NDA 217470

NDA APPROVAL

Opiant Pharmaceuticals, Inc.
c/o Pacific-Link Consulting
8195 Run of the Knolls Court
San Diego, CA 92172

Attention: Richard E. Lowenthal, MSc, MBA
U.S. Agent

Dear Mr. Lowenthal:

Please refer to your new drug application (NDA) dated and received November 22, 2022, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Opvee (nalmefene) nasal spray.

This NDA provides for the use of Opvee (nalmefene) nasal spray for the emergency treatment of known or suspected overdose induced by natural or synthetic opioids in adults and pediatric patients aged 12 years and older, as manifested by respiratory and/or central nervous 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.

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, Patient Package Insert, Instructions for Use, and Quick Start Guide) 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 *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 217470**." 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 Opvee (nalmefene) nasal spray shall be 28 months from the date of manufacture when stored at 15°C – 25°C (59°F – 77°F).

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.

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.

4451-1 Conduct a clinical pharmacokinetic, pharmacodynamic, and safety study of Opvee in pediatric patients aged 3 to less than 12 years of age.

Draft Protocol Submission:	10/2024
Final Protocol Submission:	02/2025
Study Completion:	03/2027
Final Report Submission:	09/2027

4451-2 Conduct a clinical pharmacokinetic, pharmacodynamic, and safety study of Opvee in pediatric patients from birth to less than 3 years of age.

Draft Protocol Submission:	12/2026
Final Protocol Submission:	03/2027
Study Completion:	09/2028
Final Report Submission:	03/2029

4451-3 Conduct a juvenile animal study in rats to support the initiation of clinical studies in pediatric patients from 3 to less than 12 years of age. This study will evaluate the effect of the drug on growth and development, specifically reproductive performance/sexual maturation, local tissues including the nasal and respiratory tract, immune capacity, and central nervous system histopathology and long-term behavioral effects.

Draft Protocol Submission:	09/2023
Final Protocol Submission:	01/2024
Study Completion:	05/2024
Final Report Submission:	02/2025

4451-4 Conduct a juvenile animal study in rats to support the initiation of clinical studies in pediatric patients from birth to less than 3 years of age. This study will evaluate the effect of the drug on growth and development, specifically reproductive performance/sexual maturation, local tissues including the nasal and respiratory tract, immune capacity, and central nervous system histopathology and long-term behavioral effects.

Draft Protocol Submission:	09/2023
Final Protocol Submission:	01/2024
Study Completion:	06/2024
Final Report Submission:	03/2025

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 the protocols to your IND 136851, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies 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 these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED**

[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.

PEDIATRIC ASSESSMENTS" in large font, bolded type at the beginning of the cover letter of the submission.

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 identify an unexpected serious risk that may occur from the presence of dodecylmaltoside (DDM).

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:

4451-5 Conduct a fertility and early embryonic development study in rats with dodecylmaltoside (DDM).

The timetable you submitted on May 16, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2023
Final Protocol Submission:	11/2023
Study Completion:	10/2024
Final Report Submission:	04/2025

4451-6 Conduct an embryo-fetal development study in rats with dodecylmaltoside (DDM).

The timetable you submitted on May 16, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2023
Final Protocol Submission:	11/2023
Study Completion:	02/2024
Final Report Submission:	08/2024

4451-7 Conduct an embryo-fetal development study in rabbits with dodecylmaltoside (DDM).

The timetable you submitted on May 16, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2023
Final Protocol Submission:	11/2023
Study Completion:	09/2024
Final Report Submission:	03/2025

4451-8 Conduct a pre- and postnatal development study in rats with dodecylmaltoside (DDM).

The timetable you submitted on May 16, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2023
Final Protocol Submission:	12/2023
Study Completion:	01/2025
Final Report Submission:	07/2025

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.[4]

Submit clinical protocols to your IND 136851 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(a)(1) 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(a)(1) 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

[4] 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.

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.*[5]

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.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

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

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.[8]

ENHANCED PHARMACOVIGILANCE REQUEST

We request that for Opvee you submit all serious and non-serious occurrences of severe, prolonged, and/or precipitated opioid withdrawal in cases where more than two doses of Opvee are used in a single rescue as 15-day “Alert reports” (described under 21 CFR 314.80(c)(1)) through the 5th year following initial U.S. approval.

Provide a separate narrative summary and analysis of these adverse events, apart from your required analysis of 15-day “Alert reports,” in each required postmarketing periodic safety report [e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)], quarterly during the first 3 years post-approval and annually thereafter, through the 5th year following initial U.S. approval.

---

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[8] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

These narrative summary and analyses should include an assessment of all new information obtained during the reporting interval and cumulatively since initial U.S. approval related to these adverse events (i.e., severe, prolonged, and/or precipitated opioid withdrawal in cases where more than two doses of Opvee are used in a single rescue) with the aim of further characterizing these risks (e.g., indication, temporal association, action taken, outcome, confounders, underlying risk factors, use in unapproved populations, and assessment of causality).

If you have any questions, call Sandy Truong, Senior Regulatory Project Manager, at 301-796-5719.

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
  - Quick Start Guide
- 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
05/22/2023 04:03:55 PM