CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

215457Orig1s000

Trade Name:	N/A
Generic or Proper Name:	NALOXONE HYDROCHLORIDE injection, for intramuscular or subcutaneous use
Sponsor:	Kaleo, Inc.
Approval Date:	February 28, 2022
Indication:	NALOXONE HYDROCHLORIDE injection is indicated for use by military personnel and chemical incident responders for: • Emergency treatment of patients 12 years of age and older where use of high-potency opioids such as fentanyl analogues as a chemical weapon is suspected. • Temporary prophylaxis of respiratory and/or central nervous system depression in military personnel and chemical incident responders entering an area contaminated with high-potency opioids such as fentanyl analogues.

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APPROVAL LETTER

NDA 215457/Original 1

NDA APPROVAL

Kaleo, Inc.
111 Virginia Street, Suite 300
Richmond, VA 23219

Attention: Glen Kelley
Vice President, Regulatory Affairs

Dear Mr. Kelley:

Please refer to your new drug application (NDA) dated and received August 31, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Naloxone Hydrochloride Injection, 10 mg.

NDA 215457/Original 1 provides for use by military personnel and chemical incident responders for:

- Emergency treatment of patients 12 years of age and older where use of high-potency opioids such as fentanyl analogues as a chemical weapon is suspected.
- Temporary prophylaxis of respiratory and/or central nervous system depression in military personnel and chemical incident responders entering an area contaminated with high-potency opioids such as fentanyl analogues.

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.

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 and Instructions for Use) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST

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

may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 215457**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Naloxone Hydrochloride injection, 10 mg shall be 24 months from the date of manufacture of the drug component (b) (4) when stored at controlled room temperature 15°C - 25°C (59°F - 77°F); excursions permitted between 4°C and 40°C (39°F and 104°F).

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labeling must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. (See the guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names* and *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022*.)

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for

[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.

the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies for ages birth to less than 12 years of age for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed. Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

4228-1 Conduct allometric scaling of PK/PD models of naloxone-opioid interaction to establish the minimal effective dose of naloxone HCl required to reverse respiratory depression induced by fentanyl and carfentanil in pediatric patients from birth to less than 12 years of age.

Draft Protocol Submission:	03/2022
Final Protocol Submission:	04/2022
Trial Completion:	10/2022
Final Report Submission:	04/2023

4228-2 Conduct a juvenile animal toxicology study in rats to support clinical dosing in pediatric patients from birth to less than 12 years of age. This study will evaluate the effects of naloxone on the developing central nervous system, endocrine, and reproductive system.

Draft Protocol Submission:	07/2022
Final Protocol Submission:	10/2022
Study Completion:	10/2023
Final Report Submission:	02/2024

FDA considers the term “final protocol” to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

Submit the protocols to your IND 112292, with a cross-reference letter to this NDA. Reports of this required pediatric post marketing study must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)(3)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of genetic and general organ system toxicity for drug product degradants and potential leachables from the container closure system.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risk(s).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4228-3 Conduct a GLP in vitro genetic toxicology Ames assay testing the potential for the naloxone degradant, (b) (4) to induce point mutations.

Draft Protocol Submission:	04/2022
Final Protocol Submission:	06/2022
Study Completion:	09/2022
Final Report Submission:	01/2023

4228-4 Conduct a GLP in vitro genetic toxicology study characterizing the potential of the naloxone degradant, (b) (4) to induce chromosomal damage.

Draft Protocol Submission:	04/2022
Final Protocol Submission:	06/2022
Study Completion:	09/2022
Final Report Submission:	01/2023

4228-5 Conduct a GLP repeat-dose toxicology study of at least 14 days duration in a single species to characterize the toxicologic potential of the naloxone degradant, (b) (4)

Draft Protocol Submission:	08/2022
Final Protocol Submission:	11/2022
Study Completion:	07/2023
Final Report Submission:	11/2023

4228-6 Perform structural identification of the specified unknown impurities observed at relative retention time (RRT) of [redacted] (b) (4) The chemical structures of these impurities should be confirmed using physical and chemical techniques such as elemental analysis, mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy, ultraviolet (UV) spectroscopy, infrared (IR) spectroscopy, X-ray crystallography, and other tests (e.g., functional group analysis, derivatization, complex formation).

Draft Protocol Submission:	04/2022
Final Protocol Submission:	07/2022
Study Completion:	07/2023
Final Report Submission:	09/2023

4228-7 Conduct a study in order to provide product stability and leachables data through the proposed shelf-life for three batches of to-be-marketed (TBM) drug product stored at both inverted and horizontal orientations. Manufacture these batches at the commercial site and collect stability data including leachables determination at multiple stability time-points per the testing frequency recommended in ICH Q1A(R2).

Draft Protocol Submission:	04/2022
Final Protocol Submission:	07/2022
Interim Report (Batch #1):	09/2024
Interim Report (Batch #2):	09/2025
Study Completion:	07/2026
Final Report Submission:	09/2026

FDA considers the term “final protocol” to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial

Submit clinical protocols to your IND 112292 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise

undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action

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]

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

REPORTING REQUIREMENTS

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

[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

If you have any questions, please contact Jane Mun, PharmD, Regulatory Project Manager, via email at Jane.Mun@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Director
Division of Anesthesiology, Addiction Medicine and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Instructions for Use
- Carton and Container Labeling

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.

/s/

RIGOBERTO A ROCA
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