NDA 210730

NDA APPROVAL

Trevena, Inc.
955 Chesterbrook, Suite 110
Chesterbrook, PA 19087

Attention: Mark A. Cierpial, PhD, RAC
Regulatory Consultant

Dear Dr. Cierpial:

Please refer to your new drug application (NDA) dated and received November 2, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Olinvyk (oliceridine) injection, for intravenous use, 1 mg/mL.

We acknowledge receipt of your amendment dated February 7, 2020, which constituted a complete response to our November 2, 2018, action letter.

This new drug application provides for the use of Olinvyk in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate.

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.

CONTROLLED SUBSTANCE SCHEDULING

You were previously informed that FDA intends to recommend scheduling of oliceridine under the Controlled Substances Act (CSA). The scheduling of this product in accordance with the CSA (21 U.S.C. 811) is not yet complete as of the date of this letter. Therefore, in accordance with the FDCA (21 U.S.C. 355(x)), the date of approval for Olinvyk shall be the date on which the Drug Enforcement Administration (DEA) publishes a notice in the Federal Register announcing the interim final scheduling of oliceridine.

We note that, when the drug is scheduled by the DEA, you will need to make appropriate revisions to the Prescribing Information and carton and container labeling by submitting a supplement to your NDA. This would include the statements in the labeling detailing the scheduling of oliceridine, as the scheduled substance in Olinvyk, as required under 21 CFR 201.57(a)(2) and (c)(10)(i). Therefore, Olinvyk may be

marketed only after DEA has published the notice in the Federal Register announcing the interim final scheduling of oliceridine and you submit a supplement to your NDA to revise all applicable drug labeling to reflect the drug scheduling described in the notice. For changes to the Prescribing Information and carton and container labeling to describe the scheduling of Olinvyk, you can submit a Changes Being Effected supplement described in 21 CFR 314.70(c)(6). Permission to use a Changes Being Effected supplement for this purpose reflects a waiver by the Agency, pursuant to 21 CFR 314.90, of the requirement to submit a Prior Approval Supplement for changes to reflect the scheduling to the Highlights of Prescribing Information for Olinvyk described in 21 CFR 314.70(b)(2)(v)(C).

We note that Olinvyk will be listed in the Orange Book upon the date of approval in accordance with 21 U.S.C. 355(x). With respect to the submission of patent information, as required under 21 CFR 314.53(c)(2)(ii), we note that you must submit Form FDA 3542 within 30 days after the date on which DEA has published the notice in the Federal Register announcing the interim final scheduling of oliceridine.

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) 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]

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 carton and container labeling submitted on July 22, 2020, 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 210730**." Approval of this submission by FDA is not required before the labeling is used.

[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.

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 according to the timetables listed below, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act is required postmarketing study. The status of this 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 is listed below.

3902-1 Conduct a randomized, controlled trial evaluating the pharmacokinetic, safety, tolerability, and efficacy profiles of OLINVYK in pediatric patients aged 6 to less than 17 years for whom parenteral opioid therapy is warranted.

Final Protocol Submission: 12/2020
Study Completion: 12/2022
Final Report Submission: 06/2023

3902-2 Conduct a randomized, controlled trial evaluating the pharmacokinetic, safety, tolerability, and efficacy profiles of OLINVYK in pediatric patients aged 3 to less than 6 years for whom parenteral opioid therapy is warranted.

Final Protocol Submission: 12/2020
Study Completion: 12/2022
Final Report Submission: 06/2023

3902-3 Conduct a randomized, controlled trial evaluating the pharmacokinetic, pharmacodynamic, safety, tolerability, and efficacy profiles of OLINVYK in pediatric patients aged birth to less than 3 years of age for whom parenteral opioid therapy is warranted.

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

3902-4 Conduct a randomized, controlled trial evaluating the safety, tolerability, and efficacy profiles of OLINVYK in pediatric patients aged birth to less than 3 years of age for whom parenteral opioid therapy is warranted.

Final Protocol Submission: 08/2025
Study Completion: 08/2027
Final Report Submission: 02/2028

3902-5 Conduct a juvenile animal study in the rat model to support pediatric dosing in patients 3 years of age to less than 17 years of age.

Draft Protocol Submission: 09/2020
Final Protocol Submission: 12/2020
Study Completion: 09/2021
Final Report Submission: 01/2022

3902-6 Conduct a juvenile animal study in the rat model to support pediatric dosing in patients less than 3 years of age.

Draft Protocol Submission: 09/2020
Final Protocol Submission: 12/2020
Study Completion: 09/2021
Final Report Submission: 01/2022

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 113537, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as a new drug application (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.

[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.

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]

EXPIRATION DATING

Olinvyk (oliceridine) injection, for intravenous use, 1 mg/mL, is granted an expiry dating of 48 months when stored at 20-25°C (68-77°F) with excursions permitted between 15-30°C (59-(b) (4)°F).

REPORTING REQUIREMENTS

You must comply with the reporting requirements described in 21 CFR 314.80(c)(1) (e.g., 15-day alert reports) beginning on the date of **this** letter. The due dates for the periodic (including quarterly) adverse drug experience reports described in 21 CFR 314.80(c)(2) should be calculated from the date of this letter. Annual reports described in 21 CFR 314.81(b)(2) are due within 60 days of the anniversary of the date of approval in accordance with 21 U.S.C. 355(x).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.[7]

[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
[7] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Eva Yuan, PharmD, Regulatory Project Manager, at (240) 402-2476.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director (Acting)
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
- 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/

ERIC P BASTINGS
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