CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212045Orig1s000

OTHER ACTION LETTERS

NDA 212045

COMPLETE RESPONSE

Hikma Pharmaceuticals USA Inc.
1809 Wilson Road
Columbus, OH 43228

Attention: Jerald Andry, MS
Senior Director, Drug Regulatory Affairs and Medical Affairs

Dear Mr. Andry:

Please refer to your new drug application (NDA) dated and received April 30, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for naloxone nasal spray, 8 mg.

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.

Product Quality

1. We have identified the following deficiencies regarding the extractables studies:

   a. Different maximum daily doses (MDD) have been used to calculate the analytical evaluation thresholds (AETs) for the extractables studies. Specifically, in the (b) (4) 2011 report, an MDD of 8 mg/day was used to calculate the AET for volatile, semi-volatile and non-volatile, while in (b) (4) report TTP-IOX-M0083, 32 mg/day (i.e., 4 doses per day) was used for the calculation of AETs for polar compounds and elemental impurities. Clarify the discrepancies and provide the revised AETs with the correct MDD.

   b. You stated that the profile (b) (4) contained (b) (4) (b) (4) However, we cannot locate the information. Provide this information in your resubmission.

2. We have identified the following deficiencies regarding the leachable studies:

   a. We do not agree with your design for leachables testing following the concept of ICH Q1D "Bracketing and Matrixing designs for the stability testing of new

drug substance and products." Potential leachables may decompose to generate secondary leachables over time. Therefore, the full stability protocol must be followed in order to determine the full leachable trend throughout the product life cycle.

b. You stated that all the naloxone nasal spray samples were stored in horizontal orientation as a worst-case scenario during the stability studies. However, inverted position will maximize stopper/drug product solution contact. Re-run the leachables studies in the inverted position or justify why the horizontal position is the worst case scenario for leachable determination.

c. In 3.2.P.2.4.10.4. Characterization of Leachables and the original report IOXM0085 report: Semi-Quantitation of Extractables from (b) (4) Stoppers, you have adopted an AET of (b) (4) µg/mL, which is 100-fold higher than the AET (b) (4) used for extractables studies. In addition, 3 of 4 reporting limits for the target leachables (b) (4) (b) (4) are much higher than the AET (b) (4) as shown in Table 9 and Table 11 below. Clarify these discrepancies and provide a revised AET based on a SCT of (b) (4) µg/day.

3. The acceptance criterion for "Total Impurities" (b) (4) is too wide in the release and stability specification. Tighten the acceptance criterion based on the data trend.

4. Include the acceptance criterion for the potential degradation impurity (b) (4) (b) (4) in both release and stability specification as per ICH Q3B. Alternatively provide sufficient batch data to show it is absent in the drug product with validated methods.

5. We acknowledge that (b) (4) has been controlled in the vendor's Certificate of Analysis (COA) for dehydrated ethyl alcohol. (b) (4) (b) (4) in the formulation, demonstrate that your analytical method can detect (b) (4) and that (b) (4) is absent in the drug product.

6. We have identified the following deficiencies regarding the method validation:

   a. Provide the forced degradation studies for CH.0103: Assay and Identification of Naloxone in Naloxone Nasal Spray, 8 mg/Spray.

   b. Provide system suitability requirements for the following validation reports:

      i. Method CH.0151: Assay of Ethanol by GC-FID
      ii. Method CH.0109: Impurities (b) (4) by HPLC

iii. Method CH.0117: Impurity (b) (4) by HPLC
iv. Method CH.0110: Impurity (b) (4) by HPLC.

c. Provide a complete method validation report for Impurity (b) (4).

d. Provide the details for the referenced Report.CH.0046 for Method CH.0109: Method Validation Report for Impurities (b) (4) by HPLC method.

7. We have identified the following deficiencies regarding the structural assignment for Impurity (b) (4)

a. You have assigned Impurity (b) (4) (b) (4) based on the presence of the signal (b) (4) (b) (4) Provide the sources (b) (4) (b) (4) on page 4 of Analysis Report: (b) (4) (b) (4) and clarify why (b) (4) is a diagnostic (b) (4).

b. Since reference standard for (b) (4) is not available to verify the structure of Impurity (b) (4), provide direct spectroscopic evidences for (b) (4) (b) (4) Impurity (b) (4)

c. If you cannot unambiguously assign the structure of Impurity (b) (4) list the impurity as a specified unknown impurity with RRT in the release and stability specification.

8. Provide the design and materials of construction of the labels used on the primary container for naloxone hydrochloride nasal spray.

9. Provide the vendor COA for (b) (4) vial.

10. In 3.2.P.2.2 the stability study results have demonstrated that formulations with EDTA at a concentration of (b) (4) % w/w at a pH of (b) (4) yielded the most stable formulations with an optimum impurity profile. However, you have adopted a much wider pH range (b) (4) for both release and stability specification. Justify the wider pH ranges by providing data to demonstrate the continued stability of the API and Edetate Disodium at higher or lower pH's or revise the pH specification (range) for release and stability, based on the observed values for drug product batches tested thus far.

Manufacturing

11. (b) (4)

[redacted] Revise the proposed commercial batch record in 3.2.P.3.3 [redacted].

12. Leachable and extractable studies are critical to assure no elements or chemical substances are extracted from the manufacturing components under stress conditions to compromise quality of the drug product. We acknowledge you have presented extractable and leachable study results for [redacted] rubber stopper and leachable screen of aged naloxone nasal spray DP in 3.2.P.2 to profile potential extractable contaminants. However, you did not offer any leachable or extractable studies result for all product-contact materials used in manufacturing process to demonstrate that no elemental or chemical impurities were extracted from your manufacturing [redacted] under the given process operation conditions. Provide leachable and extractable data for all the formulation contacting [redacted] components used during the manufacturing process and confirm all formulation contacting [redacted] components used in manufacturing of the drug product meet the ASTM standards [redacted]. In addition, provide a statement of compliance to pertinent CFR sections for indirect food additives for all formulation contacting components used in manufacturing of the drug product.

13. You have not proposed any acceptance limits for pH, viscosity, and density for the [redacted] solution. Include this information as part of the in-process controls per 21 CFR 211.110. Note that the acceptance limits must be justified with exhibit batch and/or development studies data. Further, provide a side-by-side comparison table listing all in-process tests and their acceptance limits for commercial and exhibit batches. For exhibit batches, summarize their in-process test results. In addition, revise contents in 3.2.P.3.4 and the commercial MBR in 3.2.P.3.3 accordingly.

14. Measurement of yield is an estimation of robustness of the process, since deviation investigations are typically performed if yield in the reconciliation section is outside of the specification limits. Your use of reconciliation yield limits for batch reconciliation in commercial MBR are not acceptable [redacted] and is not an accurate reflection of manufacturing process performance. Per CFR 211.103 and CFR211.186(b)(7), revise your proposed commercial MBR in 3.2.P.3.3 to include actual yield and actual yield target specification for each unit operation and total production, wherever is applicable.

15. Our field investigator could not complete inspection of the West-Ward Columbus Inc. (FEI: 1510690) manufacturing facility at Columbus, Ohio because the facility

was not ready for inspection. Satisfactory inspection is required before this NDA may be approved. Notify us in writing when this facility is ready for inspection.

Center for Devices and Radiological Health

16. In your October 18, 2019, response to our October 11, 2019, information request, you provided several responses (Questions 12 to 25) with target timelines for completion of June 30, 2020. In your resubmission, provide full responses to the questions within this request that were left unanswered. These include the following questions that were left without a full response: 12, 14, and 16 through 23.

17. In your October 18, 2019, response to Question 21c, you provide a justification to support using one lot of the (b) (4) alcohol formulation as a part of your reliability study. While we acknowledge that the to-be-marketed 20% alcohol formulation was used as well, you did not provide an adequate justification to support using the (b) (4) alcohol formation to support the reliability of the to-be-marketed 20% alcohol formulation. In your justification you state: "*Hikma acknowledges that the (b) (4) alcohol formulation may have slightly different spray characteristics compared to that of the 20% alcohol formulation due to minor differences in (b) (4) properties including viscosity, specific gravity, and density".* Given that the spray characteristics will likely be influenced by the alcohol content in the respective drug product, provide spray actuation content/dose accuracy, spray pattern, spray content uniformity, droplet size distribution, plume geometry, and actuation force reliability verification testing with the to-be-marketed 20% alcohol formulation of your product.

18. In your October 18, 2019, response to Question 24d, you provided a brief summary of your CAPA procedure and referenced your internal CAPA procedure; however, there is limited detail regarding your CAPA procedures and a determination of the adequacy of the procedure cannot be made. Provide your internal CAPA procedure for our review. Ensure that your procedure includes the following elements:

    a. Requirements to analyze processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems.

    b. Review and disposition process of nonconforming product, including documentation of disposition. Documentation should include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use.

c. Appropriate statistical analysis of these quality data to detect recurring quality problems.

d. Investigations into the cause of nonconformities relating to product, processes, and the quality system.

e. Requirements for identification and implementation of actions needed to correct and prevent recurrence of nonconformities and other quality problems.

f. Verification or validation of the corrective and preventive actions taken to ensure that such action is effective and does not adversely affect the finished device.

g. Procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, and to ensure that the product meets its current approved specifications.

h. Requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems.

i. Ensure that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems.

j. Submission of relevant information on identified quality problems, as well as corrective and preventive actions, for management review.

k. Documentation of all CAPA activities.

Nonclinical

19. You have not provided adequate extractable leachable data to permit a toxicological risk assessment of leachable compounds. Update the extractable leachable assessment to address the Chemistry, Manufacturing, and Controls deficiencies in the resubmission. Submit a toxicological risk assessment for any compound detected in the leachable study present at 5 mcg/day or greater.

Human Factors

20. There is insufficient information to support the design of your proposed user interface. We refer you to our April 26, and August 9, 2019, Advice Letters

regarding your Human Factors Validation Study under IND 134954. Update your product's user interface and use-related risk analysis, and submit the results of your HF validation study.

PRESCRIBING INFORMATION

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Submit draft labeling that addresses our proposed revisions in the attached labeling.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at FDA.gov.[3]

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling revised as follows:

1. Provide the amount of alcohol in terms of percent volume of absolute alcohol on carton labeling.

2. In order to comply with the Guidance for Industry *Naming of Drug Products Containing Salt Drug Substances*[4] and USP salt policy, add equivalency statement in section 11 of the PI indicating the strength in terms of the active moiety, i.e. naloxone hydrochloride 8 mg (equivalent to 7.2 mg naloxone) in 0.1 mL. The equivalency statement should also appear on the carton labeling text and if space permits, on container label as well.

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.

[4] https://www.fda.gov/media/87247/download

- 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.

ADDITIONAL COMMENTS

Product Quality

1. Include a statement that [redacted] (b) (4) is equivalent to 8.0 mg of naloxone hydrochloride below the composition table in 3.2.P.1. Description and Composition of the Drug Product.

2. If there is any change in the material composition of the rubber stopper, provide the Routine Extractables Studies as per the Guidance for Industry *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation (2002)*.[5]

Proprietary Name

3. The review of your proposed proprietary name has been terminated due to the deficiencies with the application as described in this letter. Resubmit the proposed proprietary name when you respond to the application deficiencies.

[5] https://www.fda.gov/media/70857/download

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 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 guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

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 Sandy Truong, PharmD, Regulatory Project Manager, at (301) 796-5719.

Sincerely,

{See appended electronic signature page}

Naomi Lowy, MD
Acting Deputy Director
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE:

- Labeling

17 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

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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/

NAOMI N LOWY
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