NDA 021539/S-019

**SUPPLEMENT APPROVAL**

Cumberland Pharmaceuticals Inc
Attention: Beth A. Zaborny
Director Regulatory Affairs
1600 West End Avenue
Suite 1300
Nashville, TN 37203

Dear Beth A. Zaborny:

Please refer to your supplemental new drug application (sNDA) dated and received January 26, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Acetadote (acetylcysteine) injection.

This Prior Approval supplemental new drug application provides for the addition of a two-bag dosing regimen.

## APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

## WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

## PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

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[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

## REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

## REQUESTED PHARMACOVIGILANCE

We request that you submit all U.S. cases describing a wrong dose error or the potential for a wrong dose error involving Acetadote as 15-day "Alert reports" (described under 21 CFR 314.80(c)(1)) through the 3rd year following U.S. approval of the supplemental NDA.

We request that you provide a separate narrative summary and analysis for the cases of wrong dose error or the potential for a wrong dose error involving Acetadote in each required postmarketing periodic safety report (e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)).

Your narrative summary and analysis should include an interval and cumulative assessment of each wrong dose error or the potential for a wrong dose error involving Acetadote. The following items should be included:

- The number of cases reporting that a patient was administered a wrong dose
- The number of cases or complaints describing the potential for a wrong dose error (including close call/near miss or intercepted errors, or circumstances capable of leading to a wrong dose error)
- The reported contributing factors that led to or could lead to a wrong dose error (e.g., calculation errors, incorrect diluent volume, wrong infusion bag, wrong rate, wrong infusion time, confusion with the labeling instructions)
- Reporter recommendations or actions taken to mitigate the risk of a wrong dose error involving Acetadote
- Adverse events and outcomes attributed to the wrong dose error involving Acetadote

Your submission should also include a line listing of the cases for the reporting interval that includes the following data elements:

- case number;
- patient age and weight (kg);
- serum acetaminophen concentration at least 4 hours after ingestion;
- intended 2-bag or 3-bag regimen;
- calculated dose, diluent volume, and infusion time for each bag according to the approved labeling;
- delivered dose, diluent volume and identity, and infusion time for each bag;
- contributing factors for the wrong dose error;
- reporter recommendations or actions taken;

- adverse events and outcomes.

If you have any questions, contact Taiye Adedeji, PharmD, Senior Regulatory Project Manager, at (240) 402-8561 or Taiye.Adedeji@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Frank A. Anania, MD, FACP, AGAF, FAASLD
Director
Division of Hepatology and Nutrition
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Content of Labeling
  - Prescribing Information

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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FRANK A ANANIA
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