



NDA 208411

NDA APPROVAL

Adapt Pharma Operations Limited
c/o Pacific-Link Consulting
8195 Run of the Knolls Court
San Diego, CA 92127

Attention: Richard E. Lowenthal, MS, MBA
President, Pacific-Link Consulting,
Adapt Pharma Regulatory Representative

Dear Mr. Lowenthal:

Please refer to your New Drug Application (NDA) dated July 17, 2015, received July 20, 2015, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Narcan Nasal Spray (naloxone hydrochloride), 4 mg.

This new drug application provides for the use of Narcan Nasal Spray (naloxone hydrochloride), for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

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, Instructions for Use, and Quick Start Guide). 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*, available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

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 208411.**” Approval of this submission by FDA is not required before the labeling is used.

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

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Diana L. Walker, PhD, Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3240
10903 New Hampshire Avenue
Silver Spring, Maryland

*Use zip code **20903** if shipping via United States Postal Service (USPS).*

*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

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(s) 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 required at this time.

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 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 untreated respiratory arrest that may result from device failure and subsequent loss (i.e., failure) of the expected pharmacologic action of Narcan Nasal Spray (naloxone hydrochloride).

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:

- 2990-1 Establish reliability requirements for the combination product Narcan Nasal Spray (naloxone hydrochloride), and complete testing which verifies the combination product reliability.

The timetable you submitted on November 17, 2105, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/2016
Study Completion:	09/2016
Final Report Submission:	11/2016

Please note the following considerations regarding 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 to elements outlined within c, 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. Perform a test to verify the reliability requirements specified above.
- d. Devices assessed within the reliability test should be preconditioned to reasonably foreseeable worst-case conditions. We recommend the following preconditioning activities. 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.

- Shipping
 - Aging
 - Storage orientation and conditions
 - Vibration handling
 - Shock handling (e.g., resistance to random impacts, such as being dropped)
- e. Devices assessed within the reliability analysis should be activated under reasonably foreseeable worst-case conditions. We recommend the following circumstances of activation. However, you should provide rationale supporting the final circumstances of activation chosen.
- Activation orientation
 - Environmental temperature

2990-2 Establish procedures for monitoring reports of failure of the combination product Narcan Nasal Spray (naloxone hydrochloride) to activate or failure of the combination product to deliver the full-labeled dose. Provide interim and final reports to the NDA, which contain a detailed analysis of reported device failures (including reported malfunctions that did, as well as did not result in patient harm), full event narratives of the failure and any subsequent adverse events, and the results of root cause analysis performed for the reported failure.

The timetable you submitted on November 17, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/2016
Interim Report Submission:	01/2017
Final Report Submission:	01/2018

Submit the protocol(s) to your IND 114704, with a cross-reference letter to this NDA. Submit 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).”**

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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2990-3 Conduct an adequate leachable safety assessment for the [REDACTED] (b) (4) [REDACTED] used in your container closure system. This assessment must include leachable data from long-term stability studies testing at least three batches (taking into consideration the proposed shelf-life) to determine if the identified extractables leach into the drug product over time. Using this information, conduct a toxicological risk assessment justifying the safety of the leachables, taking into consideration the maximum daily dose of the identified materials for this drug product. Submit a toxicological risk assessment for any leachable that exceeds 5 mcg/day. From a genetic toxicology perspective, any leachable that contains a structural alert for mutagenicity must not exceed 120 mcg/day for an acute indication, or be adequately qualified for safety. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples.

The timetable you submitted on November 17, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 02/2016
Interim Report Submission: 01/2017
Final Report Submission: 11/2017

2990-4 Conduct a long-term stability evaluation placing at least three (3) manufactured lots of NARCAN Nasal Spray, 40 mg/mL, on long-term stability evaluation at the following temperatures:

- a. 2 to 8°C
- b. 40°C/75% RH - to extend the time points out to 24 months

The timetable you submitted on November 17, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 02/2016
Interim Report Submission: 06/2017
Final Report Submission: 06/2018

Submit clinical protocols to your IND 114704 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **“Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,”** or **“Postmarketing Commitment Correspondence.”**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
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>).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. 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>.

EXPIRY DATING PERIOD

A 24-month expiry dating period is granted for Narcan Nasal Spray, when stored at 59°F to 77°F (15°C to 25°C). Excursions permitted between 4°C to 40°C (39°F to 104°F).

REPORTING REQUIREMENTS

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

SPECIAL REPORTING REQUESTS

- Submit both serious and non-serious outcomes as expedited reports within 15 days of receipt for the following:
 - All reports in patients less than one year of age
- Include a summary evaluation of each of these reports requested in the submission of the periodic reports for each reporting period, with an analysis of treatment failures and adverse events of airway obstruction, respiratory distress, or respiratory arrest; in addition to a summary of these events in the context of all similar events reported for Narcan Nasal Spray.

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
11/18/2015