CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210730Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210730

COMPLETE RESPONSE

Trevena, Inc.
955 Chesterbrook Blvd. Suite 200
Chesterbrook, PA 19087

Attention: Paul M. Kirsch
Vice President, Regulatory Affairs

Dear Mr. Kirsch:

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 for Oliceridine injection, 1 mg/mL.

We also acknowledge receipt of your amendment dated October 31, 2018, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. You have not submitted adequate data to support the safety of oliceridine for the management of moderate-to-severe acute pain in adult patients for whom an intravenous (IV) opioid is warranted due to concerns related to QT prolongation.

   Your thorough QT (tQT) study, CP130-1008, showed that single doses of oliceridine prolong the QTcF in a dose-dependent manner with a delayed onset (3 mg: 6.6 ms [upper 90% confidence interval (CI) 8.9 ms]: 6 mg: 11.6 ms [13.7 ms]). The delayed onset of QTcF prolongation suggests that the QTcF prolongation may not be mediated via direct inhibition of the hERG potassium channel by oliceridine. The proposed mechanism for the delayed onset of the QTcF prolongation observed with oliceridine remains unclear.

   In your Phase 3 studies, only limited ECG monitoring was obtained in patients after baseline (i.e., at 1, 24, and 48-hours post-loading dose for Study 3001, 1 and 24 hours for Study 3002, and 1 hour and every 24 hours of oliceridine treatment in Study 3003). Further, you have proposed a wide range of doses up to a maximum daily dose of 40 mg,

and oliceridine would be used in clinical situations in which patients may receive other drugs that can prolong the QTc.

Interpretation of the ECG data from your clinical studies has limitations. Specifically, none of the studies were designed to characterize the QT prolonging effects of oliceridine. In Study 3003, there was a lack of ECG replicates at each nominal time point and lack of a control arm. Despite these limitations, there were cases of QTc prolongation in Study 3003.

You have not provided adequate data to support that the QT prolonging effects of oliceridine can be mitigated by labeling or monitoring.

Information Needed to Resolve the Deficiency
To address the safety concern of QT prolongation at the maximum proposed daily dose, provide data from a randomized active-controlled study that will include 24-hour Holter monitoring and replicate QT measurements extracted every hour from the Holter monitors and compared to the control group. The study should be of adequate duration and sample size to allow reliable evaluation of oliceridine's QT prolongation effects.

2. The submitted exposure database is not of adequate size to evaluate and support the safety of oliceridine for the proposed labeling. You have proposed a maximum daily dose of 40 mg (b) (4) You were advised at the End-of-Phase 2 and pre-NDA meetings that the safety database needed to include at least 350 patients exposed to the highest doses for the longest duration of use. In your Phase 2 and Phase 3 studies, the highest dose that at least 350 patients were exposed to during the first 24 hours was 27 mg of oliceridine. The highest dose with the longest actual duration that had at least 350 patients exposed was 37.2 mg administered over an actual duration of at least 35.5 hours.

   Information Needed to Resolve the Deficiency
   Provide an exposure database that is of adequate size to evaluate and support the safety of oliceridine for the proposed labeling. Specifically, the safety database must include at least 350 patients exposed to the highest dose proposed for the longest duration of use indicated in the labeling.

NONCLINICAL

3. You have not provided adequate data to confirm that levels of TRV0109662, a major human metabolite, have been adequately characterized for potential embryo-fetal effects in either the rat or the rabbit embryo-fetal development study. You have not provided any data to document that the metabolite is formed in rabbits. Based on the data obtained to date, this metabolite does not appear to be formed at acceptable levels in the rat compared to the human, and the existing analytical assays for human and rat plasma

levels of TRV0109662 do not appear to be consistently reproducible (i.e., failed rat incurred sample reanalysis for pivotal study).

Information Needed to Resolve the Deficiency:
Either conduct a dedicated embryo-fetal development study in either the rat or rabbit with TRV0109662 or provide validated, reproducible pharmacokinetic data to support your conclusion that the existing rat or rabbit embryo-fetal development study resulted in exposures to TRV0109662 that were at least 50% of the levels present in humans at the proposed maximum recommended human dose of 40 mg/day.

PRODUCT QUALITY

4. The analytical methods used for controlling identified leachables must be validated. Validation reports for the analytical methods used for the leachables study have not been provided to the Agency.

   Information Needed to Resolve the Deficiency
   Validate your newly developed analytical methods for leachables as per the ICH Q2 recommendation and provide the validation reports to the Agency. Further, also provide the data for the leachables found in the stability samples that are analyzed by your newly developed methods.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

CONTAINER LABELS, CARTON LABELING, AND PROPRIETARY NAME

Submit draft carton and container labeling revised as follows:

1. The proprietary name, “OLINVO”, is included on the container label and carton labeling. Refer to our March 9, 2018, letter informing you that the proprietary name, “OLINVO”, was found unacceptable. Remove all references to “OLINVO”. Also, see comments below regarding resubmission of the proposed proprietary name, OLINVYK.

2. Please refer to correspondence dated August 9, 2018, which addresses the proposed proprietary name, OLINVYK. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

3. The container label has the same package code portion of the National Drug Code (NDC) as the carton for all the product strengths. For example, for the 1 mg/1 mL product strength the NDC is 71308-011-10 for both the container label and carton labeling. The package code portion of the NDC on the container and carton are usually different if the quantity within the carton is greater than one unit (i.e., 1 vial). During distribution, dispensing and administration, the NDC is often used to confirm a drug product. Revise the NDC's for the carton labeling for each strength so that the package code for each carton labeling is different from its corresponding container label.

4. On all container labels and carton labeling, the statement "Discard unused portion" is located several lines away from the statement "(b) (4)". There is a risk that the user may be unaware that there may be overfill in each vial that should be discarded after a single dose. Failure to discard this unused portion could result in an overdose. Revise each container label and carton labeling so that the statement "Discard unused portion" appears directly after the statement "(b) (4)" to minimize the risk of the entire contents of the vial being given as a single dose. For example: "(b) (4). Discard unused portion."

5. All container labels and carton labeling contain the statement "(b) (4)." Post-marketing reports have shown that negative statements may have the opposite of the intended meaning because the word "(b) (4)" can be overlooked resulting in interpretation of the warning as an affirmative action. Instead, warning statements should be written in affirmative language. On container labels and carton labeling, revise the statement "(b) (4) (b) (4)." to read, "Protect from freezing."

6. The format of the expiration date has not been defined on the container labels or carton labeling. Expiration dates have been misinterpreted leading to deteriorated drug medication errors based on confusing formats. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorating drug medication errors, identify the format you intend to use. We recommend using one of the following formats:

   DDMMMYYYY (e.g., 31JAN2013)
   MMMYYYY (e.g., JAN2013)
   YYYY-MM-DD (e.g., 2013-JAN- 31)
   YYYY-MM-DD (e.g., 2013-01- 31)

7. For the 1 mg/1 mL container label and carton labeling, the product strength (b) (4)

[redacted] statement from the container label and carton labeling.

8. [redacted] Revise the statement "[redacted]" to "FOR INTRAVENOUS USE ONLY" OR "FOR INTRAVENOUS USE". To accommodate this change, consider relocating the "Sterile" and "Rx only" statements.

9. [redacted]

10. The 30 mg/30 mL container label contains [redacted] on the 30 mg/30 mL label is not a required statement and is not consistent with the 1 mg/1 mL and 2 mg/2 mL container labels, which do not have the [redacted] statement. To maintain consistency with the 1 mg/1 mL and 2 mg/2 mL container labels and because this information is present on the carton labeling, consider removing the [redacted] statement from the 30 mg/30 mL container label.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug/product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.

- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," December 2017 at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Regulatory Project Managers, Eva Yuan at (240) 402-2476 and/or Shelly Kapoor at (240) 402-2787.

Sincerely,

{See appended electronic signature page}

Mary T. Thanh Hai, MD
Acting Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

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/

MARY T THANH HAI
11/02/2018