CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209575Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209575

COMPLETE RESPONSE

Lannett Holdings, Inc.
13200 Townsend Road
Philadelphia, PA 19154

ATTENTION: Katy Rudnick
Manager, Regulatory Affairs

Dear Ms. Rudnick:

Please refer to your New Drug Application (NDA) dated and received September 21, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cocaine Hydrochloride Topical Solution, 4% and 10 %.

We also acknowledge receipt of your amendment dated June 28, 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, 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 provided adequate information to characterize the effects of your product on the QT_c interval.

   To resolve this deficiency:
   Submit the results of a thorough QT study.

NONCLINICAL

2. You have not provided adequate leachables evaluation to justify the safety of the proposed container closure system. Specifically, your leachables evaluation did not evaluate at least three batches of your to-be-marketed drug product for leachables and include assessments at multiple timepoints over the course of your stability studies as we advised at the Pre-NDA meeting and in accordance with best practices per USP <1664>: Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems. Further, you have not provided an adequate extractables-leachables correlation to ensure that leachable compound

levels can be extrapolated from data collected from simulation studies under accelerated conditions.

To resolve this deficiency:
Conduct a new leachables study under standard storage conditions that evaluates at least three batches of the to-be-marketed topical cocaine solution products for leachables and include assessments at multiple timepoints over the course of your stability studies (beginning, middle, and end of proposed shelf-life) in order to identify trends in leachable levels over time. Evaluate all container closure systems you intend to market. Clearly delineate how you leveraged the existing extraction studies to inform your leachables assessment. Submit a toxicological assessment justifying the safety of the maximum level achieved over the course of stability for any leachable that exceeds 5 mcg/day, taking into consideration the maximum daily dose of the drug product. Submit a discussion of the extractables leachables correlation of the findings.

3. Several of your final study reports did not report the purity of the test articles.

   To resolve this deficiency:
   Revise the final study reports for Study 16-01138-G2, 16-01139-G2, and 16-01140-G2 to include purity information of the test articles evaluated.

REGULATORY

4. Your annotated draft labeling [redacted] (b) (4) as the sources of the proposed language.

   To resolve this deficiency:
   [redacted] (b) (4). If the studies upon which the non-US conclusions are based have been published, you may be able to rely upon that literature. If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug you must identify the listed drugs in accordance with the Agency's regulations at 21 CFR 314.54. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which you intend to rely. In addition, you must establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. [redacted] (b) (4) submit revised labeling and identify the appropriate source(s) of information upon which you propose to rely.

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

PROPRIETARY NAME

Please refer to correspondence dated, December 20, 2017, which addresses the proposed proprietary name, NUMBRINO. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name request when you respond to the application deficiencies.

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 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.

If you have any questions, call Shelly Kapoor, PharmD, Regulatory Project Manager, at (240) 402-2787.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Deputy Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
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/

RIGOBERTO A ROCA
07/20/2018