CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207916Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 28, 2016
Requesting Office or Division:	Division of Gastroenterology & Inborn Error Products (DGIEP)
Application Type and Number:	NDA 207916
Product Name and Strength:	Cetylev (acetylcysteine) effervescent tablets for oral solution 500 mg; 2.5 grams
Submission Date:	January 15, 2016
Applicant/Sponsor Name:	Arbor Pharmaceuticals, LLC
OSE RCM #:	2015-747
DMEPA Primary Reviewer:	Matthew Barlow, RN, BSN
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMO

DGIEP requested that we review the revised carton labels for Cetylev (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.[1][2]

2 CONCLUSION

The revised carton labeling for Cetylev is acceptable from a medication error perspective. We have no further recommendations at this time.

[1] Barlow M. Label and Labeling Review Memo for Cetylev (NDA 207916). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Jan 07. 9 p. OSE RCM No.: 2015-747.

[2] Barlow M. Label and Labeling Review for Cetylev (NDA 207916). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 DEC 18. 17 p. OSE RCM No.: 2015-747.

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/s/

MATTHEW J BARLOW
01/28/2016

MISHALE P MISTRY
01/28/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 7, 2016
Requesting Office or Division:	Division of Gastroenterology & Inborn Error Products (DGIEP)
Application Type and Number:	NDA 207916
Product Name and Strength:	Cetylev (acetylcysteine) effervescent tablets for oral solution 500 mg; 2.5 grams
Submission Date:	December 30, 2015
Applicant/Sponsor Name:	Arbor Pharmaceuticals, LLC
OSE RCM #:	2015-747
DMEPA Primary Reviewer:	Matthew Barlow, RN, BSN
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMO

DGIEP requested that we review the revised carton, blister pack labels, and prescribing information (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSIONS

The revised prescribing information is acceptable from a medication error perspective. However, the revised carton labels are unacceptable from a medication error perspective. We note that the prominence of the established name and strength can be increased. We provide specific recommendations for the Applicant in Section 2.1.

[1] Barlow M. Label and Labeling Review for Cetylev (NDA 207916). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 DEC 18. 17 p. OSE RCM No.: 2015-747.

2.1 RECOMMENDATIONS FOR ARBOR PHARMACEUTICALS, LLC.

We recommend the following be implemented prior to approval of this NDA:

A. Carton labeling:

1. We recommend increasing the prominence of the established name and dosage form using bold in accordance with 21 CFR 201.10(g)(2), taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
2. We recommend increasing the prominence of the strength by increasing the print size (and colored box) to further emphasize this pertinent information. As currently presented, the statement "LEMON MINT FLAVOR" competes in size and prominence with the product strength, which is considered essential information on the carton labeling.
3. We recommend revising the dosage form to include the complete dosage form with route of administration for consistency with USP General Chapter <1121> Nomenclature requirements.[2] We recommend the following:

    Cetylev
    (acetylcysteine) effervescent tablets for oral solution
    500 mg

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[2] USP General Chapter <1121> Nomenclature:

"In some instances, the drug is supplied in one dosage form for the preparation of the intended dosage form. In such cases, the dosage form provided in the container is named first and the word "for" appears, followed by the final dosage form that is suitable for administration. The general format becomes [DRUG] [DOSAGE FORM] for [ROUTE OF ADMINISTRATION] [DOSAGE FORM]., e.g. Aspirin Effervescent Tablets for Oral Solution.

The term "for" is included in the names of solid preparations which must be dissolved or suspended in a suitable liquid to obtain a dosage form suitable for administration, and the general format becomes [DRUG] for [ROUTE OF ADMINISTRATION] [DOSAGE FORM]. e.g. Ampicillin for Oral Suspension, Cytarabine for Injection."

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/s/

MATTHEW J BARLOW
01/13/2016

MISHALE P MISTRY
01/13/2016

505(b)(2) ASSESSMENT

Application Information		
NDA # 207916	NDA Supplement #: S- n/a	Efficacy Supplement Type SE- n/a
Proprietary Name: Cetylev Established/Proper Name: acetylcysteine effervescent tablets for oral solution Dosage Form: tablets Strengths: 500 mg and 2.5 g		
Applicant: Arbor Pharmaceuticals, LLC		
Date of Receipt: March 30, 2015		
PDUFA Goal Date: January 30, 2016	Action Goal Date (if different): January 29, 2016	
RPM: CDR Anissa Davis-Williams		
Proposed Indication(s): antidote to prevent or lessen hepatic injury (b) (4) ingestion of a potentially hepatotoxic quantity of acetaminophen.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 013601Mucomyst (acetylcysteine) Solution (Discontinued; therefore ANDA 203853 acetylcysteine solution labeling was utilized)	*INDICATIONS AND USAGE; CONTRAINDICATIONS;WARNINGS & PRECAUTIONS; ADVERSE REACTIONS; DOSAGE AND ADMINISTRATION; ACETAMINOPHEN ASSAYS - INTERPRETATION AND METHODOLOGY* *DOSAGE GUIDE AND PREPARATION, only the subsection containing the nomogram: Estimating Potential for Hepatotoxicity.*
Published literature	*Embryo-fetal development studies in rats and rabbits, fertility studies in rats, Ames test* *Pharmacokinetic parameters other than the conducted BE study, including bioavailability, plasma protein binding, in vivo metabolites, volume of distribution, hepatic impairment, renal impairment, and drug-drug interaction.* *Dosage and administration update section* *update indication to include both acute ingestion and repeated supratherapeutic ingestions*

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1].

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

The Applicant completed comparative bioavailability study AR10.001, involving healthy adult subjects to assess the bioequivalence (BE) of CETYLEV in oral solution versus acetylcysteine solution (ANDA 203853) given orally because the relied upon listed drug, Mucomyst Solution, is discontinued (as agreed with FDA at the January 29, 2013 meeting).

AR10.001 was 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 (Innopharma's Acetylcysteine solution; Oral 20% [200mg/ml]) in Healthy Adult, Human Subjects, Under Fasting Conditions.

AR10-001 was a single-center, open-label, randomized, two-arm, single-dose, two-period, crossover relative bioavailability study involving healthy fasting subjects to compare the relative bioavailability of a single dose of CETYLEV acetylcysteine effervescent tablets (code named AR10) in oral solution versus acetylcysteine oral 20% solution (ANDA 203853) diluted per labeling.

The drug product is scientifically bridged to the published literature, because the publications contained data generated from studies using the same active pharmaceutical ingredient as contained in the Sponsor's drug product.

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.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Mucomyst (acetylcysteine) solution	013601	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☒ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing: Mucomyst Solution

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a change in dosage form, from oral solution to tablets.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s): Mucomyst

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of ☐

approval

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/s/

ANISSA A DAVIS
12/23/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 18, 2015
Requesting Office or Division:	Division of Gastroenterology & Inborn Error Products (DGIEP)
Application Type and Number:	NDA 207916
Product Name and Strength:	Cetylev (acetylcysteine) effervescent tablets for oral solution 500 mg; 2.5 grams
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Arbor Pharmaceuticals, LLC
Submission Date:	March 30, 2015; September 23, 2015
OSE RCM #:	2015-747
DMEPA Primary Reviewer:	Matthew Barlow, RN, BSN
DMEPA Team Leader:	Kendra Worthy, PharmD

1 REASON FOR REVIEW

This review is in response to a request by DGIEP for DMEPA to review the proposed label and labeling for any areas that may lead to medication errors. The applicant submitted the proposed label and labeling on March 30, 2015 and September 23, 2015 to be evaluated under application NDA 207916.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A-C
ISMP Newsletters	N/A-D
FDA Adverse Event Reporting System (FAERS)*	N/A-E
Other	N/A-F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Arbor Pharmaceuticals, LLC submitted the proposed carton and blister-pack labels and prescribing information (PI) on March 30, 2015. Additionally, the applicant submitted their revised proposed blister-pack labels on September 23, 2015. We performed a risk assessment of the submitted proposed labels and labeling for any areas that may lead to medication errors. We found areas of the proposed carton labels and prescribing information that could be revised to improve clarity and organization, thus increasing understanding of the information. The specific recommended revisions for the proposed carton labels can be found in section 4.2, and our recommendations for PI revisions have been communicated to the division team.

4 CONCLUSION & RECOMMENDATIONS

We found areas of the proposed labels that can be revised to improve clarity and organization, thus increasing understanding of the provided information.

4.1 RECOMMENDATIONS FOR THE ARBOR PHARMACEUTICALS, LLC

We recommend the following be implemented prior to approval of this NDA 207916:

A. Carton Labels
   1. We recommend revising the established name and dosage form font color to the same color as the proprietary name. In accordance with 21 CFR 201.10(g)(2), to increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
   2. We recommend modifying the font color of the statement "LEMON MINT FLAVOR" to a font color that would decrease the prominence of this statement as it distracts from the proprietary name, established name, dosage form, and strength. Additionally, we recommend removing the bolding from this statement as well.

B. Blister Pack Labels
   1. See comment A.2
   2. Please submit blister pack labels including the lot number & expiration date.
   3. We recommend having the product strength expressed in mg per single unit to make it clear the designated strength is per unit.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Cetylev that Arbor Pharmaceuticals, LLC submitted on March 30, 2015, and the listed drug (LD).

Table 2. Relevant Product Information for Cetylev and the Listed Drug		
Product Name	**Cetylev**	**Mucomyst**
Initial Approval Date	N/A	1963
Active Ingredient	Acetylcysteine	Acetylcysteine
Indication	is an antidote for acetaminophen overdose indicated to prevent or lessen hepatic injury after ingestion of a potentially hepatotoxic quantity of acetaminophen in patients with acute ingestion or from repeated supra-therapeutic ingestion	is indicated as adjuvant therapy for patients with abnormal, viscid, or inspissated mucous secretions in such conditions as:
Route of Administration	Oral	Oral
Dosage Form	Tablets for Oral Solution	Solution
Strength	500 mg; 2.5 grams	10% (100 mg/mL); 20% (200 mg/mL)
Dose and Frequency	Dependent on Clinical presentation	Dependent on clinical presentation
How Supplied	CETYLEV effervescent tablets are supplied as white, round, flat tablets with a lemon mint smell packaged in 2-count peel-able foil blister packs	MUCOMYST is available in rubber stoppered glass vials containing 4, 10, or 30 mL. The 20% solution may be diluted to a lesser concentration with either Sodium Chloride for Injection, Sodium Chloride for Inhalation, Sterile Water for Injection, or Sterile Water for Inhalation. The 10% solution may be used

		undiluted.
Storage	Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature.] Protect from moisture. Store tablets in original blister package until use.	Store unopened vials at controlled room temperature, 59° to 86°F (15° to 30°C).
Container Closure	See How Supplied	See How Supplied

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On November 20, 2015, we searched the L:drive using the terms, Cetylev, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review, but it was a proprietary name review.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design

N/A

C.2 Results

N/A

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

N/A

D.2 Results

N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

N/A

E.2 Results

N/A

E.3 List of FAERS Case Numbers

N/A

APPENDIX F.

F.1 Methods

N/A

F.2 Results

N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post-market medication error data, we reviewed the following Cetylev labels and labeling submitted by Arbor Pharmaceuticals, LLC on March 30, 2015 and September 23, 2015.

- Carton labeling
- Hospital Unit-Dose Blister labels
- Unit-Dose Carton Labeling
- (b) (4)

G.2 Label and Labeling Images

(b) (4)

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MATTHEW J BARLOW
12/18/2015

KENDRA C WORTHY
12/18/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 7, 2015
To:	Donna Griebel, MD Director **Division of Gastroenterology and Inborn Errors Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	CETYLEV (acetylcysteine)
Dosage Form and Route:	Effervescent tablets, for oral solution
Application Type/Number:	NDA 207916
Applicant:	Abor Pharmaceuticals LLC

1 INTRODUCTION

On March 30, 2015, Abor Pharmaceuticals, submitted for the Agency's review a New Drug Application (NDA 207916) for CETYLEV (acetylcysteine) effervescent tablets, for oral solution , for use as an antidote for acetaminophen overdose. CETYLEV (acetylcysteine) is indicated to prevent or lessen hepatic injury after ingestion of a potentially hepatotoxic quantity of acetaminophen in patients with acute ingestion or from repeated supratherapeutic ingestion.

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 Gastrenterology 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.

2 MATERIAL REVIEWED

- Draft CETYLEV (acetylcysteine) PPI received on April 12, 2015, and received by DMPP and OPDP on November 30, 2015.
- Draft CETYLEV (acetylcysteine) Prescribing Information (PI) received on April 12, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 30, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
12/07/2015

MEETA N PATEL
12/07/2015

MARCIA B WILLIAMS
12/07/2015

LASHAWN M GRIFFITHS
12/07/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: December 2, 2015

To: Anissa Davis-Williams, RN, BSN, MPH, CPHM
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 207916
OPDP Comments for draft CETYLEV (acetylcysteine) effervescent tablets, for oral solution PI and PPI

OPDP has reviewed the proposed draft PI for CETYLEV (acetylcysteine) effervescent tablets, for oral solution, sent to us on November 30, 2015, and have no additional comments. Comments on the draft PPI will be sent under separate cover as a joint review with DMPP.

Thank you for the opportunity to comment on the proposed PI.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
12/02/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: October 13, 2015

From: Suchitra M. Balakrishnan, MD, PhD. Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Gastroenterology and Inborn Errors of Metabolism (DGIEP)

Drug: CETYLEV (acetylcysteine) effervescent tablets for oral solution

NDA: 207916
Applicant: Arbor Pharmaceuticals, LLC.

Subject: Pregnancy and Lactation Labeling

Proposed Indication: (b) (4) indicated to prevent or lessen hepatic injury

Materials Reviewed:

- DPMH consult request dated April 12, 2015, DARRTS Reference ID 3730377
- Sponsor's response to DPMH information request dated August 25, 2015
- Applicant's proposed labeling for NDA 207916 dated September 1, 2015.

Consult Question:
"The reason for this consult is to invite the Maternal Health team to attend meetings and assist in the labeling review pertaining to this NDA and offer any assistance as necessary"

INTRODUCTION

On March 30, 2015, Arbor Pharmaceuticals LLC, submitted a 505(b)(2) new drug application (NDA) for CETYLEV (acetylcysteine) effervescent tablets, (b) (4) indicated to prevent or lessen hepatic injury (b) (4) ingestion of a potentially hepatotoxic quantity of acetaminophen. The active ingredient, N-acetylcysteine is a widely recognized acetaminophen antidote used since the late 1970's to prevent or reduce hepatic injury due to acetaminophen overdose[1], and is available as intravenous (Acetadote) and oral formulations.

No clinical efficacy or safety studies have been conducted in support of this 505(b)2 NDA. This application refers to and relies on findings of efficacy and safety for the Mucomyst innovator, NDA13601, and based on the bridging relative bioavailability study AR10.001.

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

BACKGROUND

Acetylcysteine Drug Characteristics and Mechanism of Action

Acetaminophen hepatotoxicity is caused by the acetaminophen metabolite N-acetyl parabenzoquinonimine (NAPQI). At therapeutic doses, ≤10% of acetaminophen is metabolized to toxic metabolite NAPQI, and endogenous glutathione converts this small amount to harmless inactive metabolites preventing hepatic damage. However, with acetaminophen overdose, NAPQI exposure increases and endogenous glutathione stores may deplete resulting in NAPQI-induced hepatotoxicity. Additional events contributing to hepatocellular toxicity include: production of reactive oxygen and nitrogen radicals, mitochondrial oxidative stress, mobilization of the hepatic immune systemand elicitation of stress proteins/gene transcription mediators . 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[2].

The standard course for oral acetylcysteine therapy is a loading dose of 140 mg/kg and maintenance doses of 70 mg/kg repeated every 4 hours for a total of 17 doses. The Rumack-Matthew nomogram is used to guide treatment with acetylcysteine following an acetaminophen overdose[2]. Without acetylcysteine treatment about 58% of patients with toxic acetaminophen levels above the Rumack-Matthew nomogram "treatment line" develop hepatotoxicity and about 5-6% die[2,3]. When acetylcysteine is started within 0 to 24 hours of overdose the mortality rate is reportedly reduced to 0.7%, and hepatotoxicity is < 10% when administered within 8 hours. Most deaths from hepatic failure occur within the first week

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

2 Hodgman MJ, Garrard AR. A review of acetaminophen poisoning. *Crit Care Clin*, 2012; 28: 499-516.

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

following acetaminophen overdose, and patients who recover generally do well and do not develop chronic liver dysfunction[4].

CETYLEV effervescent tablets are to be produced in 0.5 gram and 2.5 gram strengths with dosing instructions based on patient weight. The applicant states that (b) (4) loading and maintenance doses for this antidote. Once dissolved, CETYLEV is purported to confer a relatively pleasant taste and smell. (b) (4)

After an oral dose of N-acetylcysteine (NAC) 200 to 400 mg, the peak plasma concentration of 3.5 to 4 mg/L is achieved within 1 to 2 hours. Following oral administration, total NAC has a terminal half life of 6.25 hours[5].

Acetaminophen Overdose and Pregnancy:
Based on a report by the American Association of Poison Control Centers, exposures to poisonous substances during pregnancy in the U.S. occurred in 7,384 women (0.3% of all human exposures) in the year 2013. Around 20% were reported as intentional exposures and the most frequent generic drug category reported (11.61%) was analgesics[6]. Another report by the Toxicology Investigators Consortium (ToxIC) Registry of the American College of Medical Toxicology identified all poisoning cases involving pregnant women that were catalogued by the medical toxicology services across the 37 sites between January 2010 and December 2012[7]. Of the 17,529 poisonous substance exposure cases reported in the ToxIC Registry, 103 (0.6 %) involved pregnant women. In this report, the majority of pregnant cases (n = 53; 51.5 %) involved intentional exposures. Non-opioid analgesics were the most common class of agents encountered (n=32, 31 %), with 26 out of these 32 patients having overdosed on acetaminophen. Therefore, it appears that while pregnant women form a small fraction of patients treated for drug overdose, non-opioid analgesic overdoses are the most frequent.

Pregnancy and Nursing Mothers Labeling
On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[8] also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories

4 Algren DA. Review of N-acetylc ysteine for the treatment of acetaminophen (paracetamol) toxicity in pediatrics. *Second Meeting of the Subcommittee of the Expert Committee on the Selecti on and Use of Essential Medicines*, Geneva, 29 S eptember to 3 October, 2008.
5 Section 1.3, *Summary of Biopharmaceutic Studies and Associated Analytical Methods, eCTD 2.7.1, NDA 207916*
6 2013Annual Report of the American Association of Poison Control Centers National Poison Data System (NPDS): 31st Annual Report
7 Zelner, Irene et al, Acute Poisoning During Pregnancy: Observations from the Toxicology Investigators Consortium., Journal of Medical Toxicology, 2015, 11 (3), 301-308
8 *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

(A, B, C, D and X) are being removed from all prescription drug and biological product labeling and a new format is being required for all products that are subject to the 2006 Physicians Labeling Rule[9] format to include information about the risks and benefits of using these products during pregnancy and lactation. The PLLR did take effect on June 30, 2015.

DISCUSSION

Nonclinical Experience:

Nonclinical data proposed by the applicant, that was considered relevant for labeling, as determined during labeling meeting discussions in between DGIEP and the Maternal Health Team (MHT), are reviewed below. MHT defers to the nonclinical team regarding the final non-clinical data that is included in Sections 8 and 13.1 of the labeling.

No (b) (4) effects were observed in embryo-fetal development studies in rats at oral doses (b) (4) up to 2000 mg/kg/day ((b) (4) times the maximum recommended human dose based on body surface area) or in rabbits at oral doses up to 1000 mg/kg/day ((b) (4) times the maximum recommended human dose based on body surface area) administered during organogenesis.

(b) (4) the effects of acetylcysteine on (b) (4)

(b) (4) in the Ames test.

In a reproduction study of acetylcysteine, male rats were treated orally for *15 weeks* prior to mating and during the mating period. A "slight non-dose related reduction in fertility" was observed at oral doses of 500 and 1000 mg/kg/day ((b) (4) and (b) (4) times the recommended human dose, respectively, based on body surface area).

Reviewer's Comment: DPMH concludes that the (b) (4)

Clinical Experience:

The applicant conducted a literature search on August 26, 2015. The Medline, Embase, BIOSIS, ToxCenter, and Chemical Abstracts databases were searched, using the term "*oral acetylcysteine use in pregnancy and lactation.*" Findings reported in the publications retrieved are summarized in the sections below.

9 *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

(b) (4)

DPMH also searched PubMed for publications related to acetaminophen use in pregnancy and lactation. The information obtained was consistent with the applicant's literature search.

Pregnancy

Published reports evaluating concentrations of acetylcysteine in mother and neonate indicate that acetylcysteine crosses the placenta. In a published report of intravenous acetylcysteine administered to 11 women diagnosed with chorioamnionitis, placental transfer of acetylcysteine was rapid, umbilical cord concentrations often exceeded maternal concentrations with fetal exposure occurring rapidly[12]. A case series of 4 pregnant women with acetaminophen overdose treated with oral or intravenous acetylcysteine reported that acetylcysteine was detected in the cord blood of 3 viable infants and in the cardiac blood of the fourth infant sampled at time of autopsy; the mean acetylcysteine cord blood concentration was within the range associated with adult therapeutic doses[13].

McElhatton *et al.,* published a case series to investigate the outcome of pregnancy in 300 women who had self-administered an overdose of paracetamol, either alone, or as part of combined preparations[14]. Thirty-three of these women were treated with acetylcysteine. Their pregnancy outcomes were: 24 normal infants, one live-born with hypospadias, three spontaneous abortion or fetal death, and five electively terminations. Nine of these women were in their first trimester when overdosed; of these, two had spontaneous abortions, two had elective terminations, and five delivered normal infants. Other case reports referenced by the applicant addressing acetylcysteine administered during pregnancy provide similar limited information. These were either single case reports[15] [16, 17] or a case series with a smaller sample size than reported by McElhatton *et al*[18][19].

There are suggestions from these case reports that pregnant women with acetaminophen overdose, and a potentially toxic acetaminophen plasma level, should be treated with acetylcysteine as soon as possible. [20,19, 17,15] Delays in administering acetylcysteine may increase the risk of maternal and infant morbidity and mortality. During a nationwide acetaminophen overdose study conducted at the Rocky Mountain Poison and Drug Center

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12 Wiest DB, Chang E, Fanning D, Garner S, Cox T, Jenkins DD. Antenatal Pharmacokinetics and Placental Transfer of N-Acetylcysteine in Chorioamnionitis for Fetal Neuroprotection. *J Pediatr*, 2014;165:672-677.
13 Horowitz RS, Dart RC, Jarvie DR, Bearer CF, Gupta U. Placental Transfer of N-Acetylcysteine Following Human Maternal Acetaminophen Toxicity. *Clinical Toxicology*, 1997;35:447-451.
14 McElhatton PR, Sullivan FM, Volans GN. Paracetamol Overdose In Pregnancy; Analysis Of The Outcomes Of 300 Cases Referred To The Teratology Information Service. *Reproductive Toxicology*, 1997; 11:85-94
15 Wang PH, Yang MJ, Lee WL, Chao HT, Yang ML, Hung JH. Acetaminophen Poisoning in Late Pregnancy. A Case Report. J *Reprod Med*. 1997 Jun;42(6):367-71.
16 Crowell C, Villacorta Lyew R, Givens M, Deering SH. Case Report. Caring for the Mother, Concentrating on the Fetus: Intravenous N-Acetylcysteine in Pregnancy. *American Journal of Emergency Medicine*, 2008;26:735.e1–735.e2
17 Shah A, Karlapudi K. Paracetamol Over Dosage in Third Trimester of Pregnancy; A Clinician's Challenge towards Managing It. *International Journal of Gynaecology and Obstetrics*, 2009:107:S682
18 Bailey B. Are There Teratogenic Risks Associated With Antidotes Used In The Acute Management Of Poisoned Pregnant Women? *Birth Defects Research*, 2003;67:133-140.
19 Riggs BS, Bronstein AC, Kulig K, Archer PG, Rumack BH. Acute Acetaminophen Overdose during Pregnancy. *Obstet Gynecol*, 1989;74:247-253.
20 Wilkes JM, Clark LE, Herrera JL. Acetaminophen Overdose in Pregnancy. *Southern Med J*, 2005;98:1118-1122 (Review).

from 1976-1985, 113 women who entered into the study were reported to be pregnant at the time of the overdose[19]. Follow-up, including appropriate laboratory and pregnancy outcome data, was available for 60 women. Of the 24 women with acetaminophen levels above the acetaminophen overdose nomogram line, ten were treated with N-acetylcysteine within 10 hours post-ingestion. Of these ten women, eight delivered normal infants with no reported malformations (term-7, premature-1) and two had elective abortions. The reasons for the elective abortions are not reported in the document. Of the ten women treated with N-acetylcysteine 10-16 hours post-ingestion, five delivered normal infants (term 4, premature-1), two had elective abortions, and three had spontaneous abortions. Of the four women treated with N-acetylcysteine 16-24 hours post-ingestion, one mother died on the fifth day post-ingestion due to disseminated intravascular coagulation after a spontaneous abortion. The other three pregnancy outcomes in this group were stillbirth, elective abortion, and live birth. A statistically significant correlation was reported between the time to loading dose of N-acetylcysteine and probability of fetal death (p=0.002), with an increase in the incidence of spontaneous abortion or fetal death when time to loading dose was delayed over 10 hours from acetaminophen ingestion.

DPMH Assessment:
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.

Lactation
A search of published literature in the Drugs and Lactation Database (Lactmed)[21] and Pubmed for available human lactation data was performed to update the Lactation subsection of labeling for this application. There is no information in published literature on the presence of acetylcysteine in human milk, the effects on the breastfed infant, or the effects on milk production. No animal studies have been conducted.

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). DPMH proposes including the following statement:

[21]The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT

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

Females and Males of Reproductive Potential:
See reviewer comments under nonclinical experience.

CONCLUSIONS
CETYLEV (acetylcysteine) labeling has been revised to comply with the PLLR. DPMH has the following recommendations for acetylcysteine labeling:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" subsection of acetylcysteine labeling was formatted in the PLLR format to include "Risk Summary," "Clinical Considerations," and "Data" subsections[22].

- **Lactation, Section 8.2**
  - The "Lactation" subsection of acetylcysteine labeling was formatted in the PLLR format to include the "Risk Summary" subsection[23].

RECOMMENDATIONS

1.) DPMH revised subsections 8.1 and 8.2 (b) (4) in CETYLEV (acetylcysteine) labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited case reports and case series on acetylcysteine use during pregnancy are insufficient to inform a drug-associated risk of birth defects and miscarriage. However, there are clinical considerations *[see Clinical Considerations]*. In animal reproduction studies, no teratogenic effects were observed with oral administration of acetylcysteine to pregnant rats and rabbits during organogenesis at doses up to (b) (4) times the maximum recommended human dose of about 560 mg/kg (total dose on first day) *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of

22 Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.
23 Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Acetaminophen and acetylcysteine cross the placenta. Delaying treatment in pregnant women with acetaminophen overdose and potentially toxic acetaminophen plasma levels may increase the risk of maternal and fetal morbidity and mortality.

Data

Animal Data

No teratogenic effects were observed in embryo-fetal development studies in rats at oral doses up to 2000 mg/kg/day ((b) (4) times the maximum recommended human dose based on body surface area) or in rabbits at oral doses up to 1000 mg/kg/day ((b) (4) times the maximum recommended human dose based on body surface area) administered during organogenesis.

8.2 Lactation

Risk Summary

There is no information regarding the presence of acetylcysteine in human milk, or the effects of acetylcysteine on the breastfed infant or on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for CETYLEV and any potential adverse effects on the breastfed infant from CETYLEV or from the underlying maternal condition.

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/s/

SUCHITRA M BALAKRISHNAN
11/10/2015

TAMARA N JOHNSON
11/12/2015

LYNNE P YAO
11/12/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs – ODE IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200

MEMORANDUM AND PEDIATRIC LABELING REVIEW

From:	Donna Snyder, MD, Medical Officer Pediatric and Maternal Health Staff (PMHS)
Through:	Hari Cheryl Sachs, MD, Pediatric Team Leader Linda Lewis, Acting Deputy Director Division of Pediatric and Maternal Health (DPMH)
To:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
NDA:	207916
Drug:	Cetylev® (N-acetylcysteine effervescent tablets)
Sponsor:	Arbor Pharmaceuticals, Inc.
Proposed Indication:	An antidote for acetaminophen overdose indicated to prevent or lessen hepatic injury (b) (4) ingestion of a potentially hepatotoxic quantity of acetaminophen
Consult request:	To assist the Division in the review of the this 505(b)(2) NDA application and with labeling

Materials Reviewed:

- Draft Labeling submitted by the sponsor to NDA 207916 on March 30, 2015
- Study Report for the Bioavailability Study submitted on March 30, 2015 by the sponsor.

- Non-Agreed iPSP Letter, dated September 19, 2014, DARRTS Reference ID: 3630785
- Pediatric Review Committee Minutes from September 3, 2014, dated September 15, 2014, DARRTS Reference ID: 3627399
- Initial Pediatric Study Plan (iPSP) submitted by the sponsor on June 23, 2014
- Medical Officer Review of 30 Day IND Safety Review, dated March 20, 2014, DARRTS Reference ID: 3474501
- Clinical Pharmacology 30 Day IND Safety Review, Dated March 20, 2014, DARRTS Reference ID: 3472333
- Acetadote® (acetylcysteine) Injection labeling, dated June 5, 2013 from Drugs@FDA
- Medical Review of studies submitted in response to PREA PMR for Acetadote® (acetylcysteine) Injection, dated November 23, 2004
- Approval letter for Acetadote® (acetylcysteine) Injection dated January 23, 2004 from Drugs@FDA
- Acetadote® (acetylcysteine) Injection Clinical Pharmacology and Biopharmaceuticals Review, dated December 6, 2002
- Division Files for NDA 13601 (Mucomyst®) acetylcysteine dated 1982 -1987

Introduction:
On March 30, 2015, Arbor Pharmaceuticals, Inc. submitted a 505(b)(2) application under NDA 207916, for Cetylev® (N-acetylcysteine effervescent tablets). Cetylev® relies on the previous findings of safety and effectiveness for Mucomyst® (acetylcysteine, NDA 13601) solution, originally approved in 1963 and withdrawn from marketing in 2007 and ANDA 72547 (Luitpold Pharmaceuticals), acetylcysteine solution; inhalation, oral, 20% approved in 1995. Acetylcysteine solution 20% is indicated as a mucolytic agent when administered via nebulization and as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen when given orally. Acetylcysteine solution 20% labeling for treatment of acetaminophen intoxication includes dosing information down to birth, but pediatric information is otherwise absent from labeling. The recommended dosing is a 140 mg/kg loading dose, followed by maintenance doses of 70 mg/kg every 4 hours for a total of 17 doses.

Acetylcysteine (Acetadote®, NDA 21539) is also 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.

Cetylev® is an oral formulation intended to be dissolved in water before administration, and is indicated specifically for treatment of acetaminophen overdose. The applicant has conducted a bioequivalence study in healthy adult volunteers to bridge the proposed formulation to the RLD.

Background:
Hepatotoxicity induced by acetaminophen may occur with a single overdose or when excessive doses are given repeatedly and is potentially fatal. When dosed appropriately, acetaminophen is conjugated with glucuronide and sulfate. About 10% of the drug is converted to a toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is hepatotoxic and can cause cellular necrosis, but since only small amounts of NAPQI are formed under normal dosing conditions, NAPQI is generally metabolized by glutathione and excreted in the urine or bile. Toxicity may occur if there is increased metabolism to NAPQI or if detoxification is reduced due to reduced glutathione levels. Nutritional influences and drugs that inhibit the metabolic pathway can further contribute to the risk of toxicity.[1]

Acetylcysteine's (also known as n-acetylcysteine or NAC) mechanism of action is not completely understood, but NAC is thought to reduce acetaminophen levels in the first 24 hours by direct binding of NAPQI, creating a non-toxic metabolite, by conversion to cysteine which repletes glutathione stores and by induction of sulfonation, promoting non-toxic acetaminophen metabolism.[2] NAC may also be beneficial in treating late acetaminophen overdose and fulminant hepatitis because of its anti-inflammatory and antioxidant effects.[3]

The minimal single toxic dose of acetaminophen in pediatric patients associated with hepatocellular injury is generally accepted to be 150 mg/kg based on initial work by Rumack and Matthew and supported subsequently by clinical experience.[4,5] Patients who have ingested toxic amounts of acetaminophen initially have no symptoms or symptoms are vague and consist of anorexia, vomiting, nausea and pallor (Stage 1). These symptoms typically resolve within 24 hours. However, after 24 hours (Stage 2), symptoms of hepatic toxicity may develop, such as right upper quadrant abdominal pain, elevation of transaminases and bilirubin. By day 3 to 4 (Stage 3), patients who have not recovered will develop fulminate hepatic failure, including metabolic acidosis, jaundice, coagulopathy and continued abdominal pain and encephalopathy. By day 4 to 14 (Stage 4) patients who have not recovered die due to liver failure or complications of liver failure unless a liver transplant is performed. Treatment consists of use of activated charcoal, administration of NAC and close monitoring of liver function. If the time of ingestion is known and is less than 24 hours, the acetaminophen nomogram can be used to determine if treatment is needed based on the blood acetaminophen blood levels.[4] For patients who begin treatment more than 24 hours after ingestion, if liver function tests are elevated, levels may not be helpful, toxicity should be assumed and treatment with NAC started. See treatment nomogram and treatment algorithm below:

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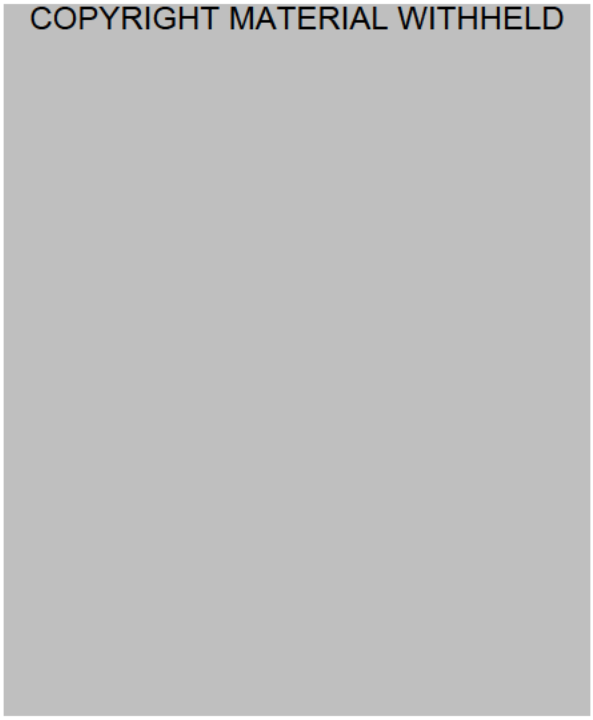
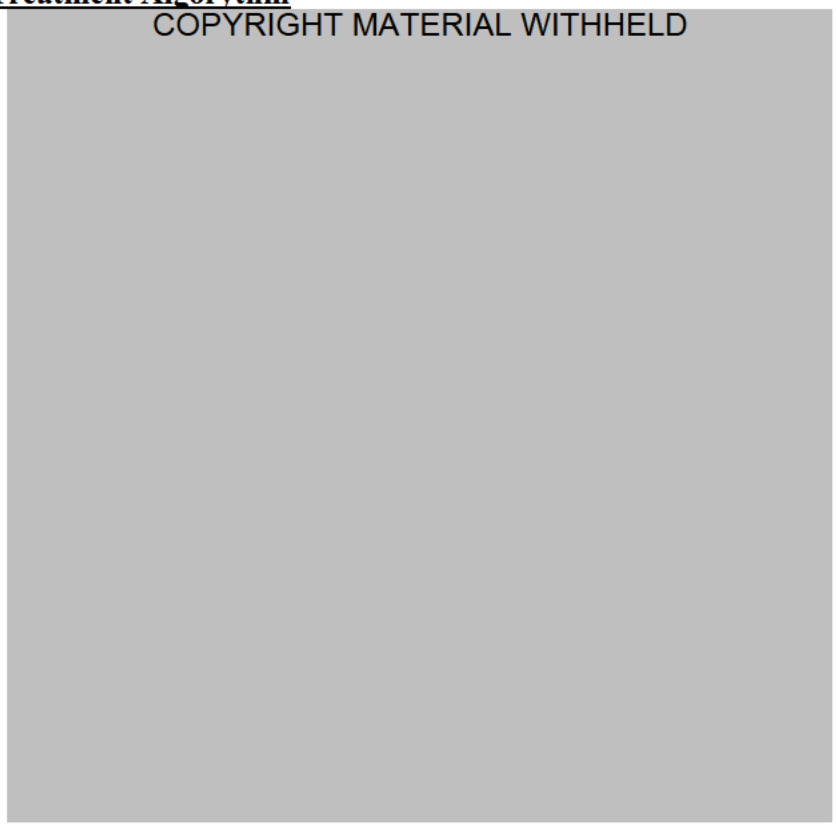
[1] American Academy of Pediatrics Committee on Drugs. Acetaminophen Toxicity in Children. Pediatrics, Vol. 108, No. 4, October 2001; pages 1020-1024.
[2] Ogilvie, J et al. Acetaminophen Overdose in Children, CMAJ, 2013: 184 (13)
[3] Baren, Jill (ed). Pediatric Emergency Medicine, "Common Pediatric Overdoses" Elsevier Health Sciences, 2008, pages 941-944
[4] Rumack, B and Matthew, H. Acetaminophen Poisoning and Toxicity. Pediatrics.1975; 55: 871-876.
[5] Aripin, K and Choonara, I The Management of Paracetamol Poisoning. Pediatrics and Child Health: 2009 19(11): 942-947

Acetaminophen Nomogram (Rumack-Matthew)[3,4]



Treatment Algorythm[3]



Regulatory History:
Under the Pediatric Research Equity Act, any application submitted for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration must submit a pediatric assessment. 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 on the grounds that the product does not represent a meaningful therapeutic benefit over existing treatments for 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.

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.

Available Pediatric Information:
A 2009 Cochrane review explored the literature on various treatment interventions for acetaminophen poisoning. The review included trials preventing absorption, charcoal hemoperfusion, antidotes including methionine, cysteine, cysteamine, dimercaprol and NAC and other interventions such as heparin and fresh frozen plasma. In regards to NAC, there have been no randomized trials to evaluate NAC compared to other antidotes or other interventions, including no randomized studies in pediatric patients.[6] NAC became the antidote of choice after publication of a study comparing IV NAC to historical controls treated with IV cysteamine, methionine or supportive therapy. The study found NAC to be superior to supportive care and potentially to the other comparator products. Because NAC has a more favorable safety profile, NAC became standard of care for treatment of acetaminophen poisoning despite the limitations in the study.[7] Continued use

[6] Buckley, B and Gluud, C. Interventions for Paracetamol (acetaminophen) Overdose (Review). The Cochrane Collaboration. John Wiley and Sons, 2009.

of the product is supported by clinical practice, a limited number of studies comparing NAC to historical or non-randomized controls[8] and analysis of data related to use which indicates increasing hepatic toxicity when NAC treatment is delayed.[9]

The sponsor for Acetadote® submitted an analysis of the Hunters Toxological Center Service (HATS) Database to fulfill the PREA PMR for pediatric studies for Acetadote®. This database included information on 148 acetaminophen overdoses in patients 1 month to 15 years of age over a period of 16 years from January 16, 1987 to January 10, 2003. Of note, 82% of these patients were between 12 to 15 years of age and there were no patients between 5 to 11 years of age. Only 23/148 patients received NAC. The sample size was not large enough to perform a valid statistical analysis of the data comparing patients treated with NAC to the remaining patients. None of the patients treated with NAC developed hepatotoxicity. The clinical review states that "I concur with the sponsor in its conclusion, i.e., 23 NAC treated pediatric patients do not allow for a statistical analysis. From a clinical standpoint, however, the prevention of liver failure observed in these NAC treated pediatric patients, particularly those treated within 8 hours from the acetaminophen overdose; mimic the beneficial protective effect observed in adult patients treated with Acetadote®. The 16 year span needed to accrue the rather small pediatric sample size points to the logistic difficulty in attempting to obtain further efficacy information in pediatric acetaminophen overdoses." As stated above, the Division considered this data sufficient to fulfill the PREA PMR.

Acetadote® includes the following statement in Section 8.4: "No adverse effects were noted during intravenous infusion with acetylcysteine at a mean rate of 4.2 mg/kg/h for 24 hours to 10 preterm newborns ranging in gestational age from 25 to 31 weeks and in weight from 500 to 1380 grams in one study or in 6 newborns ranging in gestational age from 26 to 30 weeks and in weight from 520 to 1335 grams infused with acetylcysteine at 0.1 to 1.3 mg/kg/h for 6 days. Elimination of acetylcysteine was slower in these infants than in adults; mean elimination half-life was 11 hours. There are no adequate or well controlled studies in pediatric patients." The source of this information is from literature submitted by the sponsor referencing PK data collected in 16 preterm infants from 2 open-label studies. These patients were not being treated for acetaminophen toxicity.[10] The Clinical Pharmacology reviewer noted at the time of the Acetadote® review that there was no other available PK data in older pediatric patients.

Reviewer Comment: This PK data referenced above, from an article published in 1999, which was obtained for the IV formulation, was not reviewed by the Agency. The sponsor for Cetylev® (N-acetylcysteine effervescent tablets) did not include this information in labeling for their product, likely because the information is not included in the labeling

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[7] Prescott, L. Intravenous N-acetylcysteine: the Treatment of Choice for Paracetamol Poisoning. Bri Med J: 1979; 6189: 1097-100.
[8] Rumack, B and Peterson, R Acetaminophen Overdose: Incidence, Diagnosis and Management in 416 Patients. Pediatrics:1978 Nov;62 (5 Pt 2 Suppl):898-903.
[9] Smilkstein, M et al. Efficacy of Oral N-acetylcysteine in the Treatment of Acetaminophen Overdose,. N Engl J Med 1988; 319: 1557-62.
[10] Aloha, T et al. Pharmacokinetics of intravenous N-acetylcysteine in pre-term newborn infants. Eur J Clin Pharmacol: 1999; 55: 645-50/.

for the products referenced in the application and the PK data was collected in patients given the IV product.

Pediatric Dosing:
The dosage regimen used in the referenced labeling was originally introduced in studies in the 1970s and has become the accepted regimen for oral treatment. [8] According the clinical study report for the original Mucomyst® supplemental application (1982), "the dose and the duration of maintenance dosing were not experimentally established nor were they based on clinical trials." Oral dosing using the currently approved products is accomplished by mixing the oral solution in water, and measuring out the appropriate amount based on weight prior to administration. One of the disadvantages of the approved oral products is that they have a very foul odor and taste. Additionally, because the preparation of the product requires mixing and measuring out a specific quantity based on body weight, dosing errors are common. Since Cetylev® is an effervescent tablet that dissolves in water, measuring an appropriate amount of solution for dilution is not necessary (b) (4) (b) (4)

Discussion: PEDIATRIC USE LABELING
The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. Since the product will be indicated for use in pediatric patients, the information will be included throughout labeling. Our recommendations reflect labeling provided to the Division on October 22, 2015. See the approval letter for the final version of labeling.

DPMH –RECOMMENDATIONS FOR LABELING
DPMH made suggestions to improve readability of dosing instructions in Highlights and Dosage and Administration (2), but did not provide specific language to the Division.

> **8 USE IN SPECIFIC POPULATIONS**
>
> **8.4 Pediatric Use**
> Pediatric approval, including doses, is not based on adequate and well-controlled clinical studies. Pediatric dosing recommendations are based on clinical experience [see Dosage and Administration (2)].

Reviewer comment: As mentioned above, there are no adequate and well-controlled trials in pediatric patients, however there are studies that compare NAC to historical controls, non-randomized controls and open-label studies that have shown reduced hepatotoxicity when NAC is compared to other treatments. Dosing was empirically established in the

1970s and has been maintained in clinical practice despite a lack of PK data to support dosing.

Conclusion:
DPMH participated in a labeling meeting on October 22, 2015, to discuss the pediatric use subsection of Cetylev® (N-acetylcysteine effervescent tablets) labeling. DPMH also participated in team meetings during the review of the NDA. This memorandum and labeling review reflect our recommendations provided to the Division.

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/s/

DONNA L SNYDER
10/22/2015

HARI C SACHS
10/28/2015
I agree with these labeling recommendations.

LINDA L LEWIS
10/29/2015

M E M O R A N D U M

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

DATE: August 28, 2015

TO: Sarah Miksinski, Ph.D.
Director (Acting)
Office of New Drug Products
Office of Pharmaceutical Quality

FROM: Gajendiran Mahadevan, Ph.D.
Staff Fellow
Division of New Drug Bioequivalence (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

Xiaohan Cai, Ph.D.
Visiting Associate
Division of Generic Drug Bioequivalence (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Lead Pharmacologist
Division of New Drugs Bioequivalence Evaluation
Office of Study Integrity and Surveillance

and

Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence
Office of Study Integrity and Surveillance

SUBJECT: Surveillance inspection of (b) (4) Covering NDA 207916, Acetylcysteine Effervescent Tablets for Oral Solution (0.5g and 2.5 g), Arbor Pharmaceuticals, LLC., USA

At the request of the Office of New Drug Products (ONDP), the Office of Study Integrity and Surveillance (OSIS) inspected the analytical portion of the following bioavailability study:

Study Number: AR10.001

Study Title: "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 (0.5g and 2.5g) as compared to reference product (Acetylcysteine solution; oral 20% (200 mg/mL) in healthy adult, human subjects, under fasting conditions"

The analytical inspection was conducted during (b) (4) at (b) (4) by OSIS scientists Gajendiran Mahadevan, Ph.D. and Xiaohan Cai, Ph.D. The inspection included a thorough examination of study records, facilities and equipment, and interviews and discussions with the firm's staff and management.

At the conclusion of the inspection, Form FDA 483 was issued to the firm (**Attachment-1**). The firm responded to Form FDA 483 on August 21, 2015 (**Attachment-2**). The Form FDA 483, the firm's response to Form FDA 483, and our evaluation follow.

1) **Study samples were not stored in a secure and controlled environment. Specifically, subject plasma samples were stored in an unlocked -80°C freezer located in an unsecured common area in the analytical facility.**

Firm's Response: In their response to the Form FDA 483, (b) (4) acknowledged the observation and promised to implement the following corrective actions by August 31, 2015.

1. Individual freezers holding study samples for FDA regulated studies will be locked.

2. Up to three employees will be assigned as freezer custodians and would control access to the samples in the locked freezers. Samples would also be tracked in Watson LIMS.

3. Key-card access will be implemented in the processing areas providing access to freezers by end of year 2015.

4. Standard Operating Procedures and policies of (b) (4) will be updated to reflect the above changes.

OSIS Assessment: (b) (4)'s response is acceptable. Following implementation, the corrective actions would provide physical security for study samples stored in freezers. During the inspection, we reviewed source documents for sample arrival and subject sample analysis and did not find any discrepancies. Thus, the above finding is unlikely to impact the integrity of the study data.

2) **Computer system access was not limited to authorized individuals. Specifically, electronic source records were accessible to individuals from another establishment.**

Firm's Response: (b) (4) acknowledged the observation that the data servers were housed in an area accessible with their sister establishment, (b) (4). However, they claimed that although some contractors had physical access to the room and data servers, logical access to the data servers and data was limited. As a corrective action, (b) (4) stated that they are immediately limiting access to the server room to nine personnel: three representing the property management, two representing (b) (4), and four representing (b) (4). As a long-term fix for the physical security concerns of the data servers and data, the data servers will be physically relocated to a secured room in (b) (4)' facility by end of year 2015. Physical and logical access to the data and data servers would be limited. Standard Operating Procedures and policies of (b) (4) will be updated to reflect the above changes.

OSIS Evaluation: Although access to the data generated from the above study had logical access controls, physical access to the data servers was not limited to authorized personnel of (b) (4) and was also accessible to contractors and employees of (b) (4). (b) (4) did not have procedures in place to prevent accidental or intentional destruction/corruption of stored data. However, during the inspection, we did not note any discrepancies or missing data. Thus, the above finding is unlikely to impact the integrity of the study data.

Recommendations:

Following the evaluation of the inspectional findings and the firm's response, the analytical data from the audited study were found to be reliable. Therefore, we recommend that the analytical data from study AR10.001 be accepted for further Agency review.

Gajendiran Mahadevan, Ph.D.
OSIS, DNDBE

Xiaohan Cai, Ph.D.
OSIS, DGDBE

Final Classification:

VAI: (b) (4)

E-mail CC:
OSIS/Taylor/Dejernett/Fenty-Stewart/Nkha/Johnson
OSIS/DGDBE/Haidar/Skelly/Choi/Cai
OSIS/DNDBE/Bonapace/Dasgupta/Cho/Mahadevan

CDER/OPQ/ONDP/Miksinski/Ou

Draft: GM 08/18/2015; XC 08/24/2015;
Edit: AD 08/28/2015; CB 08/28/2015

OSI File: BE6906; O:\BE\EIRCOVER\207916. (b) (4)
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical Sites/ (b) (4) /NDA 207916_Acetylcysteine

FACTS: (b) (4)

6 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

GAJENDIRAN MAHADEVAN
08/28/2015

CAI XIAOHAN
08/31/2015

ARINDAM DASGUPTA
08/31/2015

CHARLES R BONAPACE
08/31/2015

M E M O R A N D U M

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

DATE: July 1, 2015

TO: Division of Gastroenterology Products (DGIEP)

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 207916

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

OSIS recently inspected the site listed below. 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.

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Clinical	Spaulding Clinical	525 S. Silverbrook Drive, West Bend, WI 53095

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/s/

SHILA S NKAH
07/01/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # NDA 207916 BLA# n/a	NDA Supplement #: S- n/a BLA Supplement #: S- n/a	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Animal Rule Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Pediatric
Proprietary Name: Cetylev Established/Proper Name: (acetylcysteine) effervescent tablets Dosage Form: Tablets Strengths: 500 mg and 2.5 g		
Applicant: Arbor Pharmaceuticals, LLC Agent for Applicant (if applicable): n/a		
Date of Application: March 30, 2015 Date of Receipt: March 30, 2015 Date clock started after UN: March 30, 2015		
PDUFA/BsUFA Goal Date: January 30, 2016	Action Goal Date (if different): January 29, 2016	
Filing Date: May 29, 2015	Date of Filing Meeting: May 13, 2015	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☒ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): **antidote to prevent or lessen hepatic injury** [redacted] (b) (4) **ingestion of a potentially hepatotoxic quantity of acetaminophen.**		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): n/a	
List referenced IND Number(s): IND 116902	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☐	☐	☐	505(b)(2) will be added to DARRTS once the Filing letter has been placed
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		No fee required; Orphan Designation Received

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☒	☐		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 7 ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☐	☒	7 year Orphan Drug Exclusivity Requested

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	However, each debarment certification mentions "in Sections 306 (a) or (b) of the Generic Drug Enforcement Act of 1992" instead of the "Federal Food, Drug and Cosmetic Act"-sent email to BS to inquire should I have the applicant resubmit- 4/13/15; applicant advised to resubmit on 4/13/15; Applicant resubmitted corrected forms on 4/27/15.
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2]	☐	☒		Orphan Designation received 2/24/15

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm

***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	Submitted 4/1/15 and coded correctly in DARRTs
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☒	☐	☐	"Non REMS" justification submitted; parties notified
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☒ Other (specify) Patient Information			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm

Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5]	☐	☐	☒	However, the applicant submitted the PI in PLLR Format
If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	Consulted 4/12/15
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	Consulted 4/12/15
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	Consulted 4/12/15
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)?	☐	☐	☐	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

If no, request in 74-day letter.				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		However, a pre-IND meeting under PIND 116902 was held on 1/29/13 regarding the submission of this NDA. Meeting Minutes dated 2/27/13
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 13, 2015

BACKGROUND: Arbor Pharmaceuticals, LLC (Arbor) submitted a new drug application which provides for a new dosage form, effervescent tablets, with the following proposed indication: antidote to prevent or lessen hepatic injury (b) (4) ingestion of a potentially hepatotoxic quantity of acetaminophen. This product was granted orphan-drug designation for *preventing hepatic injury from acetaminophen overdose* on February 24, 2015.

Arbor utilized NDA 13601 Mucomyst (acetylcysteine) solution, which was withdrawn on March 13, 2009, as the referenced listed drug (RLD) and submitted a bioequivalence study to support its efficacy and safety.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	CDR Anissa Davis-Williams	Y
	CPMS/TL:	Brian Strongin	N
Cross-Discipline Team Leader (CDTL)	Tapash Ghosh		Y
Division Director/Deputy	Donna Griebel		Y
Office Director/Deputy	N/A		N/A
Clinical	Reviewer:	Lara Dimick-Santos	Y
	TL:	Aisha Peterson	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	N/A
	TL:	N/A	N/A

Clinical Pharmacology	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Biostatistics	Reviewer:	N/A	N/A
	TL:	N/A	N/A

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Yuk-Chow Ng	Y
	TL:	David Joseph	Y
Statistics (carcinogenicity)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Immunogenicity (assay/assay validation) *(for protein/peptide products only)*	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Product Quality (CMC)	Reviewer:	Hitesh Shroff	Y
	TL:		
Biopharmaceutics	Reviewer	Mei Ou (Primary)	Y
	TL:	Tien Mien (Albert) Chen	Y
Quality Microbiology	Reviewer:	Vaikunth Prabhu	N
	TL:	Unknown	unknown
CMC Labeling Review	Reviewer:	Hitesh Shroff	Y
	TL:	N/A	N/A
Facility Review/Inspection	Reviewer:	Juandria Williams	N
	TL:	Unknown	N/A
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Sherly Abraham	N
	TL:	Kendra Worthy	N
OSE/DRISK (REMS)	Reviewer:	n/a	n/a
	TL:	n/a	N/A
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A

Bioresearch Monitoring (OSI)	Reviewer:	Susan Leibenhaut	Y
	TL:	Unknown	Unknown
Controlled Substance Staff (CSS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Other reviewers/disciplines	Reviewer:	Donna Synder (DMPH-Peds) Carrie Ceresa (DMPH-Maternal) Shawna Hutchins (DMPP) Meeta Patel (OPDP)	Y N Y N
	TL:	Hari Sachs (DMPH- Peds) Tamara Johnson (DMPH-Maternal) Marcia Britt-Williams (DMPP) Kathleen Klemm (OPDP)	Y N N N
Other attendees	Jeff Fritsch, Aleksander Winiarski, Lori Goski, Kerri-Ann Jennings		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues:	☐ Not Applicable
○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☒ NO
○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☒ YES ☐ NO
Describe the scientific bridge (e.g., BA/BE studies):	This BA/BE study is to bridge proposed acetylcysteine effervescent tablets (CETYLEV) for oral solution (b) (4) the applicant used a non-RLD ANDA 203853 from Innopharma for their bridging study. An information request is being submitted to obtain an explanation.

• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: none	☐ Not Applicable ☒ No comments
CLINICAL **Comments**: None	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: none ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**: none	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**: none	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL MICROBIOLOGY **Comments**: none	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: none	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: none	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (protein/peptide products only) **Comments**: none	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: none	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested?	 ☒ YES ☐ NO

If no, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: The information was sent to the officer (Ron Bloom) on April 13, 2015.	☐ YES ☐ NO ☒ YES ☐ NO
Quality Microbiology • Was the Microbiology Team consulted for validation of sterilization? **Comments**: Solid Oral Tablets	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**: CMC reviewer stated that all substance and manufacturing sites are acceptable	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**: n/a	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**: none	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO

• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Andrew Mulberg

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): N/A

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

Milestone Meetings	
Filing Meeting	**5/13/15**
Planning Meeting	**5/28/15**
Mid-Cycle Meeting	**9/3/15**
PeRC ***PeRC Paperwork Due:***	**N/A (Orphan Designated** **(2/24/15)**

Wrap-up Meeting	12/17/15

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review

	ACTIONS ITEMS
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	351(k) BLA/supplement: If filed, send filing notification letter on day 60
☐	If priority review: • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

ANISSA A DAVIS
05/29/2015

BRIAN K STRONGIN
05/29/2015

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 207916

Application Type: New NDA

Name of Drug/Dosage Form: Cetylev (acetylcysteine) effervescent tablets

Applicant: Arbor Pharmaceuticals, LLC

Receipt Date: March 30, 2015

Goal Date: January 30, 2016

1. Regulatory History and Applicant's Main Proposals

Arbor Pharmaceuticals, LLC (Arbor) submitted a new drug application which provides for a new dosage form, (acetylcysteine) effervescent tablets, with the following proposed indication: antidote to prevent or lessen hepatic injury (b) (4) ingestion of a potentially hepatotoxic quantity of acetaminophen. This product was granted orphan-drug designation for *preventing hepatic injury from acetaminophen overdose* on February 24, 2015.

Arbor utilized NDA 13601 Mucomyst (acetylcysteine) solution, which was withdrawn on March 13, 2009, as the referenced listed drug (RLD) and submitted a bioequivalence study to support its efficacy and safety.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by July 3, 2015. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *HL is one-page in length. However, applicant submitted a waiver request on April 10, 2015..*

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required

• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

NO 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment: *The statement is not verbatim as above. The label states, "See 17 for PATIENT COUNSELING INFORMATION and pateint information".*

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment: *However, label resubmitted on April 10, 2015 in acordance with the PLLR (section 8 subsection title changes).*

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

NO 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment: *Verbatim statement not present in FPI. Applicant to place statement in this section of the label.*

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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

/s/

ANISSA A DAVIS
04/27/2015

BRIAN K STRONGIN
04/27/2015