

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

209862Orig1s000

Trade Name: EVZIO

Generic or Proper Name: naloxone hydrochloride injection

Sponsor: kaleo, Inc.

Approval Date: October 19, 2016

Indication: For the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, and for immediate administration as emergency therapy in settings where opioids may be present.

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RESEARCH**

APPLICATION NUMBER:

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APPROVAL LETTER



NDA 209862

APPROVAL

kaleo, Inc.
111 Virginia St.
Suite 300
Richmond, VA 23219

Attention: Glen Kelley
Director Regulatory Affairs

Dear Mr. Kelley:

Please refer to your New Drug Application (NDA) dated and received April 19, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EVZIO (naloxone hydrochloride injection), 2 mg.

This application was originally received as supplemental New Drug Application (sNDA) 205787/S-007 and was administratively converted to NDA 209862. This application proposes addition of a new 2 mg strength for the use of EVZIO for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, and for immediate administration as emergency therapy in settings where opioids may be present.

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 text.

WAIVER OF HIGHLIGHTS SECTION

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 <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content

of labeling must be identical to the enclosed labeling text for the package insert, text for the patient package insert, and text for the instructions for use, 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.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

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 MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, 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).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 209862.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

This product is appropriately labeled for use in ages birth to 17 years for this indication. Therefore, no additional studies are needed in this pediatric group.

POSTMARKETING REQUIREMENTS UNDER 505(o)

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 determined that an analysis of postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of untreated respiratory arrest that may result from device failure and subsequent loss (i.e. failure) of the expected pharmacologic action of EVZIO (naloxone hydrochloride injection).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

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

- 3135-1 Establish reliability requirements for the combination product EVZIO (naloxone hydrochloride injection) and complete testing that verifies combination product reliability.

The timetable you submitted on October 19, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2017
Final Protocol Submission:	04/2017
Study Completion:	11/2017
Final Study Report:	01/2018

ADDITIONAL INFORMATION:

Please note the following recommendations for the postmarketing requirement described above:

- a. Establish reliability requirements for your combination product. It is recommended that reliability be directly specified as $R(t) = x\%$, where t = time and $x\%$ = probability of meeting essential performance requirements. These requirements should be objective and relate to the ability of a population of devices to meet essential performance requirements after pre-conditioning as described below. The reliability requirements should be verified with a high degree of statistical confidence.
- b. Provide rationale and justification supporting the clinical acceptability of the established reliability requirements.
- c. Describe the use conditions for the product.

- d. Define the functionality required for reliability.
- e. Define failure, as it relates to assessing the reliability requirements.
- f. Provide data to verify the reliability specifications. The acceptable endpoints for this data should be linked to your definition of failure.
- g. Devices assessed within the reliability data should be preconditioned to worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended preconditioning activities, however you should provide a rationale supporting the final precondition elements chosen, and the order in which the products are conditioned. Your assessment of the preconditioning parameters should be based on your own failure analyses (e.g. fault tree analysis) in order to assure that the scope of preconditions and their boundary values are adequately correct and complete.
 - Shipping
 - Aging
 - Storage orientation and conditions
 - Vibration handling
 - Shock handling (e.g., resistance to random impacts, such as being dropped)
- h. Devices assessed within the reliability analysis should be activated under worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended circumstances of activation; however you should provide rationale supporting the final circumstances of activation chosen.
 - Activation orientation
 - Environmental temperature
 - Simulated injection through clothing (e.g., pants, jeans, etc.)
- i. Describe how manufacturing controls have been adequately implemented to achieve the reliability specification in the release product lots.

3135-2 Conduct case study analysis of reports of failure of the combination product EVZIO (naloxone hydrochloride injection) to activate, or failure of the combination product to deliver the full-labeled dose. Perform detailed analyses of reported device failures (including reported malfunctions that did, as well as did not result in patient harm). Reports should include a full narrative description of the failure, any subsequent adverse events, the results of root cause analysis performed for the reported failure, and a description of your procedures for monitoring and analyzing the reports.

The timetable you submitted on October 19, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2017
Final Protocol Submission:	04/2017
Interim Report Submission:	12/2017
Final Report Submission:	12/2018

Submit the protocols to your IND 112292, with a cross-reference letter to this NDA. Submit all interim and final report(s) 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. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

You must submit final promotional materials and package insert(s), 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 <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

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

If you have any questions, call Diana L. Walker, PhD, Regulatory Project Manager, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Carton and Container Labeling

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

/s/

SHARON H HERTZ
10/19/2016