**

Reviewer: Yuk-Chow Ng, Ph.D.

Date: 1/28/2016

The purpose of this addendum is to revise the maximum daily intake of the excipients in Cetylev, as stated in the Pharmacology/Toxicology review of NDA 207,916 dated 11/19/2015 (pages 11-14). The recommended dosages of Cetylev for adult and pediatric patients are about 140 mg/kg for the loading dose and about 70 mg/kg for the maintenance dose repeated every 4 hours for a total of 17 doses. Thus, the total dose on the first day of treatment is about 560 mg/kg, which is the maximum single-day dose given over the three-day course of treatment. Therefore, the maximum total acetylcysteine dose ingested in one day was calculated to be 33.5 g based on a 60-kg bodyweight, as stated on page 11 of the Pharmacology/Toxicology review. To achieve this dose, thirteen 2.5 g tablets and two 500 mg tablets would be ingested. Based on this dosing regimen, the maximum daily intake of the excipients was calculated to be the following: 21.4 g sodium bicarbonate, (b) (4), (b) (4) mg sucralose, (b) (4) mg lemon flavor, and (b) (4) mg peppermint flavor. Because maltodextrin (b) (4), the maximum total daily intake of maltodextrin was calculated to be in the range of approximately (b) (4) g (b) (4).

However, the proposed label recommends administration of only the 2.5 g tablets for patients with a bodyweight in the range of 60 to 69 kg, with a total of 16 tablets administered on the first day of therapy (the maximum single-day administration). Therefore, the maximum daily intake of each excipient was recalculated to reflect the actual recommended dose regimen on day 1 for patients weighing 60-69 kg. The recalculated values are as follows: 25.6 g sodium bicarbonate, (b) (4) g maltodextrin, (b) (4) mg lemon flavor, (b) (4) mg sucralose, (b) (4) mg peppermint flavor (b) (4), and (b) (4).

The supporting safety information described in the Pharmacology/Toxicology review (section 2.4) provides a reasonable assurance of safety for the recalculated maximum daily intake of excipients, which are approximately 20% higher than the original calculated values. The stated loading dose (140 mg/kg) and maintenance dose (70 mg/kg) of acetylcysteine in the labeling applies to adults and pediatric patients down to a bodyweight of 1 kg, and the recommended weight-based dosing regimens are designed to approximate the loading and maintenance doses (e.g. 10 g acetylcysteine as the loading dose and 5 g acetylcysteine as the maintenance dose for patients weighing 60-69 kg). Therefore, the assurance of safety for the intake of excipients is

applicable to adult and pediatric patients, since the excipient dose in mg/kg will be similar throughout the range of bodyweights of patients receiving Cetylev treatment.

Yuk-Chow Ng, Ph.D.
Pharmacologist
Division of Gastroenterology and Inborn Errors Products

David B. Joseph, Ph.D.
Lead Pharmacologist
Division of Gastroenterology and Inborn Errors Products

cc:
NDA 207,916
DGIEP
DGIEP/PM
DGIEP/D. Joseph
DGIEP/Y.-C. Ng
DGIEP/J. Korvick
R/D Init.: D. Joseph 1/28/16

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUK-CHOW NG
01/28/2016

DAVID B JOSEPH
01/28/2016
I concur.

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 207,916
Supporting document/s: 2
Applicant's letter date: 3/30/2015
CDER stamp date: 3/30/2015
Product: CETYLEV (acetylcysteine) effervescent tablets,
for oral solution
Indication: Antidote to prevent or lessen hepatic injury
(b) (4) ingestion of a potentially
hepatotoxic quantity of acetaminophen
Applicant: Arbor Pharmaceuticals, LLC
Review Division: Gastroenterology and Inborn Errors Products
Reviewer: Yuk-Chow Ng, PhD
Supervisor/Team Leader: David B. Joseph, PhD
Division Director: Donna Griebel, MD
Project Manager: Anissa Davis

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 207,916 are owned by Arbor Pharmaceuticals, or are data for which Arbor Pharmaceuticals has obtained a written right of reference. Any information or data necessary for approval of NDA 207,916 that Arbor Pharmaceuticals does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 207,916.

TABLE OF CONTENTS

| | | |
|-----------|--|-----------|
| 1 | EXECUTIVE SUMMARY | 3 |
| 1.1 | INTRODUCTION | 3 |
| 1.2 | BRIEF DISCUSSION OF NONCLINICAL FINDINGS | 3 |
| 1.3 | RECOMMENDATIONS | 3 |
| 2 | DRUG INFORMATION | 10 |
| 2.1 | DRUG | 10 |
| 2.2 | RELEVANT INDs, NDAs, BLAs AND DMFs | 10 |
| 2.3 | DRUG FORMULATION | 10 |
| 2.4 | COMMENTS ON NOVEL EXCIPIENTS | 11 |
| 2.5 | COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN | 14 |
| 2.6 | PROPOSED CLINICAL POPULATION AND DOSING REGIMEN | 18 |
| 2.7 | REGULATORY BACKGROUND | 18 |
| 3 | STUDIES SUBMITTED | 19 |
| 4 | PHARMACOLOGY | 19 |
| 5 | PHARMACOKINETICS/ADME/TOXICOKINETICS | 19 |
| 6 | GENERAL TOXICOLOGY | 19 |
| 7 | GENETIC TOXICOLOGY | 19 |
| 8 | CARCINOGENICITY | 19 |
| 9 | REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY | 19 |
| 10 | SPECIAL TOXICOLOGY STUDIES | 19 |
| 11 | INTEGRATED SUMMARY AND SAFETY EVALUATION | 19 |
| 12 | APPENDIX/ATTACHMENTS | 22 |

1 Executive Summary

1.1 Introduction

Cetylev effervescent tablets contain acetylcysteine formulated for oral administration. Acetylcysteine is an approved drug indicated to prevent or lessen hepatic injury (b) (4) ingestion of a potentially hepatotoxic quantity of acetaminophen. Cetylev has been developed for use as an antidote for acetaminophen overdose, and contains inactive ingredients intended to improve the palatability in comparison to the approved oral acetylcysteine drug products (solutions) for the same indication.

This NDA is submitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The Sponsor did not conduct nonclinical studies to support the current application. This NDA is supported by reference to the Agency's previous findings of safety and available publications of nonclinical studies of acetylcysteine. The reference drug is Mucomyst (NDA 13601), which has been discontinued from marketing.

1.2 Brief Discussion of Nonclinical Findings

The Sponsor did not conduct nonclinical studies to support this application. However, the Sponsor submitted two publications that provided studies on embryo-fetal development and fertility. Results from these studies were incorporated into our recommended changes in labeling sections 8.1 and 13.1.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical standpoint, there are no approvability issues.

1.3.2 Additional Nonclinical Recommendations

Recommendations for labeling changes are shown in the following section.

1.3.3 Labeling

Established Pharmacologic Class (HIGHLIGHTS)

The Sponsor's proposed EPC (established pharmacologic class) text phrase in the Highlights of Prescribing Information is (b) (4). The current official EPC list (eList) contains the following three EPC (FDA) text phrases for acetylcysteine:

antidote
antidote for acetaminophen overdose
mucolytic

The appropriate EPC text phrase for Cetylev is “antidote for acetaminophen overdose”, which is also the EPC text phrase for Acetadote (acetylcysteine) Injection, a product with the same indication as Cetylev. The labels for the reference product (Mucomyst) and other approved oral drug products (solutions) containing acetylcysteine were not written in PLR format, and therefore do not have an EPC text phrase.

Sponsor’s Proposed Version:

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

CETYLEV, an (b) (4), is indicated to prevent or lessen hepatic injury (b) (4) ingestion of a potentially hepatotoxic quantity of acetaminophen (1.1)

Recommended Version:

HIGHLIGHTS OF PRESCRIBING INFORMATION

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 (1.1)

Sponsor’s Proposed Version:

8.1 Pregnancy

Risk Summary

(b) (4)

Animal Data

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Evaluation:

This subsection should be revised to comply with the PLLR format. Published data for embryo-fetal development studies of acetylcysteine in rats and rabbits (Bonanomi and Gazzaniga. Toxicological, pharmacokinetic and metabolic studies on acetylcysteine. Eur J Respir Dis, 1980; 61 (Suppl 111): 45-51) should be added to this subsection. Data from studies

(b) (4)

Human dose multiples should be expressed based on body surface area. The recommended revisions to this subsection were developed in collaboration with the Maternal Health team (Suchitra Balakrishnan and Tamara Johnson).

Recommended Version:**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.

Sponsor's Proposed Version:



Evaluation:

[Redacted] (b) (4)

Sponsor's Proposed Version:

12.1 Mechanism of Action

[Redacted] (b) (4)

Acetylcysteine has been shown to reduce the extent of liver injury following acetaminophen overdose. [Redacted] (b) (4)

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.

Evaluation:

The statement, [Redacted] (b) (4)
[Redacted] (b) (4)
(communication from [Redacted] (b) (4))
Dr. Lara Dimick, medical reviewer for this application).

The recommended version below was developed in collaboration with the medical and clinical pharmacology teams.

Recommended Version:

12.1 Mechanism of Action

Acetylcysteine has been shown to reduce the extent of liver injury following acetaminophen overdose. 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.

(b) (4)

(b) (4)



Sponsor's Proposed Version:

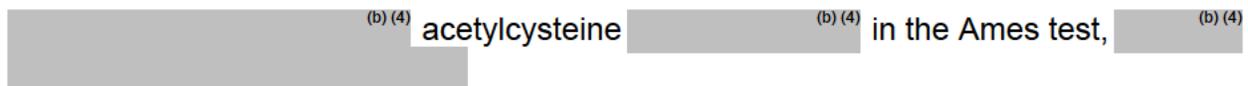
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

(b) (4)



(b) (4) acetylcysteine (b) (4) in the Ames test, (b) (4)



Evaluation:

The proposed version is incomplete due to the absence of information about fertility studies. Relevant animal data on fertility effects should be (b) (4) this subsection. It should be noted that this data is limited to male rats (Bonanomi and Gazzaniga, Eur J Respir Dis, 1980; 61 (Suppl 111): 45-51). In response to an information request, the Sponsor conducted a literature search for

nonclinical studies and submitted a publication by Harada et al. (Infertility observed in reproductive toxicity study of N-Acetyl-L-Cysteine in rats. *Biology of Reproduction*, 2003; 69: 242-247). This publication reported a profound inhibition of fertility in female rats treated with intravenous acetylcysteine. The results from this study are not included in the labeling for the reference product (Mucomyst) or for other approved acetylcysteine drug products. However, given the high quality of the study design, the main findings should be included in this subsection. Regarding the rat fertility data (b) (4) (Bonanomi and Gazzaniga (*Eur J Respir Dis*, 1980; 61 (Suppl 111): 45-51), the cited study was conducted in male rats, and this should be stated in the labeling.

The statement that indicates (b) (4) Human dose multiples should be expressed based on body surface area.

Recommended Version:

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.

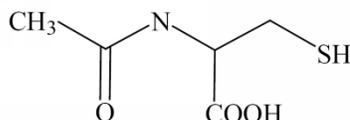
In a reproduction study of acetylcysteine, male rats were treated orally for 15 weeks prior to mating and during the mating period. A slight non-dose related reduction in fertility was observed at oral doses of 500 and 1000 mg/kg/day (0.1 and 0.3 times the recommended human dose, respectively, based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

Sponsor's Proposed Version:

(b) (4)

Evaluation:

(b) (4)

2 Drug Information**2.1 Drug****CAS Registry Number:** 616-91-1**Generic Name:** Acetylcysteine**Code Name:** None**Chemical Name:** N-acetyl-L-cysteine**Molecular Formula/Molecular Weight:** C₅H₉NO₃S / 163.2**Structure or Biochemical Description****Pharmacologic Class:** Antidote for acetaminophen overdose**2.2 Relevant INDs, NDAs, BLAs and DMFs**

IND 116,902 (Acetylcysteine effervescent tablets for oral solution for preventing or lessening hepatic injury [redacted] (b) (4) ingestion of a potentially hepatotoxic quantity of acetaminophen); Arbor Pharmaceuticals, LLC.

2.3 Drug Formulation

Cetylev Effervescent Tablets, 0.5 and 2.5 g, are formulated using acetylcysteine, sodium bicarbonate, maltodextrin, sucralose, [redacted] (b) (4), lemon flavor, and peppermint flavor. The composition of the tablets is shown in the table below (taken from the Sponsor's report).

Table 1: Quantitative Composition for Acetylcysteine Effervescent Tablets, 500 mg and 2.5 g

| Component | Quality Standard | Function | Amount (mg) per tablet | | % w/w (for both tablets) |
|--------------------|-------------------|----------|------------------------|--------------|--------------------------|
| | | | 500 mg tablet | 2.5 g tablet | |
| Acetylcysteine | USP | API | 500.00 | 2500 | 54.35% |
| Sodium bicarbonate | USP | (b) (4) | 320.00 | 1600 | 34.78% |
| Maltodextrin | NF | (b) (4) | | | (b) (4) |
| Lemon flavor | In-House Standard | (b) (4) | | | (b) (4) |
| Sucralose | NF | (b) (4) | | | (b) (4) |
| Peppermint flavor | In-House Standard | (b) (4) | | | (b) (4) |
| Edetate disodium | USP | (b) (4) | | | (b) (4) |
| | | (b) (4) | | | (b) (4) |
| | | (b) (4) | | | (b) (4) |

2.4 Comments on Novel Excipients

The recommended dosages of Cetylev for adult and pediatric patients are about 140 mg/kg for the loading dose and about 70 mg/kg for the maintenance dose repeated every 4 hours for a total of 17 doses. Thus, the total dose on the first day of treatment is about 560 mg/kg, which is the maximum single-day dose given over the three-day course of treatment. Therefore, the maximum total acetylcysteine dose ingested in one day will be 33.5 g, based on a 60-kg bodyweight. To achieve this dose, thirteen 2.5 g tablets and two 500 mg tablets will be ingested. Thus, the maximum daily intake of the excipients will be the following: 21.4 g sodium bicarbonate, (b) (4), (b) (4) mg sucralose, (b) (4) mg lemon flavor, and (b) (4) mg peppermint flavor. Because maltodextrin (b) (4), the maximum total daily intake of maltodextrin will be in the range of approximately (b) (4) g (b) (4).

Sodium bicarbonate: The maximum daily intake of sodium bicarbonate is 21.4 g for the proposed formulation. Sodium bicarbonate is designated as a direct food substance affirmed as GRAS, to be used with no limitations other than current good manufacturing practice (21 CFR 184.1736). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) established an ADI (acceptable daily intake) of “not limited” for sodium bicarbonate, since this food substance is considered to have very low toxicity (9th

JECFA, 1965). Therefore, there are no safety concerns regarding the maximum daily intake of sodium bicarbonate from the proposed formulation.

Maltodextrin: The maximum daily intake of maltodextrin is in the range of approximately (b) (4) g for the proposed formulation. Maltodextrin is designated as GRAS for its intended use as a direct food substance, with no limitation for use other than current GMP (21 CFR 184.1444). Therefore, there are no safety concerns regarding the maximum daily intake of maltodextrin from the proposed formulation.

(b) (4): The maximum daily intake of (b) (4) is (b) (4) mg for the proposed formulation, which is higher than the maximum potency (b) (4) mg in the FDA Inactive Ingredient Database. JECFA recommends that (b) (4) be permitted as a food additive and established an ADI of (b) (4) mg/kg, or (b) (4) mg/day based on a 60-kg bodyweight (17th JECFA, 1973). Therefore, there are no concerns regarding the maximum daily intake of (b) (4) from the proposed formulation.

Sucralose: The maximum daily intake of sucralose is (b) (4) mg for the proposed formulation. The FDA established the ADI for sucralose as a food sweetener at 5 mg/kg/day (Federal Register, Vol. 63, No. 64, April 3, 1998), or 300 mg/day based on a 60-kg bodyweight. For the safety assessment of sucralose intake from Cetylev, the critical issue to consider is the duration of treatment, which is only three days. In contrast, the ADI is a limit established to ensure the safety of lifetime daily exposure to food additives or substances. It should also be noted that the daily intake of sucralose will be reduced on days 2 and 3 of treatment with Cetylev due to the lower dose regimen on these days. Therefore, there are no concerns regarding the maximum daily intake of sucralose (day 1 only) from the proposed formulation, even though it is (b) (4) % higher than the ADI.

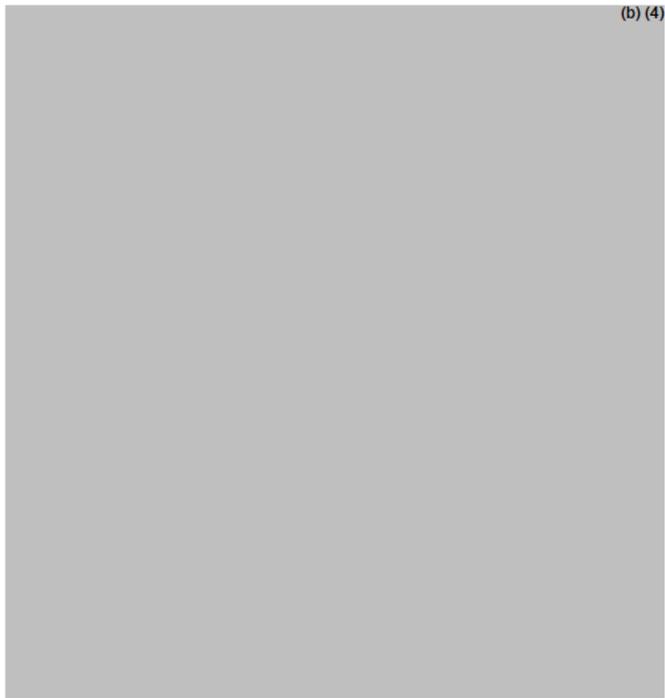
Lemon flavor: The maximum daily intake of the lemon flavor is (b) (4) mg for the proposed formulation. The lemon flavor contains ingredients that are shown in the following table (taken from Sponsor's submission).

INGREDIENT DECLARATION

Herein we declare that the product named

PRODUCT CODE : 1013043
PRODUCT NAME : LEMON FLAVOUR (b) (4)

is compound by :



The Sponsor did not specify the percentages for each ingredient. However, each of the ingredients is designated as GRAS according to the listed CFR citation, and, in some cases, by FEMA (Flavoring and Extracts Manufacturers Association). Therefore, there are no concerns regarding the maximum daily intake of the lemon flavor from the proposed formulation.

(b) (4) peppermint flavor: The maximum daily intake of the (b) (4) peppermint flavor ((b) (4)) is (b) (4) mg for the proposed formulation. The peppermint flavor was reviewed by CMC under DMF # (b) (4) (review dated 7/22/2008), for which the Sponsor has the right of reference (letter dated 2/13/2013). The DMF was judged to be “adequate” by the CMC reviewer. The peppermint flavor comprises the following ingredients (table taken from the CMC review of the DMF):

| Compound | Composition | FEMA # |
|----------|-------------|--------|
| (b) (4) | | |

The Sponsor did not specify the exact percentages for each ingredient. However, based on the composition shown in the table above, the maximum potential daily intake

for [REDACTED] (b) (4) will be [REDACTED] (b) (4) mg, respectively.

As indicated above, [REDACTED] (b) (4)

In summary, there are no safety concerns regarding any of the excipients in the proposed formulation.

2.5 Comments on Impurities/Degradants of Concern

The Sponsor listed [REDACTED] (b) (4) as impurities in the acetylcysteine drug product. The Sponsor proposed an acceptance limit of \leq [REDACTED] (b) (4) % for each of these impurities. The chemical structures of these impurities are shown in the table below (taken from the Sponsor's submission).

| Chemical Name | Chemical Structure | Acceptance Limit |
|---------------|--------------------|------------------|
| (b) (4) | | |

Based on the recommended dose of acetylcysteine for this drug product, the qualification threshold for degradation products is 0.15% according to ICH guidance Q3B(R2). However, the first FDA-approved drug product containing acetylcysteine was approved long before publication of the ICH guidances. Thus, impurity safety assessment and qualification for products containing acetylcysteine is generally exempt from ICH recommendations (i.e. M7, Q3A(R2), and Q3B(R2)).

(b) (4)

(b) (4)

[REDACTED] (b) (4)

(b) (4) are commonly present in foods. It was estimated that the mean daily combined intake of (b) (4) from food and supplements is (b) (4) g/day for all age and gender groups. Men 51 through 70 years of age had the highest intakes at the 99th percentile of (b) (4) g/day (Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids, The National Academy of Sciences, Institute of Medicine, Food and Nutrition Board, 2005). By comparison, exposure to (b) (4) as impurities from the highest daily dose of Cetylev is estimated to be (b) (4) g/day. Thus, the maximum possible combined intake of (b) (4) ((b) (4) mg) from the Sponsor's drug product is about (b) (4) % of the mean daily human dietary intake of (b) (4).

In addition, the FDA's food additive regulation (b) (4) cites (b) (4) as food additives permitted for direct addition to food for human consumption.

[REDACTED] (b) (4)
Based on the considerations described above, (b) (4) are considered as qualified at the Sponsor's proposed limit of \leq (b) (4) % for each as an individual impurity.

[REDACTED] (b) (4)

[REDACTED] (b) (4)

In a randomized, double-blind clinical trial, 153 patients with asymptomatic hypercholesterolemia received (b) (4) mg/day (b) (4) orally as a

(b) (4) for 24 weeks ((b) (4)). The (b) (4) mg daily doses of the (b) (4) are equivalent to (b) (4) mg and (b) (4) mg of the (b) (4), respectively. No serious adverse events in any of the treatment groups were reported in this 24-week clinical trial. The daily oral dose of (b) (4) mg in the clinical trial was comparable to the maximum oral dose of (b) (4) from the drug product at the proposed limit of (b) (4) %.

Taken together, these data indicate that (b) (4), and is therefore considered as qualified at the Sponsor's proposed limit of \leq (b) (4) %.

(b) (4)

(b) (4) is a known impurity in the synthesis of the acetylcysteine drug substance ((b) (4)). The acetylcysteine degradation pathway indicated that (b) (4) is also a degradation product. This degradation pathway also produces (b) (4) (figure taken from the above mentioned publication).

(b) (4)

The Sponsor proposed that these same reactions are likely to occur in vivo. The sponsor further suggested that it is chemically and biologically reasonable to expect that (b) (4) in acetylcysteine clinical PK studies. However, the Sponsor provided no direct evidence to support these speculations.

Information on the level of (b) (4) impurity in the commercial preparations containing acetylcysteine is generally difficult to obtain. However, (b) (4) reported that the

permissible (b) (4) impurity level was \leq (b) (4) % w/w (relative to acetylcysteine weight) in the pharmaceutical products, as shown in the table below from the publication.

(b) (4)

(b) (4)

The total single day oral exposure was (b) (4) mg/kg (human equivalent dose = (b) (4) mg/kg), which was approximately (b) (4) times the expected maximum oral exposure of (b) (4) mg/kg (b) (4) (based on body surface area comparison) at the proposed (b) (4) % limit in the drug product. Thus, these data provide some assurance of safety for the limit of \leq (b) (4) % (b) (4) in the drug product.

Taken together, these published reports support the qualification of (b) (4) at the proposed limit of \leq (b) (4) % in the drug product.

2.6 Proposed Clinical Population and Dosing Regimen

For adult and pediatric patients, the loading dose is about 140 mg/kg and the maintenance doses are about 70 mg/kg repeated every 4 hours for a total of 17 doses, given orally. Based on the patient's body weight, the appropriate number of 2.5 gram and 0.5 gram CETYLEV effervescent tablets will be dissolved in 300 mL ((b) (4) kg body weight) or 150 mL (20-59 kg body weight) of water and administered to adult and pediatric patients (b) (4). For (b) (4) body weights of 1 to 19 kg, two 2.5 gram effervescent tablets will be dissolved in 100 mL of water. Using an oral syringe, the appropriate dose volume will be withdrawn to administer 140 mg/kg and 70 mg/kg for the loading and maintenance doses, respectively.

2.7 Regulatory Background

This NDA is submitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The Sponsor did not conduct any new nonclinical studies to support the current

application. This NDA is supported by reference to the Agency's previous findings of safety and available publications of nonclinical studies of acetylcysteine. The reference drug is Mucomyst (NDA 13601), which is a 20% or 10% acetylcysteine solution for inhalation when used as a mucolytic agent. The 20% solution is also indicated for oral administration in the treatment of acetaminophen overdose. Mucomyst has been discontinued from marketing.

3 Studies Submitted

No new studies were submitted.

4 Pharmacology

No new studies were submitted.

5 Pharmacokinetics/ADME/Toxicokinetics

No new studies were submitted.

6 General Toxicology

No new studies were submitted.

7 Genetic Toxicology

No new studies were submitted.

8 Carcinogenicity

No new studies were submitted.

9 Reproductive and Developmental Toxicology

No new studies were submitted.

10 Special Toxicology Studies

No new studies were submitted.

11 Integrated Summary and Safety Evaluation

Cetylev effervescent tablets contain acetylcysteine formulated for oral administration. Acetylcysteine is an approved drug indicated to prevent or lessen hepatic injury (b) (4) ingestion of a potentially hepatotoxic quantity of acetaminophen. Cetylev has been developed for use as an antidote for acetaminophen overdose, and contains inactive ingredients intended to improve the palatability in

comparison to the approved oral acetylcysteine drug products (solutions) for the same indication.

Acetaminophen is extensively metabolized in the liver to form principally the sulfate and glucuronide conjugates which are excreted in urine. A small fraction of an ingested dose is metabolized in the liver by isozyme CYP2E1 of the cytochrome P-450 mixed function oxidase enzyme system to form a reactive, potentially toxic, intermediate metabolite. Following the ingestion of a large overdose, the glucuronide and sulfate conjugation pathways are saturated, resulting in a larger fraction of the drug being metabolized via the cytochrome P-450 pathway, and, therefore, the amount of acetaminophen metabolized to the reactive intermediate increases. The increased formation of the reactive metabolite may deplete the hepatic stores of glutathione, with subsequent binding of the metabolite to proteins within the hepatocyte resulting in cellular necrosis. Acetylcysteine protects the liver by maintaining or restoring the levels of glutathione, or by acting as an alternate substrate for conjugation with, and thus detoxification of, the reactive metabolite.

The dosages of Cetylev for adult and pediatric patients are about 140 mg/kg for the loading dose and about 70 mg/kg for the maintenance dose repeated every 4 hours for a total of 17 doses. These dosages are identical to that of the approved acetylcysteine solution as an antidote for acetaminophen overdose. In addition, the Sponsor has demonstrated that Cetylev is bioequivalent to Acetylcysteine Solution 20% (ANDA 203,853) (see Biopharmaceutics review by Mei Ou). The comparator product in the bioequivalence study was used in place of Mucomyst, the reference drug product that has been discontinued from marketing. The Agency concurred with use of the generic drug product as the comparator in the bioequivalence study, since it was approved through a biowaiver link and with reliance on Mucomyst as the reference listed drug. Therefore, there are no significant safety concerns regarding acetylcysteine, the active pharmaceutical ingredient in the drug product.

Nonclinical toxicology of acetylcysteine has been described in the Mucomyst label and in published reports (Bonanomi and Gazzaniga, *Eur J Respir Dis*, 1980, 61 (Suppl 111): 45-51; Johnston et al., *Seminars in Oncology*, 1983, 10 (Suppl 1): 17-24). There were no clinically significant general toxicities with acetylcysteine. In a fertility study, rats were treated intravenously with 0, 100, 300, or 1000 mg/kg/day acetylcysteine (Harada et al. *Biology of Reproduction*, 2003; 69: 242-247). Male rats were treated from four weeks before mating to 22-25 days after mating and female rats were treated from two weeks before mating to gestation day 17. Mating was unaffected, and acetylcysteine had no effects on the reproductive ability of male rats. However, 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 the effect on female fertility was not evaluated. The severe fertility effects in female rats are notable, given that these occurred at a dose (HED = 161 mg/kg) that is substantially lower than the daily dose that humans will receive on each day of treatment

(approximately 560, 420, and 350 mg/kg on days 1, 2, and 3, respectively). In addition, the intravenous route of administration in the rat fertility study does not diminish the relevance of the study results with respect to possible fertility effects in female humans, where substantial drug absorption is clearly expected with oral administration of Cetylev and other acetylcysteine drug products. However, any risk of impaired fertility may be considered as acceptable, given that the indication, acetaminophen overdose, can be a life-threatening condition. The results from the rat fertility study by Harada et al. (Biology of Reproduction, 2003; 69: 242-247) are not included in the labeling for the reference product (Mucomyst) or for other approved acetylcysteine drug products. However, given the high quality of the study design, the main findings should be included in the Cetylev label.

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 (Bonanomi and Gazzaniga, Eur J Respir Dis, 1980; 61 (Suppl 111): 45-51).

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) (Bonanomi and Gazzaniga, Eur J Respir Dis, 1980; 61 (Suppl 111): 45-51).

Acetylcysteine was negative in the Ames test (Bonanomi and Gazzaniga, Eur J Respir Dis, 1980; 61 (Suppl 111): 45-51). However, carcinogenicity studies in animals have not been performed with acetylcysteine.

CETYLEV (acetylcysteine) effervescent tablets for oral solution contain acetylcysteine, sodium bicarbonate, maltodextrin, sucralose, (b) (4), lemon flavor, and peppermint flavor. There are no safety concerns regarding any of the excipients. Sodium bicarbonate, maltodextrin, sucralose, and (b) (4) are considered safe because they are either GRAS designated as a direct food substance, will be consumed at below the recommended ADI levels, and/or will be consumed only in a very short duration based on the recommended duration of treatment with Cetylev (three days). Each of the ingredients in the lemon flavor is designated as GRAS according to 21 CFR, and, in some cases by FEMA. Each of the ingredients in the (b) (4) peppermint flavor is designated as GRAS according to 21 CFR. Therefore, there are no safety concerns regarding any of the excipients in the proposed formulation.

The Sponsor identified (b) (4) as impurities in the Cetylev drug product. The Sponsor proposed an acceptance limit of \leq (b) (4) % for each of these impurities. Based on the recommended dose of acetylcysteine for this drug product, the qualification threshold for degradation products is 0.15% according to ICH guidance Q3B(R2). However, the first FDA-

approved drug product containing acetylcysteine was approved long before publication of the ICH guidances. Thus, impurity safety assessment and qualification for products containing acetylcysteine is generally exempt from ICH recommendations (i.e. M7, Q3A(R2), and Q3B(R2)). The available safety information on the impurities provides a reasonable assurance of safety for the proposed acceptance limit of \leq (b) (4) %. Therefore, the impurities are considered as qualified at the proposed limit.

In summary, based on FDA's previous finding of safety for Mucomyst, the available published nonclinical reports, and the clinical experience with acetylcysteine, Cetylev appears to be safe for the proposed use.

Recommendations:

From a nonclinical standpoint, there are no approvability issues.

Suggested labeling: The labeling should be changed as described in the "EXECUTIVE SUMMARY" section of this review.

cc:

ORIG NDA 207,916

DGIEP

DGIEP/PM

DGIEP/D. Joseph

DGIEP/Y.-C. Ng

DGIEP/L. Dimick-Santos

DGIEP/S. Omokaro

OPQ/ONDP/DB/T. Ghosh

R/D INIT.: D. Joseph 10/30/15

12 Appendix/Attachments

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUK-CHOW NG
11/19/2015

DAVID B JOSEPH
11/19/2015
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 207916

**Applicant: Arbor
Pharmaceuticals, LLC**

Stamp Date: 3/30/2015

**Drug Name: Cetylev
(acetylcysteine)**

NDA Type: 505 (b)(2)

On **initial** overview of the NDA application for filing:

| | Content Parameter | Yes | No | Comment |
|---|--|------------|-----------|--|
| 1 | Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin? | | | N/A This application does not contain a pharmacology/toxicology section. |
| 2 | Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin? | | | N/A |
| 3 | Is the pharmacology/toxicology section legible so that substantive review can begin? | | | N/A |
| 4 | Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)? | | | N/A |
| 5 | If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA). | | | N/A |
| 6 | Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route? | | | N/A |
| 7 | Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations? | | | N/A This application does not include any pivotal pharm/tox studies. |

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

| | Content Parameter | Yes | No | Comment |
|----|---|------------|-----------|--|
| 8 | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | | | N/A |
| 9 | Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57? | | X | In the proposed labeling, human dose multiples are expressed based on mg/kg. |
| 10 | Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.) | X | | |
| 11 | Has the applicant addressed any abuse potential issues in the submission? | | X | |
| 12 | If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted? | | | N/A |

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes__

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Comment: None

Yuk-Chow Ng, Ph.D. 5/12/2015

 Reviewing Pharmacologist Date

David B. Joseph, Ph.D. 5/12/2015

 Team Leader/Supervisor Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUK-CHOW NG
05/13/2015
Fileable

DAVID B JOSEPH
05/13/2015