NDA 212854

NDA APPROVAL

Adamis Pharmaceuticals Corporation
c/o Target Health LLC
3800 Paramount Parkway, Suite 100
Morrisville, NC 27560

Attention: Adam Harris, MM, RAC
Director, Regulatory Affairs

Dear Mr. Harris:

Please refer to your new drug application (NDA) dated and received May 13, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zimhi (naloxone hydrochloride injection), 5 mg/0.5 mL.

We acknowledge receipt of your amendment dated May 13, 2021, which constituted a complete response to our November 13, 2020, action letter.

This NDA provides for the use of Zimhi (naloxone hydrochloride injection) in adult and pediatric patients for the emergency treatment of known or suspected opioid over dose, as manifested by respiratory and/or central nervous system depression.

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, agreed-upon via email on October 15, 2021.

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 (Prescribing Information, Patient Package Insert, Instructions for Use) 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 *SPL Standard for Content of Labeling Technical Qs and As.*[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[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 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 *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 212854**." 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 Zimhi (naloxone hydrochloride injection) shall be 18 months from the date of manufacture when stored at room temperature, 68-77°F (20-25°C) with excursions permitted to 59-86°F (15-30°C) in the packaging provided. Do not refrigerate. Protect from light, extreme heat and freezing.

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

This product is appropriately labeled for use in all relevant pediatric populations. Therefore, no additional pediatric studies are needed at this time.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (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 assess a signal of serious risk of needlestick injuries and known serious risk related to combination product reliability of successful injection of Zimhi.

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 risks.

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

4153-1 Conduct a study to complete testing which evaluates the combination product reliability of successful injection of Zimhi.

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

Note the following considerations regarding the postmarketing requirement described above:

1. Testing must include a fault tree analysis to demonstrate your device will provide successful injection with at least 99.999% reliability at the 95% confidence interval.
    a. The fault tree analysis must include information from your combination product's design and manufacturing methods by identifying all basic failure modes anticipated
    b. The data supporting the fault tree analysis must be provided
2. Devices assessed within the reliability test should be preconditioned to reasonably foreseeable worst-case conditions. We recommend the following preconditioning activities, below. However, you should provide 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.
    a. Aging
    b. Storage orientation and conditions
    c. Vibration handling
    d. Shock handling (e.g., resistance to random impacts, such as being dropped)

3. Verification of product reliability must employ Corrective And Preventative Action Process (CAPA) standards, and Standard Operating Procedures, which at a minimum must include:
    a. Active searching of product field failures such as those reported by news outlets, or are otherwise publicly available on social media; or by contacting product users directly
    b. Statistical analyses to detect recurring quality problems
    c. Retesting and reevaluation of any non-conforming product (after rework), to ensure the product meets current approve specifications
    d. Recording of changes in methods and procedures needed to correct and prevent identified quality problems
    e. Dissemination of information related to quality problems and information on corrective action so as to assure the quality of the product or prevention of the identified problem

4153-2 Conduct a study of needlestick injuries associated with the use of Zimhi. Provide a detailed analysis of incidents (including reported incidents that did, as well as did not, result in patient and/or provider harm), full event narratives of the incidents and any subsequent adverse events, and the results of root cause analysis performed for the reported event.

Draft Protocol Submission:	02/2022
Final Protocol Submission:	07/2022
Study Completion:	07/2025
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FDA considers the term *final* 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.[3]

Submit clinical protocol(s) to your IND 136148 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all 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).**

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Submission of the protocol for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

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.*[4]

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.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

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

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.[7]

If you have any questions, call Joyce Chin, PharmD., Regulatory Health Project Manager, at (301) 348-1772.

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
  - Patient Package Insert
  - Instructions for Use
- Carton and Container Labeling

[7] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

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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.

/s/

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