

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207916Orig1s000

MEDICAL REVIEW(S)

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 207916

Submission Date(s): March 30, 2015

Applicant: Arbor Pharmaceuticals, Inc.

Product: Cetylev (acetylcysteine) effervescent tablets

Reviewer: Dr. Lara Dimick-Santos

Date of Review: 01/20/2016

Covered Clinical Study (Name and/or Number): AR10.001 bioequivalence study – single-center, open-label, cross-over study

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>1</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p style="padding-left: 40px;">Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p style="padding-left: 40px;">Significant payments of other sorts: <u>0</u></p> <p style="padding-left: 40px;">Proprietary interest in the product tested held by investigator: <u>0</u></p> <p style="padding-left: 40px;">Significant equity interest held by investigator in sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.¹ Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

This was a single-center, open-label, bioequivalence study performed by Carlos, Sanabria, MD for the sponsor (Arbor Pharmaceuticals). Dr. Sanabria declared no financial interest in the product or Arbor.

¹ See [web address].

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

/s/

LARA DIMICK-SANTOS
01/22/2016

STEPHANIE O OMOKARO
01/22/2016

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207-916
Priority or Standard	Standard
Submit Date(s)	3/30/2015
Received Date(s)	3/30/2015
PDUFA Goal Date	1/30/2016
Division / Office	Division of Gastroenterology and Inborn Errors Products
Reviewer Name(s)	Lara Dimick-Santos, MD
Review Completion Date	11/20/2015
Established Name	N-acetylcysteine
(Proposed) Trade Name	CETYLEV
Therapeutic Class	Antidote to prevent or reduce hepatic injury due to acetaminophen overdose
Applicant	Arbor Pharmaceuticals, LLC
Formulation(s)	Effervescent tablets (oral)
Dosing Regimen	Per protocol
Indication(s)	Antidote to prevent or lessen hepatic injury [REDACTED] (b) (4) [REDACTED] ingestion of a potentially hepatotoxic quantity of acetaminophen

Intended Population(s) Adults and children

Template Version: March 6, 2009

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	8
1.1	Recommendation on Regulatory Action	8
1.2	Risk Benefit Assessment	8
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies	9
1.4	Recommendations for Postmarket Requirements and Commitments	9
2	INTRODUCTION AND REGULATORY BACKGROUND	9
2.1	Product Information	10
2.2	Tables of Currently Available Treatments for Proposed Indications	11
2.3	Availability of Proposed Active Ingredient in the United States	11
2.4	Important Safety Issues With Consideration to Related Drugs	11
2.5	Summary of Presubmission Regulatory Activity Related to Submission	11
2.6	Other Relevant Background Information	12
3	ETHICS AND GOOD CLINICAL PRACTICES	14
3.1	Submission Quality and Integrity	14
3.2	Compliance with Good Clinical Practices	15
3.3	Financial Disclosures	15
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	16
4.1	Chemistry Manufacturing and Controls	16
4.2	Clinical Microbiology	16
4.3	Preclinical Pharmacology/Toxicology	16
4.4	Clinical Pharmacology	16
4.4.1	Mechanism of Action	16
4.4.2	Pharmacodynamics	16
4.4.3	Pharmacokinetics	16
5	SOURCES OF CLINICAL DATA	16
5.1	Tables of Studies/Clinical Trials	16
5.2	Review Strategy	17
5.3	Discussion of Individual Studies/Clinical Trials	17
	Study Design	17
6	REVIEW OF EFFICACY	22
	Efficacy Summary	22
6.1	Indication	22
6.1.1	Methods	22
6.1.2	Demographics	22
6.1.3	Subject Disposition	23
6.1.4	Analysis of Primary Endpoint(s)	23

6.1.5	Analysis of Secondary Endpoints(s).....	24
6.1.6	Other Endpoints	24
6.1.7	Subpopulations.....	24
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	24
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects	24
6.1.10	Additional Efficacy Issues/Analyses	25
	Preference Surveys	25
7	REVIEW OF SAFETY	27
	Safety Summary.....	27
7.1	Methods.....	29
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	29
7.1.2	Categorization of Adverse Events	29
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence	29
7.2	Adequacy of Safety Assessments	29
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	29
7.2.2	Explorations for Dose Response.....	30
7.2.3	Special Animal and/or In Vitro Testing	30
7.2.4	Routine Clinical Testing.....	30
7.2.5	Metabolic, Clearance, and Interaction Workup	30
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class...30	
7.3	Major Safety Results.....	30
7.3.1	Deaths	30
7.3.2	Nonfatal Serious Adverse Events.....	30
7.3.3	Dropouts and/or Discontinuations	31
7.3.4	Significant Adverse Events.....	31
7.3.5	Submission Specific Primary Safety Concerns	31
7.4	Supportive Safety Results	32
7.4.1	Common Adverse Events.....	32
7.4.2	Laboratory Findings.....	34
7.4.3	Vital Signs	35
7.4.4	Electrocardiograms (ECGs)	35
7.4.5	Special Safety Studies/Clinical Trials	35
7.4.6	Immunogenicity	35
7.5	Other Safety Explorations.....	35
7.5.1	Dose Dependency for Adverse Events	35
7.5.2	Time Dependency for Adverse Events.....	36
7.5.3	Drug-Demographic Interactions	36
7.5.4	Drug-Disease Interactions.....	36
7.5.5	Drug-Drug Interactions	36
7.6	Additional Safety Evaluations	36
7.6.1	Human Carcinogenicity	36

7.6.2	Human Reproduction and Pregnancy Data.....	36
7.6.3	Pediatrics and Assessment of Effects on Growth	36
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound	36
7.7	Additional Submissions / Safety Issues	36
8	POSTMARKET EXPERIENCE	37
9	APPENDICES	38
9.1	Literature Review/References	38
9.2	Labeling Recommendations	40
9.3	Advisory Committee Meeting	41

Table of Tables

Table 1: Study Calendar	18
Table 2: Test and Reference Product Formulations	20
Table 3: Demographics and Baseline Characteristics	22
Table 4: Overall Summary of Treatment-Emergent Adverse Events – Safety Population	32
Table 5: Frequency of Subjects Experiencing TEAEs by System Organ Class and Preferred Term - Safety Population	33

Table of Figures

Figure 1: Rumack-Matthew Nomogram for Acetaminophen Poisoning (From Rumack BH, Hess AJ [editors]: Poisindex. Denver, Micromedix, 1995. Adapted from Rumack BH, Matthew H: Acetaminophen poisoning and toxicity. Pediatrics 1975; 55: 871-876.)..... 14

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval

1.2 Risk Benefit Assessment

This was a single-center, open-label, randomized, two-arm, single-dose, two-period, crossover relative bioavailability study, intended to compare and evaluate the relative bioavailability of a single dose of AR10 and the reference product. The Office of Pharmaceutical Quality Hitesh Shroff PhD. and Mei Ou, PhD performed the review and considered that the product met requirements for bioequivalence. This reviewer reviewed the safety and no safety signals were identified. Acetylcysteine has been on the market since the 1950's and has a well know safety profile. There are very rare hypersensitivity reactions, but these occur mainly with the intravenous formulations.

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. This reviewer concludes that there is no improvement in gastrointestinal tolerance with the effervescent formulation (AR10) of acetylcysteine.

Bad taste and odor also are a known deterrent to successful oral administration of the already approved oral solution. The sponsor did perform surveys to assess patients preference in taste, flavor and smell compared to the reference solution of acetylcysteine

(b) (4)

(b) (4)

This reviewer agrees that

(b) (4)

however the sponsor provided no documentation of this claim.

In summary, this new formulation appears to be bioequivalent and have the same gastrointestinal tolerance/intolerance as the marketed solution of acetylcysteine. There are no new safety signals noted in the single-dose study. The risk benefit evaluation favors approval of the new formulation.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I recommend ongoing surveys via routine post-marketing surveys for evidence of medication errors.

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

This is a 505(b)(2) application for a new dosage form of N-acetylcysteine as an antidote to prevent or lessen hepatic injury [REDACTED] (b)(4) ingestion of a potentially hepatotoxic quantity of acetaminophen. The sponsor has performed a single bioequivalence study to support the application. No formal efficacy and safety studies were performed.

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 [REDACTED] (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 RLD, is FDA-approved but was discontinued from the market in 2009 (NDA 13-601). [REDACTED] (b)(4)

[REDACTED] 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, [REDACTED] (b)(4) [REDACTED] 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.).

[REDACTED] (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.

The Office of Drug Safety Inspections (DSI) reviewed the request to inspect the bioequivalence study site and declined to inspect the site as it had recently been inspected. 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.

2.1 Product Information

Acetylcysteine Effervescent Tablets, 500 mg and 2.5 g, contain the active ingredient acetylcysteine USP, a pharmacological agent known as an antidote for hepatic injury secondary to acetaminophen overdose, it is also used as mucolytic agent by inhalation.

However, the current application is only for the antidote to prevent or lessen hepatic injury (b) (4) ingestion of a potentially hepatotoxic quantity of acetaminophen. The chemical name is N-Acetyl-L-cysteine.

2.2 Table of Currently Available Treatments and Proposed Indications

Drug	Indication	Other information
NDA# 13-601 Mucomyst (acetylcysteine) Oral Solution for Inhalation	<ol style="list-style-type: none">antidote for acetaminophen overdose indicated to prevent or lessen hepatic injury after ingestion of a potentially hepatotoxic quantity of acetaminophenadjuvant therapy for patients with abnormal, viscid, or inspissated mucous secretions	The original NDA is withdrawn, there are multiple ANDAs and generic suppliers
NDA# 21-539 Acetadote (acetylcysteine) Injection	<ol style="list-style-type: none">antidote for acetaminophen overdose indicated to prevent or lessen hepatic injury after ingestion of a potentially hepatotoxic quantity of acetaminophen	There are multiple generic suppliers

2.3 Availability of Proposed Active Ingredient in the United States

Mucomyst, the Reference Listed Drug (RLD), is FDA-approved but was discontinued from the U.S. market (NDA 13-601) in 2009 by the manufacture as a business decision but not for reasons of safety and efficacy. There are multiple generic acetylcysteine oral formulations on the market.

2.4 Important Safety Issues With Consideration to Related Drugs

The only other drugs available to treat this indication are intravenous N-acetylcysteine or oral N-acetylcysteine. The safety issues are the same with all three formulations of N-acetylcysteine.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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 for the treatment of 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. The approach regarding this NDA program is consistent with FDA recommendations provided at the FDA meeting held January 29, 2013 (see FDA minutes dated 27Feb2013, PIND 116902).

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

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).

2.6 Other Relevant Background Information

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.ⁱ 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.^{i,ii}

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".

Acetaminophen is largely eliminated by hepatic metabolism; about 85% undergoes glucuronidation and sulfation. Sulfation is predominant in children ≤ 12 years of age, and glucuronidation is predominant in adults.^{i,ii}

Depletion of glutathione is foremost in the pathology of acetaminophen-induced hepatotoxicity. However, this is only one of several implicated toxicologic events as

previously described. If hepatic cell death occurs, it is usually necrotic. Centrilobular hepatic necrosis is typical of acetaminophen overdose.ⁱⁱⁱ

Generally, there are four clinical stages of acetaminophen toxicity. In the first stage, 12-24 hours after ingestion, patients may experience anorexia, malaise, diaphoresis, nausea and vomiting. The second stage begins 24-48 hours after ingestion and is comprised of elevated liver enzymes, liver enlargement, right upper quadrant abdominal pain, or patients may be asymptomatic. Three to five days after ingestion, anorexia, nausea, vomiting and malaise may recur, liver enzyme levels may worsen, and signs of hepatic failure may present including jaundice, hypoglycemia, coagulopathy, and encephalopathy. Stage 4 is either complete recovery or progression to liver failure.ⁱⁱ

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.^{iv}

Without acetylcysteine treatment, about 58% of patients with acetaminophen levels above the Rumack-Matthew nomogram (Figure 2.5-1) “treatment line” develop hepatotoxicity; approximately 5-6% of patients will die. When acetylcysteine is started within 0 to 24 hours of overdose the mortality rate is reduced to 0.7%.^{i,v}

Figure 1: Rumack-Matthew Nomogram for Acetaminophen Poisoning (From Rumack BH, Hess AJ [editors]: *Poisindex*. Denver, Micromedix, 1995. Adapted from Rumack BH, Matthew H: Acetaminophen poisoning and toxicity. *Pediatrics* 1975; 55: 871-876.)^{vi}

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3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The study protocol, study protocol amendment, written study subject information, informed consent form (ICF), and any other appropriate study-related information were reviewed and approved by (b) (4)

The IRB approval for the protocol amendment and related documents were obtained before subjects were screened for entry into the study.

The submission quality was adequate for review.

3.2 Compliance with Good Clinical Practices

This study was conducted in accordance with relevant standard operating procedures (SOPs) and other applicable regulatory requirements, including:

- Accordance with the principles that have their basis in the World Medical Association Declaration of Helsinki;
- International Conference on Harmonization (ICH) - E6 Guideline for Good Clinical Practice (GCP) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonization of Pharmaceuticals for Human Use;
- United States (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR, including parts 50 and 56 concerning Informed Patient Consent and IRB regulations);
- Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations - US Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER) March 2003; and,
- Applicable local regulatory requirements.

The Principal Investigator (PI) or designee provided information to each subject through the informed consent process about the essential elements of the study including the purpose, procedures to be carried out, potential hazards, and rights of the subjects including the right to claim compensation in the case of study-related injury or death. The subject was given ample time to read the ICF and was required to participate in a verbal discussion with the PI/designee and answer verbal questions to ensure the subject understood all information regarding the study pbefore signing the ICF prior to study participation. Subjects provided written informed consent (including date and time) and the Health Insurance Portability and Accountability Act (HIPAA) authorization prior to the commencement of any other study procedures. Documentation of the process was maintained. The subject received a copy of the ICF and HIPAA documents.

3.3 Financial Disclosures

This single-center study was conducted by Carlos Sanabria, MD at Spaulding Clinical (West Bend, Wisconsin). The sponsor reported no financial disclosures or conflicts with this investigator.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Tapash Ghosh – CDTL
Hitesh Shroff/Mei Ou (Biopharm) OPQ

4.2 Clinical Microbiology

N/A Vaikunth Prabhu

4.3 Preclinical Pharmacology/Toxicology

Yuk-Chow Ng

4.4 Clinical Pharmacology

Elizabeth Shang labeling assistance only

4.4.1 Mechanism of Action

See Section 2.6 Other Relevant Background Information on page 12.

4.4.2 Pharmacodynamics

See Section 2.6 Other Relevant Background Information on page 12.

4.4.3 Pharmacokinetics

See Section 6.1.4 on page 23

5 Sources of Clinical Data

This NDA relies on a single bioequivalence study AR10.001.

5.1 Tables of Studies/Clinical Trials

This NDA relies on a single bioequivalence study AR10.001.

5.2 Review Strategy

Hitesh Shroff, PhD. (Team leader) and Mei Ou PhD. (Primary reviewer) from the Office of Pharmaceutical Quality (OPQ) will review the bioequivalence study for quality and acceptability of the design and outcome. This reviewer will review the safety information in the bioequivalence study.

5.3 Discussion of Individual Studies/Clinical Trials

Study Design

This was a single-center, open-label, randomized, two-arm, single-dose, two-period, crossover relative bioavailability study, intended to compare and evaluate the relative bioavailability of a single dose of AR10 and the reference product in a minimum of 24 healthy adult subjects under fasting conditions. This study consisted of a Screening Period, two dosing periods (Period 1 and Period 2) separated by a 7-day washout period, and a follow-up telephone call. See Table 1 on page 18.

The primary objective of study AR10.001 was to assess the relative bioavailability of a single 11 gram dose of AR10 acetylcysteine effervescent tablets for oral solution (two 0.5 g and four 2.5 g), and the Reference Listed Drug (reference product, acetylcysteine solution; oral 20% [200 mg/mL] from (b) (4)) in healthy adult, human subjects under fasting conditions.

The secondary objective was to compare the safety and tolerability of AR10 and the reference product, as measured by treatment-emergent adverse events (TEAEs), concomitant medications, vital signs (pulse, temperature and respiratory rate), and assessment of well-being.

Supplemental objectives were the following:

- To assess subject preference between AR10 and the reference product.
- To assess the healthcare provider preference between AR10 and the reference product.

During the Screening Period (Day -30 to -1), subjects provided informed consent before undergoing screening procedures. Thirty subjects were planned to be enrolled in the study on the basis of inclusion and exclusion criteria, with the intent that least 24 subjects complete the study. Fifteen eligible subjects were to be randomized to each study arm using a balanced block randomization schedule that was generated before the start of dosing.

Subjects were assigned to receive one of two formulations in each period, with equal allocation of subjects to one of the possible sequences T1T2 and T2T1 (where T1 = AR10 and T2 = reference product).

Subjects received the first formulation on Day 1. Samples for PK analysis were collected pre-dose and at scheduled post-dose time points through 48 hours. Preference surveys were completed by subjects within 15 minutes of dosing and by health care providers within 30 minutes of completing dosing activities. Clinical examination, vital signs, and assessment of well-being were performed at scheduled time points after dosing. Subjects were discharged from Period 1 on Day 3 and returned for check-in on Day 7. On Day 8 (Period 2), subjects who continued to meet the protocol requirements received the alternate formulation under fasting conditions, per the group assignment, and underwent the same PK and safety assessments as those performed during Period 1, with discharge on Day 10. There was a 7-day washout period between consecutive dose administrations in each period.

Following the last PK sample collection in each period and prior to discharge from the clinic, subjects were evaluated to determine if they had developed any clinically significant changes from baseline or adverse events (AEs), which in the PI's opinion could pose a risk to the subject's well-being. The following assessments were conducted prior to discharge on Day 3 and Day 10: hematology, biochemistry, urinalysis (Day 10 only), 12-lead electrocardiogram (ECG), clinical examination, vital signs and assessment of well-being, and beta-human chorionic gonadotropin (beta-human chorionic gonadotropin [β -hCG]) pregnancy test (female subjects only, Day 10 only). Assuming no safety concerns, the study physician would discharge subjects from Period 1 and 2 approximately 48 hours after administration of study drug. Subjects with significant findings were to remain in the clinic for further observation or treatment until the condition was either explained or resolved. Subjects were to be contacted to return to the clinic if clinically significant results were found on laboratory test results after discharge.

Subjects were contacted on Day 12 (+2 day window) by the site's clinical staff to follow up on any AEs and concomitant medications and to ask in general how the subject was feeling.

Table 1: Study Calendar

Study Phase	Day(s)	Activity
Screening	-30 to -1	Screening window
Period 1	0	Admission
	1	Dosing + sampling
	2	Sampling
	3	Discharge from Period
Washout period	2-8	Period between dosing
Period 2	7	Admission
	8	Dosing + sampling
	9	Sampling
End of Study	10	Discharge
Follow-up	12	Telephone

Inclusion Criteria

1. Subjects (males or females) between 18–50 years of age inclusive.
2. Body weight at least 154 pounds (70 kg) and a body mass index (BMI) no greater than 30 kg/m².
3. Healthy as determined by medical history, clinical examination, and laboratory examination performed within 30 days prior to admission for the first period of the study.
4. Subjects willing and able to provide a written informed consent, HIPAA and to adhere to the protocol requirements.
5. If female and of childbearing potential (defined as a pre-menopausal female who was biologically capable of becoming pregnant), the subject had to agree to remain abstinent or practice a medically acceptable form of contraception from screening until the close out visit of the clinical study. Acceptable forms of contraception included intrauterine devices, implantable devices, and barrier methods. If a barrier method was chosen, a double barrier (eg, condom plus foam) was required.
6. Negative β -hCG test, consistent with no pregnancy (females only).
7. Non-smokers.

Exclusion Criteria

1. Known hypersensitivity, allergy, idiosyncratic reaction or adverse reaction to acetylcysteine, its excipients, and other related compounds with similar chemical characteristics or any severe allergic reaction to any drug or multiple food/drug allergies.
2. History or current evidence of clinically significant medical condition including, but not limited to, hepatic, renal, cardiac, vascular, gastrointestinal, or thyroid disease, diabetes, epilepsy, respiratory or hematological disease, acute narrow angle glaucoma, or psychiatric disorder that, in the opinion of the PI, would confound the study results or present a risk to the subject.
3. Subjects were to be without symptoms of nausea and/or vomiting. Subjects with a history of chronic nausea/vomiting were excluded. Subjects who had an acute illness/condition and had not had any nausea and/or vomiting episodes in the past 2

weeks could have been screened provided they were medically cleared from the acute illness/condition involving nausea and/or vomiting episode(s).

4. Existence of any surgical or medical condition that in the judgment of PI could have interfered with the absorption, distribution, metabolism, or elimination of the study drug.
5. Any clinically significant abnormality in the 12-lead ECG.
6. Laboratory values that were considered clinically significant (clinical chemistry, hematology, coagulation, urinalysis, or pregnancy test) - NOTE: In the event of any parameter lying outside of the normal range, the sample could have been repeated once. This value was to be accepted if it was within the normal range.
7. Consumption of grapefruit juice/grapefruit within 14 days prior to Period 1 admission.
8. Use of alcohol or caffeine containing products within 72 hours of each dose of study drug.
9. History or presence of alcoholism or drug abuse within 1 year of study participation.
10. Known or suspected carcinoma.
11. Presence of the disease markers of the human immunodeficiency virus (HIV) 1 or 2, hepatitis B or C viruses.
12. Positive urine test for drug(s) of abuse testing (amphetamines, barbiturates, benzodiazepines, tetrahydrocannabinol, morphine, and cocaine, and alcohol).
13. History of intake/administration of any investigational treatment in a clinical study within the last 30 days prior to the onset of the study admission in Period 1.
14. History of significant blood loss (≥ 350 mL) due to any reason, including blood donation, within the last 12 weeks prior to admission in Period 1 of the study.
15. Intake/administration of any enzyme-modifying drugs or drugs that could have increased or decreased acetylcysteine levels within 30 days of study drug administration, or over-the counter (OTC) drugs including vitamins and natural supplements within 21 days of the first dose of study drug administration and throughout study unless approved by the PI or Sponsor.
16. Requirement of special diet preventing consumption of standard, healthy meals during the in-clinic portions of the study. In such cases, subject selection was at the discretion of the PI in discussion with Medical Monitor, if required.
17. Any subject who, in the opinion of the PI, could not have followed instructions.
18. Difficulty in swallowing a liquid solution.
19. Female subjects with a self-reported history of anemia during menstrual cycle that could have coincided with any of the dosing day(s) during the study period.
20. Pregnant and lactating females.
21. Employee of the Sponsor, clinical site, or contract research organization (CRO).

Table 2: Test and Reference Product Formulations

Drug Information	AR10 Test Formulation	Reference Formulation
Generic Name	Acetylcysteine	Acetylcysteine
Strength	0.5 g and 2.5 g	20% (200 mg/mL)
Formulation	Effervescent Tablet	Solution (Not for Injection)
Source of Supply	Alpex Pharma SA Via Cantonale 6805 Mezzovico (Lugano) Switzerland for Arbor Pharmaceuticals, LLC	Manufactured by Gland Pharma Limited, INDIA for APP Pharmaceuticals, LLC Schaumburg, Illinois 60173
Lot Number	0.5 g: Lot number 030L13 2.5 g: Lot number 033L13 Expiration date [REDACTED] (b) (4)	Lot number SG362 Expiration date June 2015

AR10 effervescent tables were packaged in silver 2 count blister packs and stored under controlled room temperature (20° to 25°C [68° to 77°F]) conditions in a controlled access pharmacy, with room temperature documented in the appropriate site study manual. Blister packs were not opened until ready to use.

The reference product was a liquid solution in a rubber stoppered glass vial containing 30 mL and was stored at 20° to 25°C (68° to 77°F), with excursions permitted to 15° to 30°C (59° to 86°F). After opening, the solution was stored in the refrigerator at 2° to 8°C (36° to 46°F). Dilutions of acetylcysteine were used within 1 hour of preparation.

A balanced block randomization schedule was generated before the start of dosing by using SAS® software. According to the randomization schedule, subjects received the assigned formulation in each period, with the possible sequences T1T2 and T2T1. The equal allocation of subjects to each sequence was ensured.

An 11 g dose of acetylcysteine was selected for evaluation in this bioavailability study. This is a 70 kg adult dose that also allowed use of both the 0.5 mg and 2.5 mg effervescent tablets.

Concomitant Medications

Other than protocol-allowed treatments, subjects were not allowed prescription or over-the-counter (OTC) drugs (including vitamins and natural supplements) throughout the study duration. Medication other than the study drug was to be recorded as a concomitant medication.

Study Restrictions

Subjects were advised not to consume caffeine-containing beverages (tea, coffee, cola drinks), and foods (chocolates), and alcohol for at least 72 hours before admission to the study and during the entire duration of the study. Grapefruit juice/grapefruit was prohibited at least 14 days before admission to Phase 1 and during the entire duration of the study.

Subjects were restricted from drinking water at least 1 hour before dosing and for at least 1 hour after dosing, except for the water used for administration of the test solution. At all other times, subjects had free access to drinking water. All subjects maintained a fasting state for at least 10 hours prior to dosing and for at least 4 hours after dosing in each period. Lunch was provided approximately 4 hours after dosing in each period and standard meals were given at appropriate times during the course of the subject's stay in the clinical facility.

Subjects remained in a sitting posture for the first 4 hours after dose administration in each period, except in cases of study or procedural requirements. Subjects were restricted from doing any sort of stressful physical activity during their stay in the clinical facility.

Plasma samples were assayed for total acetylcysteine using validated liquid chromatography mass spectrometry/mass spectrometry (LC-MS/MS) procedures.

6 Review of Efficacy

Efficacy Summary

The bioequivalence study result was reviewed by the biopharmaceuticals team in the office of Pharmaceutical Quality. They have completed their review and have agreed that this effervescent formulation is bioequivalent to the RLD (listed drug used in the testing).

6.1 Indication

6.1.2 Demographics

Table 3: Demographics and Baseline Characteristics

	AR10/Ref. (N=15)	Ref./AR10 (N=15)	Total (N=30)
Age (years)			
N	15	15	30
Mean (SD)	33.2 (10.40)	37.3 (7.49)	35.2 (9.14)
Median	31.0	38.0	35.5
Min, Max	19, 50	21, 48	19, 50
Gender			
Male	13 (86.7%)	12 (80.0%)	25 (83.3%)
Female	2 (13.3%)	3 (20.0%)	5 (16.7%)
Ethnicity			
Hispanic or Latino	2 (13.3%)	1 (6.7%)	3 (10.0%)
Not Hispanic or	13 (86.7%)	14 (93.3%)	27 (90.0%)
Race			
Black or African American	7 (46.7%)	5 (33.3%)	12 (40.0%)
White	8 (53.3%)	10 (66.7%)	18 (60.0%)

max = maximum; min = minimum, ref = reference product; SD = standard deviation

6.1.3 Subject Disposition

Overall, twenty-nine of 30 subjects completed both periods of the study as planned, comprising the PK population. See Section 7.3.3 on page 23.

All 30 randomized subjects met all eligibility criteria. The following protocol deviations were reported during the study:

- Late PK sample draws, ranging from 71 seconds to 827 seconds late, were noted for 19 subjects (11 subjects in T1T2 and 8 subjects in T2T1) and were generally due to difficult draw.

No action was taken for any of these deviations. No protocol deviations resulted in discontinuation from study participation. None of the deviations were expected to alter

the PK analysis of plasma concentration data, or to affect conclusions on the PK or safety of the study drug.

6.1.4 Analysis of Primary Endpoint(s)

See biopharmaceutical review

Acetylcysteine exhibits capacity-limited elimination and small changes in absorption can result in disproportionately larger changes in maximum measured plasma/blood concentration (C_{max}) and area under the curve (AUC). In cases of acetaminophen poisoning, it is important to saturate elimination to drive unchanged drug into the liver in order to replace glutathione. Although it is generally recommended to stay within the linear pharmacokinetic (PK) range for bioavailability or bioequivalence studies, it is important to assess bioavailability at clinically relevant doses of both acetylcysteine and the excipients in the effervescent tablets.

Pharmacokinetics Conclusions

- Mean (SD) relative bioavailability of AR10 (calculated using AUC_{inf}) was 94.0 (18.5) percent.
- After administration of AR10 and the reference product, the mean (SD) total acetylcysteine C_{max} values were 26.5 (7.58) and 28.4 (7.86) $\mu\text{g/mL}$, respectively.
- After administration of AR10 and the reference product, the mean (SD) total acetylcysteine AUC_{last} values were 179 (52.3) and 195 (62.6) $\text{hr}\cdot\mu\text{g/mL}$, respectively; mean (SD) total acetylcysteine AUC_{inf} values were 186 (54.3) and 202 (64.4) $\text{hr}\cdot\mu\text{g/mL}$, respectively.
- AR10 and the reference product were bioequivalent with respect to C_{max} , AUC_{last} , and AUC_{inf} . The following point estimates (90% CIs) were calculated from the analysis of the natural log transformed values: 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} .
- The median difference in T_{max} values between AR10 and the reference product was small (0.50 hr) and the 90% CI included 0.00 (0.00–0.75).

The applicant concluded that this study demonstrated the bioequivalence of AR10 effervescent tablets for oral solution and the reference product in healthy adult subjects under fasting conditions.

6.1.5 Analysis of Secondary Endpoints(s)

See biopharmaceutical review

6.1.6 Other Endpoints

See biopharmaceutical review

6.1.7 Subpopulations

See biopharmaceutical review

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

This single dose bioequivalence study does not change the recommended dose which is the same as in previous labeling for oral N-acetylcysteine.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable

6.1.10 Additional Efficacy Issues/Analyses

The Applicant states that the current oral formulations of acetylcysteine have a strong, displeasing odor and taste (b) (4)

(b) (4)

Preference Surveys

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.

Taste		
Day 1/Day 8	AR 10 (N = 29)	Reference (N = 30)
1 = Dislike Very Much	9 (31.0%)	6 (20.0%)
2 = Dislike	7 (24.1%)	20 (66.7%)
3 = Neither Like or Dislike	5 (17.2%)	4 (13.3%)
4 = Like	7 (24.1%)	0
5 = Like Very Much	1 (3.4%)	0

n	29	30
Mean (SD)	2.4 (1.27)	1.9 (0.58)
Median	2.0	2.0
Min, Max	1, 5	1, 3
P-value [1]	0.0247	

Smell		
Day 1/Day 8	AR10 (N = 29)	Reference (N = 30)
1 = Dislike Very Much	6 (20.7%)	8 (26.7%)
2 = Dislike	12 (41.4%)	14 (46.7%)
3 = Neither Like or Dislike	5 (17.2%)	7 (23.3%)
4 = Like	5 (17.2%)	1 (3.3%)
5 = Like Very Much	1 (3.4%)	0
n	29	30
Mean (SD)	2.4 (1.12)	2.0 (0.81)
Median	2.0	2.0
Min, Max	1, 5	1, 4
P-value [1]	0.0533	

Flavor		
Day 1/Day8	AR10 (N = 29)	Reference (N = 30)
1 = Dislike Very Much	8 (27.6%)	7 (23.3%)
2 = Dislike	7 (24.1%)	19 (63.3%)
3 = Neither Like or Dislike	6 (20.7%)	4 (13.3%)
4 = Like	8 (27.6%)	0
5 = Like Very Much	0	0
Mean (SD)	2.5 (1.18)	1.9 (0.61)
Median	2.0	2.0
Min, Max	1, 4	1, 3
p-value	0.0082	

Applicants Conclusions on Preference

- 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; p values of 0.0247, 0.0082, 0.0090, and 0.0012, respectively) and approached statistical significance for the attribute of smell (p = 0.0533).
- Regardless of the order in which the products were received by the subjects, the subjects indicated that if given a choice between the two treatments, the majority would choose AR10 (68%) compared to the reference product (32%), although the difference was not statistically significant at the 5% level (p value 0.1397) in this small sample size.
- Health care providers also preferred AR10 over the reference product in the categories of preparation, recommendation, accuracy of dosing, and overall preference (80%, 80%, 90%, and 72.7%, of responses favoring AR10, respectively).

- [REDACTED] (b) (4)

MO Comment:

While there was some preference for the taste and of AR10 over the reference product

[REDACTED] (b) (4)

(b) (4). See
MO Comment on page 28.

7 Review of Safety

Safety Summary

A total of 30 healthy adult male and female subjects were exposed to at least one dose of study drug during this 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

AR10 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.

Arbor Pharmaceuticals, LLC (Arbor) is developing AR10, a product containing acetylcysteine in an effervescent tablet dosage form intended to be dissolved in only 300 mL of water before administration. The Applicant claims that the result is a pleasant tasting and smelling oral solution. (b) (4)

MO Comment:

(b) (4)

*This reviewer agrees that (b) (4)
however the sponsor provided no documentation of this claim.*

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The single bioequivalence study AR10.001 was reviewed.

7.1.2 Categorization of Adverse Events

Safety was assessed by AEs, laboratory assessments (hematology, biochemistry, and serology), β -hCG pregnancy test (female subjects only), clinical examination along with vital signs (oral temperature, heart rate, sitting blood pressure, respiratory rate) and assessment of well-being, and 12-lead ECG recordings. Subjects were monitored throughout the study and asked about how they felt at the time of each clinical examination and during the recording of vital signs. In the case of any AE/complaint that required immediate attention, subjects were instructed to consult the PI designee present in the clinical facility.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable

7.2 Adequacy of Safety Assessments

Safety assessments and tolerance to drug were based on the single dose of 11gms that would be given as a loading dose to a 70kg adult. As this drug is dosed in practice with a loading dose of 140 mg/kg followed by maintenance doses of about 70 mg/kg repeated every 4 hours for a total of 17 doses, the actual response to the drug cannot be fully evaluated with this single dose bioequivalence study.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 30 healthy adult male and female subjects were exposed to at least one dose of study drug during this study as follows:

- In T1T2, 15 subjects received AR10 in Period 1 and the reference product in Period 2.
- In T2T1, 15 subjects received the reference product in Period 1; 14 of these subjects continued on to Period 2 and received AR10.

The expected total dose for each subject was 22 g acetylcysteine (11 g acetylcysteine in AR10 and 11 g acetylcysteine in the reference product). With the exception of one subject who received 11 g of the reference product only and no Period 2 dose (described in Section 12.3.1.3), all subjects (29) received a total of 22 g acetylcysteine.

No prior and concomitant medications usage was reported during the study. The Applicant reported that there were no important differences in medical history between treatment groups.

Overall, twenty-nine of 30 subjects completed both periods of the study as planned, comprising the PK population. See Section 7.3.3 on page 31.

7.2.2 Explorations for Dose Response

Not applicable

7.2.3 Special Animal and/or In Vitro Testing

None

7.2.4 Routine Clinical Testing

See Sections 7.4.2 through 7.4.4

7.2.5 Metabolic, Clearance, and Interaction Workup

None

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable to this application

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported.

7.3.2 Nonfatal Serious Adverse Events

No SAEs were reported by the applicant, however see Section 7.3.3 below.

7.3.3 Dropouts and/or Discontinuations

One subject (#119) did not complete both treatment periods of the study. This subject experienced syncope and seizure-like activity (PT: convulsion) prior to dosing during Period 2 and was discontinued from treatment. The subject was discontinued from the study the following day.

Subject 119, a 38 year old white male, experienced a mild, unrelated AE of syncope and seizure like activity (PT: convulsion) on 15 May 2014 (Study Day 8) prior to dosing during Period 2 and was withdrawn from study drug. The event occurred >24 hours (~7days) after the subject received reference product in Period 1 and lasted approximately 2 - 4 minutes. Secondary to these events, the subject also experienced AEs of tongue injury and contusions, which were considered mild and unrelated, and resolved within 3 to 6 days. The subject discontinued the study the following day.

7.3.4 Significant Adverse Events

Two subjects experienced emesis during the study; times of emesis exceeded 2 x the median T_{max} . Subject 101 experienced emesis 4 hr. 14 min after the reference product

dose. The median T_{max} for the reference product was 1.5 hr. Therefore, data from this subject are included in the PK Population. Subject 107 experienced emesis 6 hr 16 min after AR10 treatment. The median T_{max} for the AR10 treatment was 2.0 hr.; therefore, data from this subject are included in the PK Population.

7.3.5 Submission Specific Primary Safety Concerns

The currently marketed oral form of acetylcysteine in the US requires using different volumes of the 20% solution to achieve a 5% concentration with each weight-based dose. The American College of Medical Toxicology stated that the administration of acetylcysteine is “prone to inaccurate dosing due to its complicated preparation and administration regimen”.^{vii} For the treatment to be safe and effective it is essential that acetylcysteine oral solution doses are prescribed, prepared, and administered accurately. This may require a simpler means to administer this antidote. (b) (4)



Equally important, a common problem administering oral acetylcysteine solution is nausea and vomiting attributable to its rotten-egg-like odor. It is well known that “...acetylcysteine solution will often smell like sulfur or rotten eggs” (<http://www.answers.com/topic/acetylcysteine-oral-solution>). “The solution is usually mixed with another liquid (such as cola) to decrease nausea and vomiting.” (<http://www.webmd.com/drugs/drug-8938acetylcysteine+misc.aspx?drugid=8938&drugname=acetylcysteine+misc>). Product labeling for currently marketed acetylcysteine states in the Precautions and Adverse Reactions sections, “Occasionally severe and persistent vomiting occurs as a symptom of acute acetaminophen overdose. Treatment with oral acetylcysteine may aggravate the vomiting.” “Dilution of the acetylcysteine (see Preparation of Acetylcysteine for Oral Administration) minimizes the propensity of oral acetylcysteine to aggravate vomiting.”

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A total of 52 TEAEs were reported during the study. Fourteen of 29 subjects (48.3%) experienced a total of 23 TEAEs while receiving AR10; 15 of 30 subjects (50.0%) experienced a total of 29 TEAEs while receiving reference product. The most common TEAEs, reported by more than one subject regardless of the product, were diarrhea, flatulence, nausea, dysgeusia, abdominal pain upper, headache, abdominal discomfort, vomiting, and dizziness. A similar number of subjects reported TEAEs of nausea (4 (13.8%) and 3 (10.0%)) or vomiting (1 (3.4%) and 1 (3.3%) each) after administration of AR10 and reference product, respectively.

All TEAEs were considered by the investigator to be mild in intensity. Of the subjects who experienced TEAEs, events considered related to study drug were reported for 13 of 14 subjects receiving AR10 and 14 of 15 subjects receiving reference product. All TEAEs reported by more than one subject overall were considered related to study drug. There were no apparent differences in time to onset or duration for TEAEs of diarrhea, flatulence, and nausea after administration of AR10 or reference product. For all other TEAEs, the number of subjects experiencing these events was too small (1 to 3 subjects per treatment group), to allow a meaningful comparison.

Table 4: Overall Summary of Treatment-Emergent Adverse Events – Safety Population

	AR10 (29)	Ref. (30)
Subjects Reporting at Least One TEAE	14 (48.3%)	15 (50.0%)
Subjects reporting at least one nausea or vomiting TEAE	4 (13.8%)	3 (10.0%)
Subjects Reporting at Least One Serious TEAE	0	0
Subjects Reporting at Least One TEAE leading to drug withdrawal	0	1 (3.3%)
Maximum Severity ^[1]		
Mild	14 (48.3%)	15 (50.0%)
Moderate	0	0
Severe	0	0
Closest Relationship to Study Drug ^[2]		
Related ^[3]	13 (44.8%)	14 (46.7%)
Not Related ^[4]	1 (3.4%)	1 (3.3%)

TEAE = treatment-emergent adverse event

Note: One subject discontinued in Period 2 without receiving the Period 2 treatment (AR10).

[1] Subjects reporting more than one adverse event are counted only once using the highest severity. Missing severity is summarized as severe.

[2] Subjects reporting more than one adverse event are counted only once using the closest relationship to study drug. [3] Includes all events reported as "Possible", "Probable", "Definitely", or missing relationship to study drug.

[4] Includes all events reported as "Unlikely" or "Unrelated" relationship to study drug.

Source: Sponsor Table 11 Study Report

A total of 52 TEAEs were reported; some subjects experienced more than one TEAE or the same TEAE more than once. The SOCs with the most reported TEAEs were gastrointestinal disorders (34 TEAEs reported) and nervous system disorders (12 TEAEs reported). This profile is not unexpected with oral acetylcysteine products.

Table 5: Frequency of Subjects Experiencing TEAEs by System Organ Class (SOC) and Preferred Term - Safety Population

System Organ Class/Preferred Term	AR10 (N=29)	Ref (N=30)
Subjects Reporting at Least One Treatment-Emergent Adverse Event	14 (48.3%)	15 (50.0%)
Gastrointestinal disorders	11 (37.9%)	9 (30.0%)
Diarrhea	6 (20.7%)	6 (20.0%)
Flatulence	2 (6.9%)	5 (16.7%)
Nausea	4 (13.8%)	3 (10.0%)
Abdominal pain upper	3 (10.3%)	1 (3.3%)
Abdominal discomfort	1 (3.4%)	1 (3.3%)
Vomiting	1 (3.4%)	1 (3.3%)
Nervous system disorders	4 (13.8%)	7 (23.3%)
Dysgeusia	3 (10.3%)	3 (10.0%)
Dizziness	1 (3.4%)	1 (3.3%)
Headache	0	2 (6.7%)
Convulsion	0	1 (3.3%)
Syncope	0	1 (3.3%)
General disorders and administration site conditions	0	1 (3.3%)
Infusion site pain	0	1 (3.3%)
Injury, poisoning and procedural complications	0	1 (3.3%)
Contusion	0	1 (3.3%)
Tongue injury	0	1 (3.3%)
Investigations	1 (3.4%)	0
Breath sounds abnormal	1 (3.4%)	0
Skin and subcutaneous tissue disorders	1 (3.4%)	0
Skin irritation	1 (3.4%)	0

Source Sponsor Table 12

All TEAEs were considered by the Principal Investigator as mild in intensity and were followed until resolution and subjects were considered recovered.

All TEAEs described above that were reported by more than one subject overall (i.e., diarrhea, flatulence, nausea, dysgeusia, abdominal pain upper, vomiting, dizziness, abdominal discomfort and headache) were considered related to study drug.

There were no apparent differences in time to onset or duration for TEAEs of diarrhea, flatulence, and nausea after administration of AR10 or reference product. For all other TEAEs the number of subjects experiencing these events was too small (1 to 3 subjects per treatment group), to allow a meaningful comparison.

MO Comment:

The number and type of adverse events is similar between AR10 and the reference product. Note that one more patient in the AR10 group reported nausea and vomiting than in the reference group, (b) (4)

7.4.2 Laboratory Findings

All subjects had normal chemistry, hematology, and urinalysis clinical laboratory test results, or results that were outside normal reference ranges provided by the laboratory but considered not clinically significant (NCS) by the Principal Investigator, at all visits throughout the study. All urine pregnancy test results, urine drug/alcohol screen results, and viral screen measurements were nonreactive.

MO Comment:

All laboratories were reviewed and this reviewer agrees with the PI that there were no significant laboratory abnormalities.

7.4.3 Vital Signs

Mean changes from Baseline for all vital signs parameters were small and similar between treatment groups. There were no AEs associated with vital sign changes reported during the study.

7.4.4 Electrocardiograms (ECGs)

Twelve-lead ECG recordings were obtained at screening, prior to discharge from Period 1 and at EOS.

Mean values for ECG parameters were similar between treatment groups at Baseline. Changes from Baseline in mean values for ECG parameters were small and similar between the AR10 and reference product groups with the exception of mean RR values, which demonstrated a greater decrease in the reference product group (-29.4 msec) than in the AR10 group (0.5 msec). Overall interpretation of ECG results revealed no abnormal findings at Baseline or in changes from Baseline assessments in either treatment group. Abnormal QTcF and QTcB results were not observed in either treatment group with the exception of QTcB change from Baseline of >30 msec. One subject (3.4%) in the AR10 group and 3 subjects (10%) in the reference product group

exhibited a change from Baseline in QTcB of >30 msec; none of these subjects exceeded a QTcB interval of 450 msec. These results were assessed as NCS by the PI.

7.4.5 Special Safety Studies/Clinical Trials

None

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable

7.5.2 Time Dependency for Adverse Events

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.

7.5.3 Drug-Demographic Interactions

None noted

7.5.4 Drug-Disease Interactions

Not applicable

7.5.5 Drug-Drug Interactions

None reported, patients were not taking concomitant medications during this study.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable

7.6.2 Human Reproduction and Pregnancy Data

Not applicable to this application, however the labeling was updated by the Maternal and Pediatrics Division. See their consult.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable

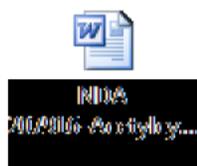
7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

There is no postmarketing experience with this effervescent formulation of acetylcysteine; however there is a lot of experience and literature from the oral solution and the intravenous formulations of N-acetylcysteine. We requested literature from the Arbor Pharmaceuticals to support updating the labeling as the labeling had not been updated in many years. See Sections 9.1 Literature Review and 9.2 Labeling.

9 Appendices



9.1 Literature Review/References

FDA request dated October 21, 2015, “Please provide literature to support inclusion in the labeling of indications for treatment of both acute acetaminophen ingestion and repeated supratherapeutic ingestion (RSI).” Literature supporting these indications is as follows.

• **Literature supporting NAC treatment of acute acetaminophen ingestion:**

Ref #1, Hodgman MJ and Garrard AR. A review of acetaminophen poisoning. Crit Care Clin, 2012; 28: 499516. See page 505-506.

Ref #4, Sud P, Strayer RJ, Bouchard NC, Jagoda A, Kulstad E, Lange EL, Nelson LW, Press GM, Rutman MS, Silvers SM, Weingart S. Current guidelines for management of patients with acetaminophen overdose in the emergency department. Ann Emerg Med, 2007; 50: 292-313. See page 5.

Ref #5, Chun LJ, Tong MJ, Busuttill RW, Hiatt JR. Acetaminophen hepatotoxicity and acute liver failure. J Clin Gastroenterol, 2009; 43: 342-349. See page 345.

Ref #6, Rowden AK, Norvell J, Eldridge DL, Kirk MA. Updates on acetaminophen toxicity. Med Clin N Am, 2005; 89: 1145-11159. See page 1148.

Ref #8, Lancaster M, Hiatt JR, Zarrinpar A. Acetaminophen hepatotoxicity: an updated review. Arch Toxicol, 2015; 89: 193-199. See page 196.

Ref #9, Bunchorntavakul C, Reddy KR. Acetaminophen-related hepatotoxicity. Clin Liver Dis, 2013; 17: 587-607. See pages 594-595 and 597.

Ref #10, Algren DA. Review of N-acetylcysteine for the treatment of acetaminophen (paracetamol) toxicity in pediatrics. Second Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines. Geneva, 29 September to 3 October 2008. See page 4.

Literature supporting NAC treatment of RSI:

Ref #1, Hodgman MJ and Garrard AR. A review of acetaminophen poisoning. Crit Care Clin, 2012; 28: 499516. See page 506.

Ref #3, Aripin KNBN, and Choonara I. The management of paracetamol poisoning. Paediatric and Child Health, 2009; 19: 492-497.

Ref #4, Sud P, Strayer RJ, Bouchard NC, Jagoda A, Kulstad E, Lange EL, Nelson LW, Press GM, Rutman MS, Silvers SM, Weingart S. Current guidelines for management of

patients with acetaminophen overdose in the emergency department. *Ann Emerg Med*, 2007; 50: 292-313. See page 5.

Ref #5, Chun LJ, Tong MJ, Busuttill RW, Hiatt JR. Acetaminophen hepatotoxicity and acute liver failure. *J Clin Gastroenterol*, 2009; 43: 342-349. See page 345.

Ref #6, Rowden AK, Norvell J, Eldridge DL, Kirk MA. Updates on acetaminophen toxicity. *Med Clin N Am*, 2005; 89: 1145-11159. See page 1149.

Ref #7, Daley FFS, O'Malley GF, Heard K, Bogdan GM, Dart RC. Prospective evaluation of repeated suprathreshold acetaminophen (paracetamol) ingestion. *Ann Emerg Med*, 2004; 44: 393-398.

Ref #8, Lancaster M, Hiatt JR, Zarrinpar A. Acetaminophen hepatotoxicity: an updated review. *Arch Toxicol*, 2015; 89: 193-199. See page 196.

Ref #9, Bunchorntavakul C, Reddy KR. Acetaminophen-related hepatotoxicity. *Clin Liver Dis*, 2013; 17: 587-607. See pages 596-597.

Ref #10, Algren DA. Review of N-acetylcysteine for the treatment of acetaminophen (paracetamol) toxicity in pediatrics. Second Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines. Geneva, 29 September to 3 October 2008. See page 4.

FDA request dated October 22, 2015, "Please provide literature support to justify that at times continued administration of CETYLEV may be necessary if there are still detectable levels of acetaminophen at the end of the maintenance dosing to support the following addition in the labeling.

Continued Therapy After Completion of Loading and Maintenance Doses

Ref #1, Hodgman MJ and Garrard AR. A review of acetaminophen poisoning. *Crit Care Clin*, 2012; 28: 499516. See page 505-506.

Ref #2, Keys R, Harrison PM, Wendon JA, Forbes A, Gove C, Alexander GHm, Williams R. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. *Brit Med J*, 1991; 2303: 1026-1029.

Ref #5, Chun LJ, Tong MJ, Busuttill RW, Hiatt JR. Acetaminophen hepatotoxicity and acute liver failure. *J Clin Gastroenterol*, 2009; 43: 342-349. See page 346.

Ref #6, Rowden AK, Norvell J, Eldridge DL, Kirk MA. Updates on acetaminophen toxicity. *Med Clin N Am*, 2005; 89: 1145-11159. See page 1152.

Ref #7, Daley FFS, O'Malley GF, Heard K, Bogdan GM, Dart RC. Prospective evaluation of repeated suprathreshold acetaminophen (paracetamol) ingestion. *Ann Emerg Med*, 2004; 44: 393-398. See page 397.

Ref #9, Bunchorntavakul C, Reddy KR. Acetaminophen-related hepatotoxicity. *Clin Liver Dis*, 2013; 17: 587-607. See pages 599-600.

Ref #10, Algren DA. Review of N-acetylcysteine for the treatment of acetaminophen (paracetamol) toxicity in pediatrics. Second Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines. Geneva, 29 September to 3 October 2008. See pages 10 and 12.

Ref #11, Chiew AL, Isblister GK, Duffull SB, Buckley NA. Evidence for the changing regimens of acetylcysteine. Br J Clin Pharmacol, 2015; September; doi:10.1111/bcp.12789. See hand-paginated pages 12-13.

Ref #12. Doyon S, Klein-Schwartz W. Hepatotoxicity despite early administration of intravenous N-acetylcysteine for acute acetaminophen overdose. Academic Emergency Medicine, 2009; 16: 34-39.

Ref #13, Smith SW, Howland MA, Hoffman RS, Nelson LS. Acetaminophen overdose with altered acetaminophen pharmacokinetics and hepatotoxicity associated with premature cessation of intravenous N-acetylcysteine therapy. Ann Pharmacother, 2008; 42: 1333-1339.

Ref #16, Blackford MG, Felter T, Gothard MD, Reed MD. Assessment of the clinical use of intravenous and oral N-acetylcysteine in the treatment of acute acetaminophen poisoning in children: a retrospective review. Clin Ther, 2011; 33: 1322-13330.

FDA request dated October 22, 2015, "Please also provide literature to justify dosing for pts weighing (b) (4) kg to support the proposed following addition to the labeling.

(b) (4)

MO Comment:

These references were reviewed and support the changes to the labeling.

9.2 Labeling Recommendations

The Dosage and Administration Section of the labeling was updated with information on acute acetaminophen ingestion, (b) (4) and repeated supratherapeutic ingestion (RSI). The following literature was submitted by the sponsor in support of these changes as requested by the Division. See Section 9.1 above with the literature references.

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

Continued Therapy After Completion of Loading and Maintenance Doses

In cases of suspected massive overdose, or with concomitant ingestion of other substances, or in patients with preexisting liver disease, the absorption and/or the half-life of acetaminophen may be prolonged, in such cases consideration should be given to the need for continued treatment with CETYLEV. 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, (b) (4) the maintenance doses should be (b) (4), 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)



9.3 Advisory Committee Meeting

None

i (b) (4)

ii Argentieri J, Morrone K, Pollack Y. Acetaminophen and ibuprofen overdosage. *Pediatrics in Review*. 2012;33:188-9.

iii Rumack BH, Peterson, Acetaminophen overdose: incidence, diagnosis and management in 416 patients. *Pediatrics*, 1978;62 (Pt 2 Suppl):898-903.

iv Algren DA. Review of N-acetylcysteine for the treatment of acetaminophen (paracetamol) toxicity in pediatrics. Second Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines, Geneva, 29 September to 3 October, 2008.

v Brok J, Buckley N, Glud C. Interventions for paracetamol (acetaminophen) overdose (review). *The Cochrane Library*, 2009, Issue 1

vi Rodgers GC Jr, Condurache T, Reed MD, Bestic M, Gal P. Poisonings. In *Nelson Textbook of Pediatrics*, Kliegman RM, Jenson HB, Behrman RE, Stanton BF, eds, 18th ed, 2007: 339-361.

vii American College of Medical Toxicology. The American College of Medical Toxicology discusses the potential for errors with both IV acetaminophen and its treatment, N-acetylcysteine, 2012, http://www.acmt.net/_Library/Press_Releases/IV_Acetaminophen_and_Its_Treatment_N-acetylcysteine_05_08_12.pdf

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

/s/

LARA DIMICK-SANTOS
11/20/2015

STEPHANIE O OMOKARO
11/20/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 207-916

Applicant: Arbor

Stamp Date: March 30th, 2015

Drug Name: Acetylcysteine
effervescent tablets
500 mg and 2.5 gm

NDA/BLA Type: 505(b)(2)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			No nonclinical required
9.	Has the applicant submitted the integrated summary of safety (ISS)?		X		Not required
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		X		Not required, brief summary of efficacy in section 2.7.3
11.	Has the applicant submitted a benefit-risk analysis for the product?		X		they do address it briefly in section 1.16 risk management plans
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(2)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?				Mucomyst (acetylcysteine) solution (NDA 13-601: FDA approved 1963)
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	X			(1) formulation work to develop CETYLEV effervescent tablets for oral solution with favorable taste and smell characteristics, and (2) comparative bioavailability study

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					AR10.001 involving healthy adult subjects to assess the bioequivalence of CETYLEV in oral solution versus the reference listed acetylcysteine solution given orally.
15.	Describe the scientific bridge (e.g., BA/BE studies)				AR10.001 see above
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (<i>i.e.</i> , appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:				N/A
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:				N/A
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			BA study design per CMC reviewer
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.				N/A
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?				N/A
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?				Only data from BA study
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?				N/A
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?		X		

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?				N/A
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?				N/A
26.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?		X		IR sent to sponsor
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?				N/A no deaths or SAEs
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?				N/A
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?				N/A
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?				N/A
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?				N/A
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?				N/A
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	Sample CRF submitted
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___yes___

If the Application is not fileable from the clinical 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

Lara Dimick-Santos, MD

 Reviewing Medical Officer

_____ Date

Aisha Peterson, MD

 Clinical Team Leader

_____ Date

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

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

/s/

LARA DIMICK-SANTOS
05/14/2015

AISHA P JOHNSON
05/14/2015