NDA 218590

NDA APPROVAL

Purdue Pharma, L.P.
One Stamford Forum
201 Tresser Blvd.
Stamford, CT 06901

Attention: Rashmi Upasani, PhD
Director, Regulatory Strategy

Dear Dr. Upasani:

Please refer to your new drug application (NDA) dated and received February 7, 2024, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Zurnai (nalmefene injection) 1.5 mg/0.5 mL for intramuscular or subcutaneous use.

This NDA provides for the use of Zurnai (nalmefene injection) for the emergency treatment of known or suspected opioid 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 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.

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, and 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 *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 218590**." 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 Zurnai (nalmefene injection) shall be 24 months from the date of manufacture when stored at 20°C to 25°C (68°F to 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.

4665-1 Conduct a clinical pharmacokinetic, pharmacodynamic, and safety study of Zurnai in pediatric patients aged birth to less than 12 years of age.

The timetable you submitted on August 1, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	07/2025
Final Protocol Submission:	12/2025
Study Completion:	10/2028
Final Report Submission:	04/2029

4665-2 Conduct a juvenile animal study in rats to support the initiation of clinical studies in pediatric patients from 3 years 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 and central nervous system histopathology and long-term behavioral effects.

The timetable you submitted on August 1, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2024 (Submitted)
Study Completion:	03/2025
Final Report Submission:	09/2025

4665-3 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 development, specifically neuroapoptosis and central nervous system histopathology.

The timetable you submitted on August 1, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2024 (Submitted)
Study Completion:	03/2025
Final Report Submission:	09/2025

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 clinical protocol to your IND 137597, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as

[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.

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

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4665-4 Conduct a 24-month real-time aging study which includes an analysis of cap removal torque test results [redacted] (b) (4) and provide completed test reports for device Essential Performance Requirements (EPRs).

The timetable you submitted on August 1, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/2024 (Submitted)
Study Completion:	08/2024
Final Report Submission:	10/2024

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 date, and any changes in plans since the last annual report. Your submission relating to this postmarketing commitment should be prominently labeled "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4665-5 Conduct a study or studies to detect any non-volatile, semi-volatile, or volatile extractables from the container closure used in this product; then, based on the revised results, repeat the leachable studies.

The timetable you submitted on July 22, 2024, states that you will conduct this study according to the following schedule:

Interim Report #1: 12/2025
(Extractables study and initial leachables timepoint)

Interim Report #2: 12/2026
(1-,3- and 6-month leachables timepoints)

Final report submission: 12/2027
(including 9- and 12-month leachables timepoints)

Additional Comments regarding PMC 4665-5

1. We note that only three (3) non-volatile, but no volatile or semi-volatile extractables (b) (4) were observed in the extractables studies, while multiple semi-volatile extractables are noted (b) (4) (b) (4) It is unusual to see these extractables (b) (4) (b) (4) Therefore, your extractables studies may not be appropriately designed to produce a complete extractables profile to guide leachables studies.

   In order to obtain a complete extractables profile, re-run the extractable studies in 5% IPA, 50% IPA, pH 3 and 9 buffer solutions and reflux the samples in each media for 12-24 hours to achieve an equilibrium. We recommend that you size the components or materials (for example, by cutting the samples to smaller pieces, or grinding them) to increase the surface area and extraction stoichiometry before extraction. Ensure all the limits of quantitation (LOQs) of the reference standards are at or lower than the analytical evaluation threshold (AET). In addition, at least a confident level of structural identification should be achieved if a confirmation level is not possible as defined in USP <1663>.

2. Repeat the leachables studies based on the revised extractables study results. To mitigate the interference from the drug product matrix or from low response or low recovery of the compound from the drug product matrix, the leachables method should be fully validated. If full validation of the leachables methods for all the extractables over AET observed in the extractables studies is not possible or feasible, multiple representative compounds (≥3) from each chemical class (i.e., antioxidants, plasticizers, curing agents, additive degradants, and fatty acids) for volatile, semivolatile and non-volatile extractables, should be chosen for method validation. Ensure all the LOQs of the reference standards are at or lower than the AET.

   In the IND 137597 End-of-Phase 2 (EOP2) meeting dated May 25, 2023, the Agency recommended, “Evaluate at least three batches of your to-be-marketed drug product for leachables and include assessments at each timepoint over the

course of your stability studies in order to identify trends in leachable levels over time (including early middle, and late time points). The materials tested should include any secondary container closure systems, if present, and be subjected to the same sterilization methods, as appropriate. These data are essential to determine the appropriate shelf life of your product". Therefore, your proposal to do leachables testing [redacted] (b) (4) is not sufficient to obtain a trend of leachables throughout the shelf-life of the product. Provide leachables study results for the first 3 commercial batches manufactured for the assembled auto injector under accelerated and long-term conditions following ICH Q1A time points (i.e., 0, 3, 6 for accelerated studies and 0, 3, 6, 9, 12, etc. for long term stability studies) with validated analytical methods.

4665-6 Provide accuracy data in triplicate for the Identification, Assay and Impurities of Nalmefene analytical method per the FDA guidance for industry *Validation of Chromatographic Methods*[4] for nalmefene in nalmefene hydrochloride injection in prefilled syringe or autoinjector, 1.5 mg/0.5 mL by High Performance Liquid Chromatography (HPLC).

The timetable you submitted on July 22, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2025

Additional Comment regarding PMC 4665-6

We acknowledge Method Validation Report for Identification, Assay and Impurities of Nalmefene in Nalmefene Hydrochloride Injection in Prefilled Syringe or Autoinjector, 1.5 mg/0.5 mL by High Performance Liquid Chromatography (HPLC) (DOC No.: [redacted] (b) (4) -REP-2481). We also note Table 4 Assay Level Linearity/Accuracy Solutions Results. Provide accuracy data in triplicate per FDA guidance *Validation of Chromatographic Methods*.[5]

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, and any changes in plans since the last annual report. Your submission relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

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-*

[4] https://www.fda.gov/media/75643/download

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]

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

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]

REQUESTED ENHANCED PHARMACOVIGILANCE (EPV)

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

We request that you provide a separate narrative summary including analysis of severe, prolonged, and/or precipitated opioid withdrawal in cases where more than two doses of Zurnai are used in a single rescue as part of your required periodic safety reports (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 date.

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[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

Your analysis should include interval and cumulative data relative to the date of approval of Zurnai for all serious and non-serious occurrences of severe, prolonged, and/or precipitated opioid withdrawal in cases where more than two doses of Zurnai are used in a single rescue. Your analysis should provide an assessment of causality, with documentation of indication, temporal association, number of doses, associated signs and symptoms, confounders, underlying risk factors, treatment given for the event, and outcome.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[9].

If you have any questions, contact Sandy Truong, PharmD, Senior Regulatory Project Manager, at 301-796-5719 or sandy.truong@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
  - Patient Package Insert
  - Instructions for Use
- Carton and Container Labeling

[9] https://www.uspnf.com/

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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