CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208969Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208969

COMPLETE RESPONSE

Amphastar Pharmaceuticals, Inc.
11570 6th Street
Rancho Cucamonga, CA 91730

Attention: Gisela Sharp
Senior Manager, Regulatory Affairs

Dear Ms. Sharp:

Please refer to your New Drug Application (NDA) dated April 18, 2016, received April 19, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Naloxone Nasal Spray.

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.

We also acknowledge receipt of your amendment dated February 7, 2017, 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.

1. Based on the results of the human factors (HF) validation study, the product user interface does not support a conclusion that all intended users can use this product safely and effectively. (b) (4)

(b) (4)

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(b) (4)

2. The design requirements specifications do not appear to contain requirements permitting (b) (4) as part of the spray characteristics, however, information provided described that the Delivery Amount includes any (b) (4)

   Information needed to resolve deficiency:
   Modify the delivery accuracy verification metho (b) (4) are not captured in the analysis and repeat the testing to be consistent with the specified device performance specifications.

3. The proposed reliability specification at expiry of (b) (4) is unacceptable for a product intended for emergency treatment of opioid overdose.

(b) (4)

(b) (4)

4. Administration of the proposed (b) (4) has the potential to lead to run-off into the posterior pharynx, especially in the youngest pediatric patients, raising safety concerns surrounding respiratory complications due to aspiration and effectiveness concerns due to inadequate absorption of naloxone. The pediatric assessment does not adequately address these concerns to support use of the product down to birth.

   Information needed to resolve deficiency:
   Because your product may be administered to someone other than the prescription recipient, including children, your application must support the use of the product in all age ranges, including children down to birth. Consider re-formulating your product (b) (4) for use in adults and pediatric patients down to birth.

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 CFR314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

PROPRIETARY NAME

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

FACILITY INSPECTIONS

During a recent inspection of the International Medication Systems Limited (FEI 2016148) manufacturing facility for this application, our field investigator conveyed device (21 CFR 820) deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

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.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

1. The description of the non-volatile leachables testing in the extractables and leachables report is inadequate to assure accurate monitoring of non-volatile extractables/leachables. Clarify which extractables/leachables standards were used when running the (b) (4) samples. Provide validation information on the (b) (4) method showing it is capable of detecting the likely extractables/leachables present.

2. There is an unexplained inconsistency in the results of the extractions studies using similar conditions in the assessment of extractables and leachables. (b) (4)

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," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf.

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 Shelly Kapoor, PharmD, Regulatory Project Manager, at (240) 402-2787.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Division 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 and this page is the manifestation of the electronic signature.

/s/

SHARON H HERTZ
02/17/2017