CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207916Orig1s000

SUMMARY REVIEW

Division Director (Signatory) Summary Review for Regulatory Action

Date	(electronic stamp)
From	Joyce Korvick, M.D., M.P.H. Deputy Director Division of Gastroenterology and Inborn Errors Products Office of New Drugs III Office of New Drugs/ CDER Food and Drug Administration
Subject	Division Director (Deputy Director) Summary Review
NDA #	**207916**
Applicant	Arbor Pharmaceuticals, Inc.
Date of Submission	March 30, 2015
PDUFA Goal Date	January 30, 2016
Proprietary Name / Non-Proprietary Name	Cetylev (acetylcysteine)
Dosage Form(s) / Strength(s)	Effervescent tablets for oral solution / 500 mg and 2.5 g
Applicant Proposed Indication(s)/Population(s)	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).
Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Lara Dimick-Santos, M.D.
Statistical Review	NA
Pharmacology Toxicology Review	Yuk-Cho Ng
OPQ Review	Xavier Ysern, Hitesh Shroff, Vaikunth Prabhu, Juandria Williams, Mei Ou, Rannan Bloom
Microbiology Review	Vaikunth Prabhu
Clinical Pharmacology Review	Elizabeth Y. Shang
OPDP	Meeta N. Patel
OSI	Gajendiran Mahadevan, Ziaohan Cai
CDTL Review	Tapash K Ghosh
OSE/DMEPA	Matthew Barlow
DPMH	Donna Snyder, Suchitra M Balakrishnan
DMMP	Shawna Hutchins

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
DMEPA=Division of Medication Error Prevention and Analysis
DMPP (Division of Medical Policy Programs

1. Benefit-Risk Summary and Assessment

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).

Cetylev (acetylcysteine) effervescent tablets for oral solution is a new oral formulation of acetylcysteine. It has been found to be bioequivalent to the currently approved reference product which was shown in a single-center, open-label randomized, two-arm, single-dose, two-period crossover relative bioavailability study comparing AR10 (Cetylev) to the reference product. The results demonstrated the mean relative bioavailability and the 90% confidence interval (CI) were calculated as 92.64% (86.84%–98.84%) for Cmax, 92.11% (86.18%-98.44%) for AUClast, and 92.28% (86.39%– 98.56%) for AUCinf.

Acetylcysteine products have been on the market since the 1950's, and have a well know adverse reaction profile. There are rare hypersensitivity reactions, mainly occurring with the intravenous formulations. Occasionally severe and persistent vomiting occurs as a symptom of acute acetaminophen overdose. Treatment with acetylcysteine 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.). Gastrointestinal intolerance with nausea and vomiting are the main adverse reaction to the oral formulation and frequently patients require conversion to intravenous treatment. Adverse events of nausea and vomiting occurred at similar frequencies while receiving AR10 and reference product (13.8% in AR10 and 10.0% in reference product; vomiting 3.4% in AR10 and 3.3% in reference product). There were no apparent differences in time to onset or duration for AEs of diarrhea, flatulence, nausea and dizziness after administration of AR10 or reference product. No new safety issues were raised during the review of this application.

Significant issues regarding the administration of the currently approved oral formulation include limited palatability and medication error. The bad odor and taste of oral acetylcysteine are a known deterrent to the successful administration of the currently approved oral solutions. The sponsor added lemon and mint flavoring in an attempt to improve the palatability. Surveys regarding taste, flavor and smell were performed by the applicant (b) (4)

Medication error reports with the currently marketed orally available acetylcysteine reported inaccurate dosing due to the complicated preparation and administration regimen. (b) (4) Standard pharmacovigilance monitoring of medication error reports will be followed post marketing.

In conclusion, the bioequivalence of Cetylev (acetylcysteine) effervescent tablets for oral solution and the safety profile are the same as the currently marketed oral solution of acetylcysteine. There

were no new safety issues identified. Therefore the risk-benefit assessment favors approval of Cetylev.

2. Background

Disease and mechanism of action
Acetaminophen hepatotoxicity is caused by acetaminophen metabolite N-acetylparabenzoquinonimine (NAPQI); systemic exposure to NAPQI increases under conditions of acetaminophen overdose. At nominal clinical acetaminophen doses only, small amounts of NAPQI are produced and endogenous glutathione converts this small amount to harmless metabolites preventing hepatic damage. However, with excessive acetaminophen doses NAPQI exposure increases and endogenous glutathione stores may deplete resulting in even greater NAPQI exposure resulting in NAPQI-induced hepatotoxicity. NAPQI mediated depletion of glutathione is foremost in the pathology of acetaminophen induced hepatotoxicity. Additional intra-hepatocellular toxic events occurring during overdose include production of reactive oxygen and nitrogen radicals, mitochondrial oxidative stress, elicitation of stress proteins and gene transcription mediators, and mobilization of the hepatic immune system.

The complex balance between these pathways determines whether NAPQI-affected hepatic cells survive or die. Acetylcysteine acts by providing cysteine to replenish and maintain hepatic glutathione stores. It also enhances the acetaminophen sulfation elimination pathway and may also directly reduce NAPQI back to acetaminophen. By virtue of these mechanisms, the pharmacologic class of acetylcysteine for this indication is probably best termed an "acetaminophen antidote".

After an acute overdose, if acetylcysteine therapy is given within 8 hours there is a <10% incidence of hepatotoxicity; 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.

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.

Regulatory History
This 505b2 application relies on FDA's finding of efficacy and safety for Mucomyst (acetylcysteine) Solution Inhalation in NDA 13601; a supplement to this NDA was approved in 1984 for use as an oral solution as an antidote for acetaminophen overdose.

The development program for this 505b2 application consisted of (1) a change in formulation to develop CETYLEV effervescent tablets for oral solution with favorable taste and smell characteristics, and (2) comparative bioavailability study AR10.001 involving healthy adult subjects to assess the bioequivalence of CETYLEV in oral solution versus the reference listed acetylcysteine oral solution. This bioequivalence study is used to bridge CETYLEV to Mucomyst the innovator NDA 13601. As agreed with FDA during the January 29, 2013 meeting, Arbor Pharmaceuticals,

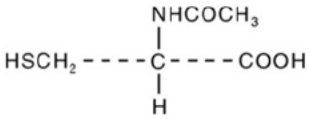
Inc. completed a comparative bioavailability study (AR10.001). The approach regarding this NDA program is consistent with FDA recommendations provided at the FDA pre-IND meeting held January 29, 2013.

At filing, discussions regarding the appropriate choice of comparator used to building the bridge with the RLD were held. Mucomyst, the RLD, is FDA approved but was discontinued from the market in 2009 (NDA 13-601). (b) (4) The applicant (b) (4) used another AN rated acetylcysteine solution Innopharma ANDA 203,853. ANDA 203,853 was granted a biowaiver. The sponsor submitted the rationale for their selection of the comparator product. Because of various constraints, the rationale supplied by the applicant is in alignment with FDA feedback. Another 20% AN rated therapeutic equivalent was selected as the reference product (FDA-approved Innopharma ANDA 203853) and used in AR10.001. This was acceptable to the FDA.

Orphan designation was granted February 24th, 2015 (#13-4017) based on the plausible hypothesis that AR10 may be clinically superior to the same drug that is already approved for the same orphan indication.

3. Product Quality

***Drug Substance*:**
Acetylcysteine is a white crystalline powder that is freely soluble in water, alcohol, practically insoluble in chloroform and in ether with the molecular formula C5H9NO3S, a molecular weight of 163.2, and chemical name of N-acetyl-L-cysteine. Acetylcysteine has the following structural formula:



The Drug Substance reviewer concluded: "Sufficient and adequate information on the quality of Acetylcysteine drug substance has been provided by the Applicant by authorized reference to (b) (4)'s Type II DMF (b) (4). DMF (b) (4) was reviewed on 27-Apr-2015 and the recommendation remains Acceptable. The quality of the described Acetylcysteine drug substance is deemed acceptable to support its use in the manufacture of the proposed drug product Acetylcysteine Effervescent Tablets as described under NDA 207-916."

***Drug Product*:**
CETYLEV (acetylcysteine) effervescent tablets for oral solution contain 500 mg or 2.5 grams of acetylcysteine. It includes the following inactive ingredients: sodium bicarbonate, maltodextrin, lemon flavor, sucralose, peppermint flavor, and edetate disodium. A clinically relevant amount of sodium is present in the tablets based on the sodium bicarbonate content.

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

The Drug Product reviewer concluded:
"The applicant has performed long-term stability at 25ºC up to 18 months, intermediate stability at 30ºC and accelerated stability at 40ºC up to 3 months on three registration batches (batch size ~ (b) (4) kg) to demonstrate that there is no degradation in the product quality during the time tested. Based on the satisfactory stability studies results, the 24-month expiration dating period was granted when stored at room temperature."

"The critical quality attributes e.g. assay, impurities, uniformity of dosage, disintegration and (b) (4) as well as critical purity attributes e.g. microbial contamination are controlled by the drug product specification. The acceptance limits and justification for the critical quality attributes are adequately provided. The drug product specification is adequate to assure the identity, strength, purity and quality during the entire shelf life."

"Information provided in manufacturing process and in-process controls are adequate"

***Facilities Review/Inspection*:**
The facilities review concluded: "There appear to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience. The facilities are determined acceptable to support approval of NDA 207916."

***Biopharmaceutics Assessment**:*
The applicant submitted a single Bioequivalence (BE) study (AR 10.001) "An Open Label, Randomized, Two-Arm, Single-Dose, Two-Period, Crossover Study to Determine the Relative Bioavailability of AR10 (Acetylcysteine) Effervescent Tablets for Oral Solution [0.5 g and 2.5 g]) as Compared to Reference Product (Acetylcysteine solution; Oral 20% [200mg/ml]) in Healthy Adult, Human Subjects, Under Fasting Conditions". This study was to bridge the proposed product CETYLEV (Acetylcysteine Effervescent Tablets) for oral solution to the reference listed drug (RLD) Mucomyst solution (NDA 13601, approved on 09/14/1963). The rationale for accepting the comparator is explained above and was found acceptable.

This study assessed the relative bioavailability of a single dose level of 11 g of test product (AR10, acetylcysteine effervescent tablets for oral solution [two 0.5 g and four 2.5 g tablets]), and 11 g of the reference product (acetylcysteine solution; oral 20% [55 mL of 200 mg/mL]) in healthy adult, human subjects under fasting conditions. Subjects received a single dose of study drug at each of two dosing periods for a total of 2 days of treatment. The duration of subject participation in the study was up to approximately 42 days, including an up to 30-day screening period, a 10-day treatment period (including two dosing visits), and a 2-day follow-up period. A wash-out period of 7 days was employed.

Thirty healthy subjects (15 subjects per treatment group) were enrolled, randomized and received study treatment. All 15 subjects in T1T2 completed Period 1 and Period 2 of the study. In T2T1, all 15 subjects completed Period 1, and 14 of 15 subjects completed Period 2 of the study. Twenty-nine of 30 subjects completed both periods of the study as planned, comprising the PK population. One subject (#119) in T2T1 discontinued the study during Period 2 due to adverse events (AEs) of syncope and seizure-like activity (Preferred Term [PT]: convulsion) that occurred prior to test drug AR10 administration. This subject was withdrawn from the study the following day. Mean (SD) age of subjects was 35.2 (9.14) years, and race, in descending order was 18 (60%) White and 12 (40%) Black/African American. Demographic and other baseline characteristics were similar between the T1T2 and T2T1 groups.

The results demonstrated the mean relative bioavailability and the 90% confidence interval (CI) were calculated as 92.64% (86.84%–98.84%) for Cmax, 92.11% (86.18%-98.44%) for AUClast, and 92.28% (86.39%– 98.56%) for AUCinf. The reviewers determined that this data supported the bioequivalence.

Regarding the professional labeling, the reviewers concluded that "In the Applicant's revised labeling section 12.3 (pharmacokinetics), the stated mean pharmacokinetic parameters, Cmax, AUCs, and plasma half-life (T1/2) obtained from the BE study AR10.001 are reviewed and found acceptable."

The biopharmaceutics reviewer also assessed the disintegration time of Cetylev and concluded that "The disintegration time of proposed effervescence tablets met the accepted specification for NMT (b) (4) minutes".

***Quality Microbiology*:**
This is a non-sterile oral product. The reviewer concluded that based on the information provided the overall assessment is considered adequate.

***Assessment of Environmental Analysis*:**
The reviewer found that "The application meets criteria for minimal environmental risk.
The cited categorical exclusion at 21 CFR 25.31(b) is appropriate for the anticipated amount of drug to be used, and a statement of no extraordinary circumstances has been submitted. The claim of categorical exclusion is acceptable."

Overall OPQ Recommendation:
Review #1:
Recommendation and Conclusion on Approvability

- The applicant has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product.

- The Office of Facility and Process has made a final overall manufacturing Inspection "Approval" recommendation for the facilities involved in this application.

- The claim for the Categorical Exclusion for the Environmental Assessment is granted.

- However, the label/labeling issues have not been completely resolved as of this review.

- Therefore, from the OPQ perspective this NDA is not deemed ready for approval at this time in its present from per 21 CFR 314.125(b)(6) until the above issues are satisfactorily resolved.

No Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps were recommended.

Review #2:

On January 15, 2016, revised package insert and the carton labels were submitted, and on January 27 2016, revised blisters labels were submitted also, which are acceptable from the CMC perspective except for the new dosage form nomenclature, effervescent tablets for oral solution. This was consulted to LNC and deemed acceptable.

Recommendation:
I concur with the conclusions reached by the OPQ chemistry and microbiology reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The sponsor did not conduct nonclinical pharmacology/toxicology studies to support the current application. This NDA is supported by reference to the Agency's previous finding of safety. In addition, the sponsor is relying upon one publication that describes the effects of acetylcysteine on embryo-fetal development in animals and the mutagenic activity of acetylcysteine in the Ames mutagenicity test, which support the current language in labeling Subsections 8.1 and 13.1[1]. The sponsor is also relying on a second publication that describes the effects of acetylcysteine on fertility in rats, which supports the current language in labeling Subsection 13.1[2]. The data described in the submitted literature is scientifically relevant to the proposed product because the studies used the same active pharmaceutical ingredient as contained in the Sponsor's drug product, and the doses used in the reported animal studies are scientifically relevant to the proposed human dose.

There are no safety concerns regarding any of the excipients in the proposed formulation. However, the amount of sodium contributed by the inactive ingredient, sodium bicarbonate, may be relevant in the care of patients. Based on dosing calculations in humans this wording was added to the prescribing information: "At the recommended dosage an average sized adult (b) (4) receive a total of 7 grams of sodium (304.3 mEq) on the first day of treatment, 5.3 grams

[1] Bonanomi and Gazzaniga. Toxicological, pharmacokinetic and metabolic studies on acetylcysteine. Eur J Respir Dis, 1980; 61 (Suppl 111): 45-51

[2] Fertility study in male and female rats: Harada et al. Infertility observed in reproductive toxicity study of N-Acetyl-L-Cysteine in rats. Biology of Reproduction, 2003; 69: 242-247.
Fertility study in male rats only: Bonanomi and Gazzaniga. Toxicological, pharmacokinetic and metabolic studies on acetylcysteine. Eur J Respir Dis, 1980; 61 (Suppl 111): 45-51

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".

The pharmacology/toxicology Reviewer, Dr. Yuk-Chow Ng, PhD mentions that there are no pharmacology/toxicology issues with this compound and Approval is recommended.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/toxicology issues that preclude approval.

5. Clinical Pharmacology

There were no new clinical pharmacology studies submitted to support this application. The Office of Clinical Pharmacology assisted with review of section 12.3 of the label. The reviewer commented that "Currently, Section 12.3 of acetylcysteine solution label contains information on (b) (4) However, this information is not consistent with current labeling regulation and guidance. The Agency requested the sponsor use pharmacokinetic information obtained from dosing healthy subjects with Cetylev tablets in the bioequivalence (BE) study and published literature data on the ADME of acetylcysteine in humans to write this section. Refer to Information Request sent on 9/25/2015. The sponsor submitted new proposed language". The reviewers were present for additional meetings after they finalized their review. Their recommended changes have been incorporated into the final labeling.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

This section is not applicable to the NDA under review.

7. Clinical/Statistical-Efficacy

There were no clinical studies conducted for the purpose of evaluating efficacy and safety. As noted above, this NDA relies on a single bioequivalence study (AR 10.001). The applicant is relying on previous finding of efficacy and safety of the referenced drug product.

A secondary endpoint of the BE study was to assess Cetylev for taste and smell characteristics compared to the control. (b) (4) To that end the applicant conducted a survey. Prior to the start of the study, all participants (volunteers and health care providers [HCPs]) were oriented to the purpose of their respective survey and how it should be completed. Participants were instructed not to discuss their opinions with others. Subjects were housed in private rooms to minimize communication and influence from other subjects. HCPs were also instructed not to discuss the product attributes or preferences with the volunteers. Compliance was monitored by study staff.

Following each dose on Day 1/Day 8, subjects were asked to evaluate the five attributes of each study product (taste, smell, flavor, texture and overall likeability of dose) using a 5 point hedonic

scale, with categories from dislike very much to like very much. After the second product was taken on Day 8, one additional question (Preferred Treatment Choice) asked which of the two products the subject would prefer to take (Period 1 or Period 2 (Preferred Treatment Choice). Surveys were completed within 15 minutes of dosing.

The applicant concluded that "Subjects preferred AR10 over the reference product for all five study drug attributes and the preference was statistically significant for four of these five attributes (taste, flavor, texture, and overall likeability) and approached statistical significance for the attribute of smell. Health care providers also preferred AR10 over the reference product in the categories of preparation, recommendation, accuracy of dosing, and overall preference."

The medical officer concluded that "While there was some preference for AR10 over the reference product (b) (4) " (see safety section for adverse reactions) I agree that the secondary aim of the study should be viewed with caution (b) (4)

I agree with the conclusions of the medical reviewer.

8. Safety

There were no clinical studies conducted for the purpose of evaluating efficacy and safety. Review of the comparative bioavailability study (AR 10.001) was performed by the medical reviewer, and no new safety issues were found. Acetylcysteine has a well-known safety profile. The most common adverse reactions were nausea, vomiting, other gastrointestinal symptoms, and rash with or without fever.

A total of 30 healthy adult male and female subjects were exposed to at least one dose of study drug during the BE study. Safety findings for this study include:

- There were no clinically significant findings or changes from baseline in ECG, PE, hematology and chemistry parameters, or vital signs. There were no post baseline abnormal CS PE findings.
- No deaths or other SAEs were reported.
- The incidence of TEAEs was similar while receiving AR10 and the reference product; 14/29 (48.3%) and 15/30, (50.0%), subjects respectively experienced 23 and 29 TEAEs, respectively.
- All TEAEs were considered by the investigator to be mild in intensity.
- All TEAEs reported by more than one subject overall were considered related to study drug.
- Most TEAEs were categorized in the gastrointestinal system organ class, which is not unexpected with oral acetylcysteine. TEAEs associated with AR10 and reported by more than one subject were diarrhea, nausea, abdominal pain upper, dysgeusia, and flatulence (in descending order). TEAEs associated with the reference product and reported by more than one subject included diarrhea, flatulence, nausea, dysgeusia, and headache (in descending order).

- TEAEs of nausea and vomiting occurred at similar frequencies while receiving AR10 and reference product (nausea in 4 [13.8%] subjects receiving AR10 and 3 [10.0%] subjects receiving reference product; vomiting in 1 [3.4%] subject receiving AR10 and 1 [3.3%] subject receiving reference product).
- There were no apparent differences in time to onset or duration for TEAEs of diarrhea, flatulence, nausea and dizziness after administration of AR10 or reference product.
- One subject was withdrawn from study drug due to a non-serious, mild, unrelated TEAE of syncope and seizure-like activity (PT: convulsion) that occurred before AR 10 (Cetylev) was administered in Period 2. The subject was withdrawn from the study the following day.
- No new safety signals with respect to AE profile, vital signs, PE, or ECG were detected as a result of this study. Additionally, no meaningful AE differences were observed between the AR10 and reference product groups, supporting a favorable safety profile for AR10.

The medical reviewer commented: (b) (4) [redacted]

The reviewer went on to comment that most likely the (b) (4) [redacted] "however the sponsor provided no documentation of this claim."

I agree with the conclusions of the medical reviewer.

9. Advisory Committee Meeting

Acetylcysteine is not an NME and no new safety or efficacy issues were identified, therefore it was not referred for review to an Advisory Committee.

10. Pediatrics

Pediatric Health Consult:

This product was granted Orphan Drug Status on 2/24/2015, and therefore the Pediatric Research Equity Act (PREA) does not apply. Based on the review of the RLD label, and literature the reviewer worked with DGIEP to enhance the wording in section 8.4 to read as follows:

> "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)*]."

Maternal Health Consult: Pregnancy and Lactation Labeling Rule (PLLR)

DGIEP consulted DPMH on April 12, 2015, to review the Pregnancy and Lactation subsections of labeling to ensure compliance with the Pregnancy and Lactation Labeling Rule formatting requirements and to provide comments to be included in the labeling that were sent to the applicant.

Based upon DPMH review the Cetylev labeling has been revised to comply with the PLLR. Recommendations were made for the following sections:

- Pregnancy, Section 8.1
  - The "Pregnancy" subsection of acetylcysteine labeling was formatted in the PLLR format to include "Risk Summary," "Clinical Considerations," and "Data" subsections.
- Lactation, Section 8.2
  - The "Lactation" subsection of acetylcysteine labeling was formatted in the PLLR format to include the "Risk Summary" subsection.

"DPMH revised subsections 8.1 and 8.2 (b) (4) in CETYLEV (acetylcysteine) labeling for compliance with the PLLR". The DPMH reviewer concluded (b) (4)

I have been involved in these discussions and negotiations and agree with the recommendations and final wording of the label. For final wording refer to the approved professional label.

11. Other Relevant Regulatory Issues

- *Office of Study Integrity and Surveillance (OSIS) Audits:* recommended that the data from study AR 10.001 was acceptable for review.

- *Financial Disclosure:* The financial disclosure was reviewed and found acceptable.

12. Labeling

The review of this label involved the conversion to PLR format, as compared to the reference product, and updating the Pediatric section of the label to PLLR format. Additional considerations are listed below.

(b) (4)

Prescribing Information

- INDICATIONS AND USAGE section*:*
  - *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).*
  - *The use of Cetylev includes adult and pediatric patients.*
  - *There is no need for a limitation of use given the risk-benefit profile of this drug.*
- DOSAGE AND ADMINISTRATION section:
  - *I agree with the proposed recommended dose regimens. They are based largely on the literature and clinical experience. The 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.) is included and used in the description the regimens. During the review this section of the labeling was improved for consistency and readability compared to the RLD label.*
- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections:
  - *This label does not contain a BOXED WARNING or CONTRAINDICATIONS.*
  - *The WARNINGS AND PRECAUTIONS section* (b) (4) . *No new items were added.*
- Information regarding the amount of sodium bicarbonate and sodium (inactive ingredients) was added to the labeling in sections 3 DOSAGE FORMS AND STRENGTHS (reference to sections 8.6 and 11), 8.6 Patients Sensitive to High Sodium Intake, 11 DESCRIPTION.

- Patient labeling Instructions for Use: These instructions were reviewed by the DMPP, OPDP. They made recommendations to the sponsor which would improve the readability of the label to patients. They also agreed with the division that the issue regarding sodium be reflected in this labeling and worked with the division to include a statement alerting the patient to (b) (4) have high blood pressure, kidney or heart problems, or have been told to lower the amount of salt (sodium) in your diet."

- *Carton and container labeling:*
  The proprietary name, Cetylev, was deemed acceptable by the Davison of Medication Error Prevention and analysis (DMEPA). Comments were sent to the sponsor regarding the cartoon labeling which the applicant accepted. These are considered resolved and final changes were found acceptable. Finally, DMEPA reviewed the prescribing information and found it to be acceptable from a medication error perspective. OPQ also found this labeling acceptable.

13. Postmarketing

- **Postmarketing Risk Evaluation and Mitigation Strategies**

  A Risk Evaluation and Mitigation Strategy (REMS) was deemed to be unnecessary for the approval of Cetylev based on the FDA's findings of safety and effectiveness of the currently

approved acetylcysteine drug products approved for use in patients after ingestion of a potentially hepatotoxic quantity of acetaminophen in patients with acute ingestion or from repeated supratherapeutic ingestion (RSI). Professional labeling is an appropriate strategy given that Cetylev will be administered to patients in the emergency care setting. The medical reviewer recommended that it would be acceptable to perform the routine post-marketing surveillance for evidence regarding possible medication errors. *I concur.*

- **Other Postmarketing Requirements and Commitments**

  No postmarketing required studies or postmarketing commitments were deemed necessary for this new formulation of a currently marketed product. *I concur.*

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/s/

JOYCE A KORVICK
01/29/2016