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APPLICATION NUMBER:

207916Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 30, 2015
From	Tapash K. Ghosh, Ph.D. Biopharmaceutics Branch Chief (Acting), OPQ
Subject	Cross-Discipline Team Leader Review
NDA	NDA 207916
Type of Submission	505(b)(2)
Applicant	Arbor Pharmaceuticals, Inc.
Date of Submission	March 30, 2015
PDUFA Goal Date	January 30, 2016
Proprietary Name / Established (USAN) names	Cetylev (acetylcysteine)
Dosage forms / Strength	Effervescent Tablets / 500 mg and 2.5 g
Proposed Indication(s)	Antidote to prevent or lessen hepatic injury (b) (4) ingestion of a potentially hepatotoxic quantity of acetaminophen.
Recommendation:	**APPROVAL** is recommended with labeling changes from all disciplines

This secondary CDTL review is based, on the primary reviews/memos of:

DICIPLINE	PRIMARY REVIEWER	FINAL REVIEW DATE
Pharmaceutical Quality (PQ)		11/12/2015
Drug Substance	Xavier Ysern	
Drug Product	Hitesh Shroff	
Process	Vaikunth Prabhu	
Microbiology	Vaikunth Prabhu	
Facility	Juandria Williams	
Biopharmaceutics	Mei Ou	
Application Technical Lead	Hitesh Shroff	
Environmental Assessment (EA)	Rannan Bloom	
Pharmacology/Toxicology	Yuk-Chow Ng, Ph.D.	11/19/2015
Clinical Pharmacology	Elizabeth Shang, Ph.D.	1/5/2016
Clinical	Lara Dimick-Santos, MD	11/23/2015
Division of Pediatric and Maternal Health (DPMH)	Donna Snyder, MD Suchitra M. Balakrishnan, MD, Ph.D	10/29/2015 11/12/2015
Office of Prescription Drug Promotion (OPDP)	Meeta N. Patel	12/07/2015
Division of Medical Policy Programs (DMPP)	Shawna Hutchins, MPH, BSN, RN	12/07/2015
Division of Medication Error Prevention and Analysis (DMEPA)	Matthew Barlow, RN, BSN	6/10/2015 (proprietary name) 12/18/2015 (labels & labeling)
Labeling (OSE)	Sherly Abraham	Outstanding
505(b)(2) Assessment	Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.	12/23/2015
Exclusivity	Joyce Korvick, M.D.	Outstanding
Regulatory Project Manager	Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.	Outstanding

Cross Discipline Team Leader Review (CDTL)

1. Introduction

The Applicant, Arbor Pharmaceuticals, LLC, submitted this original **NDA 207916** on 03/30/2015 for their proposed drug product, CETYLEV (Acetylcysteine Effervescent Tablets, 500mg and 2.5g), for the indication as an antidote to prevent or lessen hepatic injury (b) (4) ingestion of a potentially hepatotoxic quantity of acetaminophen.

This NDA 207916 is a 505(b)(2) application. No safety and efficacy study was conducted in support of this current application. A comparative pivotal bioequivalence (BE) study AR10.001 was submitted. The purpose of this BE study (AR10.001) 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).

505(b)(2) assessment was finalized on 12/23/2015 recommending approval.

Division of Medication Error Prevention and Analysis (DMEPA) has determined that the proposed proprietary name, Cetylev (acetylcysteine), for NDA 207916 is acceptable.

2. Background

Acetaminophen hepatotoxicity is caused by acetaminophen metabolite N-acetyl-parabenzoquinonimine (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 causing 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 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, and patients who recover generally do well and do not develop chronic liver dysfunction.[1]

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

The development program for this 505b2 application consisted of (1) formulation work 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 solution given orally. The approach regarding this NDA program is consistent with FDA feedback at the FDA meeting held January 29, 2013 (see FDA minutes dated 27Feb2013, PIND 116902).

No efficacy and/or safety trials were conducted on CETYLEV effervescent tablets for oral solution.

As discussed with FDA at the January 29, 2013 meeting for the acetaminophen overdose indication, this CETYLEV 505b2 application relies on FDA's finding of efficacy and safety for Mucomyst innovator NDA 13601. To bridge CETYLEV to Mucomyst innovator NDA 13601, as agreed with FDA at the January 29, 2013 meeting, Arbor completed a comparative bioavailability study (AR10.001).

3. Pharmaceutical Quality

General Quality Considerations

Drug Substance: The active pharmaceutical ingredient in the drug product is Acetylcysteine, USP. Acetylcysteine 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. It is manufactured by (b) (4) . The Applicant provided sufficient information on the raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug product. The CMC information is provided in DMF (b) (4) The DMF was reviewed on April 27, 2015 and found to be adequate by Dr. Xavier Ysern.

Drug Product: Acetylcysteine effervescent tablets are supplied in two strengths, 500 mg and 2.5 g. They are white, round, flat tablets with lemon and peppermint flavors. The 500 mg tablets are debossed with "I" on one side and the 2.5 g tablets are debossed with "O" on one side. Each tablet contains 500 mg or 2.5 g of acetylcysteine, USP and the following inactive ingredients: sodium

bicarbonate, maltodextrin, lemon flavor, sucralose, peppermint flavor and edetate disodium.

Acetylcysteine effervescent tablets are packaged in 2-count blister packs with one individual tablet in each cavity. The drug product will be supplied in cartons containing 5 blister packs (10 tablets) or 10 blister packs (20 tablets) per carton of 500 mg or 2.5 g tablets.

The drug product manufacturing process involves (b) (4)

Stability: The applicant has provided results of the long-term stability study at 25ºC/60% RH up to 18 months, intermediate stability study at 30ºC/65% RH up to 12 months and accelerated stability study at 40ºC/75% RH up to 3 months for three stability batches of 500 mg and 2.5 g tablets to assure identity, strength, purity, and quality of the drug product through the approved shelf life. Based on the stability data submitted, 24-month expiration dating period was proposed and deemed well justified when stored at room temperature in the proposed container closure system, blister packs and cartons. The overall conclusion from a CMC perspective is that the manufacturing and controls appear to be sufficient and risks are adequately mitigated to maintain adequate product quality through the life cycle (with required regulatory changes).

The NDA is recommended for **approval** from Drug Product point of view by Dr. Hitesh Shroff.

Facilities Review/Inspection: 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 by Dr. Juandria Williams.

Quality Microbiology: Microbiology testing was performed per the current USP General Chapter <61> and USP General Chapter <62>. In accordance with USP <1111> for Microbial Examination of Nonsterile Products, and based on stability data to date, the required testing for solid oral dosage forms are Total Aerobic Microbial Count, Total Yeast and Mold, and Escherichia Coli. Firm has included these tests and associated specifications are proposed for all commercial batches at release. All registration batches (Sublots A & B for Batch # 028L13, 029L13 and 030L13 for 500 mg strength and Sublots A & B for Batch # 031L13, 031L13 and 033L13 for 2.5 g strength) demonstrate compliance with the limits.

Overall, the Quality Microbiologist, Dr. Vaikunth S. Prabhu in her review dated 08/23/2015, stated that information provided in microbiology section was adequate from a Product Quality Microbiology perspective and recommended **approval** for this application.

Assessment of Environmental Analysis: Acetylcysteine does not appear to have estrogenic, androgenic, or thyroid hormone pathway activity. Non-clinical studies indicate low reproductive toxicity and no teratogenic effects. The reviewer, found no information to

indicate 'extraordinary circumstances'. The application meets criteria for minimal environmental risk. Overall, the quality EA reviewer, Raanan A. Bloom concluded that the cited categorical exclusion at 21 CFR 25.31(b) is appropriate for the anticipated amount of drug to be used. The claim of categorical exclusion is acceptable and recommended **approval** for this application.

Biopharmaceutics: The Biopharmaceutics primary basis in support of this new drug application comes from; 1) the evaluation of the pivotal bioequivalence (BE) study (AR10.001) titled as "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" and 2) the proposed disintegration method and acceptance criterion.

The regulatory history of using ANDA 203853 as reference drug for BE study in this NDA 207916 submission

Because this NDA 207916 is a 505(b)(2) application, the original listed drug being relied upon was NDA 013601 Mucomyst Oral Inhalation Solution 10% and 20% (Apothecon, approved on 09/14/1963), which had been discontinued from marketing.

The ANDAs being designated as the RLDs in the Orange Book are:

- ANDA 72489 acetylcysteine inhalation solution 10% (Luitpold, approved on 07/28/1995)
- ANDA 72547 acetylcysteine inhalation solution 20% (Luitpold, approved on 07/28/1995) – drug shortage

Other ANDAs not being designated as RLD's in the Orange Book involved in this NDA are:

- ANDA 203853 acetylcysteine inhalation solution 20% (Innopharmaa, approved on 06/21/2012)
- ANDA 72324 acetylcysteine inhalation solution 20% (Roxane, approved on 04/30/1992) – discontinued

During 01/29/13 pre-IND 116902 meeting, the Applicant asked if [redacted] (b) (4) to be relied could be [redacted] (b) (4). FDA advised the Applicant that it is appropriate to use the ANDA product [redacted] (b) (4) in the Orange Book as the comparator in bridging studies when the innovator product has been discontinued.

The Applicant then asked if it was acceptable to use Roxane's ANDA 72324 (20%), a non-RLD, in their comparison testing [redacted] (b) (4). FDA agreed.

When this NDA 207916 was submitted, it was discovered that while the Applicant was able to use Roxane's ANDA 72324 (20%), non-RLD, for the physical and chemical testing, the

Applicant used Innopharma's ANDA 203853 (20%), another non-RLD, in their BE study. Roxane's ANDA 72324 (20%) became unavailable (Roxane's ANDA 72324 is now listed as discontinued in the Orange Book). The Applicant explained that (b) (4) they chose Innopharmaa's ANDA 203853 (20%), non-RLD, (b) (4)

The review team found it is acceptable from a scientific perspective that the Applicant's use of Roxane's ANDA 72324 (20%) in the physical/chemical testing and Innopharmaa's ANDA 203853 (20%) in the BE study.

It is noted that Innopharma's ANDA 203853 (20%) was granted for waiver of bioequivalence testing compared to the RLD Luitpold's ANDA 72547 (20%) by the Division of Bioequivalence II (DB II) based on the biowaiver per Section 21 CFR 320.22(b)(3) (submitted on 01/06/2012, approved on 03/19/2012).

Test Product, Dose and Mode of Administration, Lot Number: The test products AR10, acetylcysteine effervescent tablets, used were 0.5 g (Lot number 030L13) and 2.5 g (Lot number 033L13), expiration date: (b) (4).

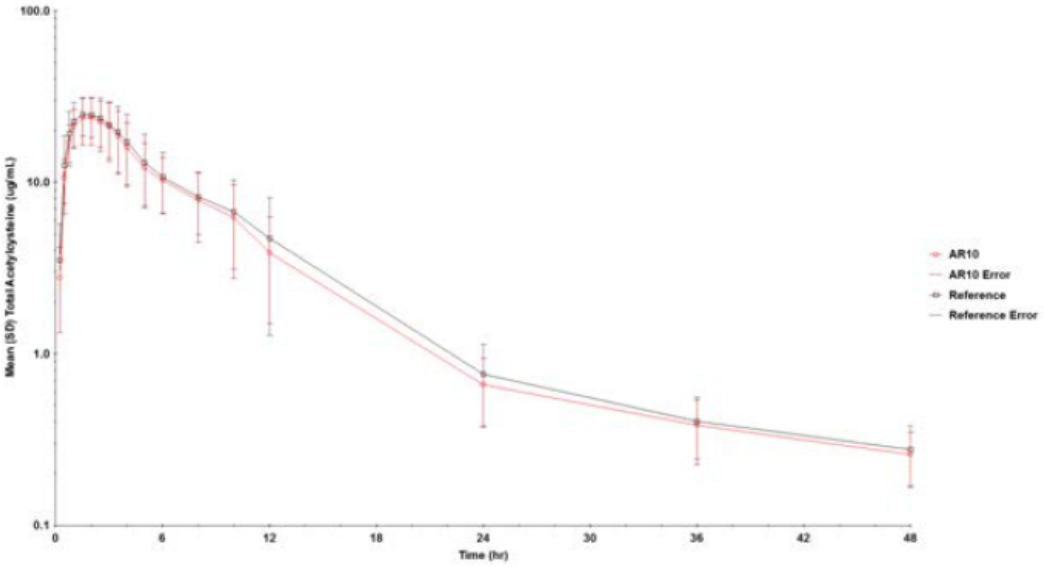
After an overnight fasting for at least 10 hours, subjects were orally administered a solution of 11 g (four 2.5 g and two 0.5 g tablets) of AR10 effervescent tablets in 300 mL water. After the complete dose was consumed, the dosing glass was rinsed with 100 mL of water and the water was swallowed.

Reference Therapy, Dose and Mode of Administration, Lot Number: The reference product is acetylcysteine 20% inhalation solution (200 mg/mL, Lot number SG362, Expiration date: June 2015). After an overnight fasting for at least 10 hours, subjects were orally administered 55 mL of 20% acetylcysteine solution (total of 11 g acetylcysteine) diluted with 165 mL of diet caffeine-free soft drink. After consuming this, 80 mL of room temperature water were poured into the same container and swallowed, for a total volume of 300 mL (equal to the test product oral volume intake). After the complete dose was consumed, the dosing glass was rinsed with 100 mL of water and the water was swallowed.

BE Study Results

Plasma Concentration: Plasma samples were assayed for total acetylcysteine using validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) procedures by the Applicant. Total acetylcysteine concentration-vs-time profiles, showing mean (±SD) concentration values for the PK population, are presented in linear and semilog scales in the following Figure.

Figure: Mean (±SD) Concentrations of Total Acetylcysteine – Semilog Scale (PK Population)



BE Analysis and Results: BE results of the test and the reference products with respect to C_{max}, AUC_{last}, and AUC_{inf} are listed in Table below. The mean relative bioavailability and the 90% confidence interval (CI) were calculated as 92.64% (86.84%–98.84%) for C_{max}, 92.11% (86.18%-98.44%) for AUC_{last}, and 92.28% (86.39%–98.56%) for AUC_{inf}.

Table: Total Acetylcysteine Bioequivalence Confidence Intervals (PK Population)

							90% CI		
Test	Reference	Parameter	Units	Ref LSM	AR10 LSM	Ratio [% Ref]	Lower Bound	Upper Bound	ANOVA CV%
AR10	Reference	AUC_{inf}	h*ug/mL	192.15	177.31	92.28	86.39	98.56	14.81
		AUC_{last}	h*ug/mL	185.54	170.90	92.11	86.18	98.44	14.94
		C_{max}	ug/mL	27.46	25.44	92.64	86.84	98.84	14.54

ANOVA = analysis of variance; CI = confidence interval; CV = coefficient of variation; LSM = least squares means; Ln = natural logarithm; LSM = least square mean; PK = pharmacokinetic; Ref = reference

The median difference in T_{max} values between the test and the reference product was small (0.50 hr).

The results from this study demonstrated acceptable bioequivalence between the proposed drug and the reference drug.

On 05/19/2015, the Division of Biopharmaceutics requested the Office of Study Integrity and Surveillance (OSIS) for the Biopharmaceutical Inspections on both the Clinical Site (Spaulding Clinical) and the Bioanalytical Site ((b) (4)). On 07/01/2015, the OSIS recommended to accept data without an on-site inspection for the Clinical Site (Spaulding Clinical, 525 S. Silverbrook Drive, West Bend, WI 53095). On 08/31/2015, the OSIS recommended that the analytical data from study AR10.001 be accepted for further Agency review, after inspecting the Bioanalytical Site ((b) (4)).

As both 0.5 g and 2.5 g tablets were used in the BE study, there was no biowaiver issue.

2. Disintegration Testing of Drug Product

The drug product is designed to disintegrate in water prior to oral administration. The disintegration (effervescence) time is therefore proposed instead of dissolution time. The disintegration testing was performed according to (b) (4) disintegration method 12101115. The proposed disintegration method and specification are summarized in Table 2 below:

Table 2: The Proposed Disintegration Method and Specification

Test	Disintegration (effervescence) time
Method Number	12101115
Analytical Conditions and Procedure	• Purified Water (150 and 300 mL) • Temperature between 15 and 25oC • When the evolution of gas around the tablet or its fragments ceases the tablet has disintegrated, being either dissolved or dispersed in the water so that no agglomerates of particles remain
Tested Samples	N = 3 per strength of tablets
Specification	NMT (b) (4) minutes (for both 0.5 and 2.5 g tablets)

The proposed disintegration (effervescence) acceptance limit for drug quality control is **NMT (b) (4) minutes** based on European Pharmacopoeia current edition were found acceptable for Quality Control (QC) regulatory purposes.

The Biopharmaceutics Reviewer recommended Approval of this NDA. For full details refer to the Biopharmaceutics review by Dr. Mei Ou dated 11/20/2015.

Overall OPQ Recommendation:

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

The biopharmaceutics review recommended approval of the application.

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 .

4. Nonclinical Pharmacology/Toxicology

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. There are no safety concerns regarding any of the excipients in the proposed formulation.

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. The sponsor is also relying on one publication that describes the effects of acetylcysteine on fertility in rats, which supports the current language in labeling Subsection 13.1. 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.

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

5. Clinical Pharmacology

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) reviewed Section 12.3 of Cetylev. 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. The sponsor responded. OCP found the labeling language in this section acceptable from an OCP standpoint. Final labeling revisions are ongoing.

The Clinical Pharmacology review by Dr. Elizabeth Shang is finalized on 1/5/2016 recommending approval.

6. Clinical

There were no clinical studies conducted for the purpose of evaluating efficacy and safety. The sponsor has performed a single bioequivalence study to support the application.

The sponsor had one pre-IND meeting with the Division prior to the application in which the regulatory requirements for a 505(b)(2) application were discussed. The Division agreed that the sponsor could use (b) (4) Acetylcysteine Solution; Inhalation, Oral 20% ANDA 72-524, as an AN (therapeutic equivalent code for solutions and powders for aerosolization) rated product, Mucomyst, the Reference Listed Drug (RLD), is FDA-approved but discontinued in the market (NDA 13-601). (b) (4) they used another AN rated acetylcysteine solution Innopharma ANDA 203,853. ANDA 203,853 was granted a biowaiver.

The Division requested the applicant to explain the use of ANDA 203,853 in the filling letter dated 5/29/2015 and the applicant responded as below:

> Since Mucomyst solution was discontinued in 2009 and was unavailable, (b) (4) the Agency agreed (FDA minutes dated 27Feb2013, page 4, PIND 116902) that an AN rated acetylcysteine solution product (therapeutic equivalent code for solutions and powders for aerosolization) could be used as the marketed equivalent of the RLD in AR10.001 (ANDA 72-324; Bedford Laboratories, manufactured for Roxane Laboratories, Inc.).
>
> (b) (4) Therefore, 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. Please refer to section 2.5 for further discussion on use of the selected comparator.

The Applicant also stated that they used ANDA 72-324 for the physical and chemical testing.

The 505(b)(2) review team reviewed the applicants use of the above ANDAs and found Arbor's use of Roxane's ANDA 72324 in the physical/chemical testing and Innopharm's ANDA 203853 in the BE study acceptable from a scientific perspective. (issue Number 56, dated 6/17/2015 (Appendix 1).

The applicant provided a patent certification for NDA 13-601 that stated there were no patents on the NDA.

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.

DSI reviewed the request to inspect the bioequivalence study site and declined to inspect the site as OSIS had recently inspected the site. The inspectional outcome from the inspection was classified as Voluntary Action Indicated (VAI). Although, the last inspection was classified as a VAI, the observations identified during the previous inspection had no impact on data reliability. Therefore based on the previous recommendation to the review division to accept the data for review, an inspection of the site will not be needed at this time.

The clinical review included the evaluation of the safety assessments of adverse events for a comparative bioavailability study (AR10.001) conducted to bridge CETYLEV to Mucomyst innovator NDA 13601. A total of 30 healthy adult male and female subjects were exposed to at least one dose of study drug during this study. No deaths or other serious adverse events were reported in this pharmacokinetic study. For full details on the safety assessments refer to the Clinical review dated 11/23/2015 by Lara Dimick-Santos, MD.

The Dosage and Administration Section of the labeling was updated with information on acute acetaminophen ingestion, (b) (4) and repeated supratherapeutic ingestion (RSI).

In addition the following sections were added to update the labeling to reflect current knowledge and practice.

<u>Continued Therapy After Completion of Loading and Maintenance Doses</u>
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. Acetaminophen levels and ALT/AST & INR should be checked after the last maintenance dose. If acetaminophen levels are still detectable, or (b) (4) 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."

(b) (4)

Dr. Dimick-Santos in her review recommends **Approval** of this 505 (b)(2) application for CETYLEV (N-acetylcysteine) Effervescent tablets (oral) for the indication of Antidote to prevent or lessen hepatic injury (b) (4) ingestion of a potentially hepatotoxic quantity of acetaminophen.

7. Clinical Microbiology

No new micro studies were submitted in the NDA and the Applicant is relying on previous findings of efficacy and safety.

8. Clinical Statistical

There were no clinical studies conducted for the purpose of evaluating efficacy and safety. Therefore, this submission did not require statistical evaluation.

9. Safety

There were no clinical studies conducted for the purpose of evaluating efficacy and safety. The Applicant is relying on FDA's previous findings of safety and effectiveness for the listed drug product. However, the safety of the comparative bioavailability study (AR10.001) was evaluated in the clinical review. No deaths or serious adverse events were reported in these studies.

10. Advisory Committee Meeting

Current submission did not go to an Advisory Committee Meeting.

11. Pediatrics

Cetylev® (N-acetylcysteine effervescent tablets) is considered to be a new dosage form under PREA. The sponsor submitted an initial Pediatric Study Plan (iPSP) on June 23, 2014 requesting a full waiver for studies in pediatric patients. DGIEP met with the Pediatric Review Committee (PeRC) on September 3, 2015 to discuss the iPSP. PeRC did not agree that a full waiver was acceptable for this product but did determine that a partial waiver would be appropriate for pediatric patients under 1 year of age because US prevalence of using oral acetylcysteine to treat acetaminophen overdose in patients less than 1 year of age is small. A partial waiver is unnecessary in pediatric patients 1 year of age and older, because sufficient data exists in pediatric patients over 1 year of age to consider the product fully assessed and no further studies would be needed. Thus, DGIEP sent a non-agreed iPSP letter to the sponsor on September 19, 2014 requesting that the sponsor update the iPSP. On February 24, 2015, the sponsor was granted orphan designation for the product, and as a result is not subject to requirements under PREA. However the sponsor plans to label the product for use in both the pediatric and adult populations.

Acetylcysteine (Acetadote®, NDA 21539) was approved (January 23, 2004) as an injectable formulation in adult and pediatric patients to be administered intravenously

within 8 to 10 hours after ingestion of a potentially hepatotoxic quantity of acetaminophen, to prevent or lessen hepatic injury. Acetadote® labeling includes dosing down to a weight of 5 kg. The product is given as 3 separate doses totaling 300 mg/kg over 21 hours.

Of note, acetylcysteine injection (Acetadote®) was issued the following PREA PMR at the time of approval:

- A deferred pediatric study under PREA for the use of acetylcysteine injection, administered intravenously within 8 to 10 hours after ingestion of a potentially hepatotoxic quantity of acetaminophen, to prevent or lessen hepatic injury in pediatric patients ages 1 month to 16 years

The sponsor submitted data on July 19, 2004 to fulfill the PREA PMR and the PREA requirement was considered fulfilled on December 2, 2004.

The memorandum and labeling review by Dr. Donna L. Snyder from DMPH finalized on 10/29/2015 reflect the recommendations provided to the Division.

DGIEP also 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 was sent to the applicant.

DPMH concludes that the (b) (4)

DPMH concludes that there is insufficient information to make a clear assessment of risk associated with acetylcysteine use in pregnancy, due to the lack of controlled data, which may be difficult to obtain in patients with acetaminophen overdose. However, there are important clinical considerations in the context of this emergency indication, to prevent or lessen hepatic injury (b) (4) ingestion of a potentially hepatotoxic quantity of acetaminophen. DPMH recommends including a statement about increased risk for maternal and fetal morbidity/ mortality when treatment is delayed in patients with potentially hepatotoxic acetaminophen plasma levels.

DPMH recommends that breastfeeding should not be contraindicated during drug therapy with acetylcysteine, considering the short duration of therapy (17 doses) for an emergency indication, and the short terminal half-life of acetylcysteine (6.25 hrs).

Dr. Suchitra M. Balakrishnan from DPMH revised subsections 8.1 and 8.2 (b) (4) in CETYLEV (acetylcysteine) labeling for compliance with the PLLR. DPMH refers to the final NDA action for final labeling.

12. Other Relevant Regulatory Issues

- **505(b)(2) Assessment:** The required assessment for 505(b)(2) NDA submissions was already completed and filed in DARRTS on 12/23/2015 by Ms. Anissa Davis, RPM.

- There are no other additional relevant regulatory issues with this application.

13. Labeling

Office of Prescription Drug Promotion (OPDP): OPDP has reviewed the proposed draft PI for CETYLEV (acetylcysteine) effervescent tablets, for oral solution, and have no additional comments. Comments on the draft PPI were sent under separate cover as a joint review with DMPP.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on April 12, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for CETYLEV (acetylcysteine) effervescent tablets, for oral solution.

The PPI is acceptable with recommended changes.

Division of Medication Error Prevention and Analysis (DMEPA): DMEPA found areas of the proposed labels that can be revised to improve clarity and organization, thus increasing understanding of the provided information.

- **Conclusion:** At the time of this review, a draft proposal labeling in the PLR format for labeling changes that include the overall labeling recommendations have been conveyed to the Applicant and the Applicant responded on December 30, 2015. A final agreement with the Applicant should be reached on the recommended labeling changes before a regulatory action is taken for this NDA.

14. Recommendations/Risk Benefit Assessment

- ***Recommended Regulatory Action:*** APROVAL with labeling changes is recommended for NDA 207916 for Cetylev (acetylcysteine) Effervescent Tablets (0.5 g and 2.5g).

- ***Risk Benefit Assessment:*** This application for acetylcysteine effervescent tablets relies on FDA's previous findings of safety and effectiveness for the reference drug,

Mucomyst solution (NDA 13601). No additional safety concerns are expected to be associated with N-acetylcysteine Effervescent Tablets / 500 mg and 2.5 g tablets.

- ***Recommendation for Postmarketing Risk Evaluation and Management Strategies***: Based on the information available in the current submission and the understanding of acetylcysteine approved therapy, there are no specific recommendations for post-market risk evaluation and mitigation strategies.

- ***Recommended Comments to Applicant:*** No comments need to be conveyed to the Applicant in the regulatory action letter. However, it is noted that the Applicant has been asked to revise the product's labeling as recommended by the Division.

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/s/

TAPASH K GHOSH
01/05/2016