



NDA 219045

**COMPLETE RESPONSE**

Hikma Pharmaceuticals USA Inc.  
Attention: George Prestash IV  
Associate Director, Regulatory Affairs  
1809 Wilson Road  
Columbus, OH 43228

Dear George Prestash IV:

Please refer to your new drug application (b) (4)

or naloxone hydrochloride (HCl) nasal spray, 4 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.

**CLINICAL**

The submitted data do not support the proposed nonprescription use of your proposed product, naloxone HCl nasal spray, 4 mg.

To support and establish the efficacy and safety of your proposed product, you are relying upon the Agency's findings of efficacy and safety for NDAs 16636 (Narcan [naloxone HCl, 0.4 mg/mL] injection) and 208411 (Narcan [naloxone HCl, 4 mg] nasal spray), as well as cross-referencing your NDA 212045 (Kloxxado [naloxone HCl, 8 mg] nasal spray).

To bridge the efficacy and safety of your proposed product, you submitted pharmacokinetic and safety data from your comparative bioavailability study NAL-NS0521-45. In this study, the proposed product demonstrated greater maximum plasma concentration ( $C_{max}$ ) and area under the plasma concentration-time curve (AUC) values compared to Narcan (naloxone HCl, 4 mg) nasal spray despite having the same nominal 4 mg dose. Compared to Kloxxado (naloxone HCl, 8 mg) nasal spray, the proposed product demonstrated lower  $C_{max}$  and AUC values. However, the systemic exposure of the proposed product more closely aligned with that of prescription Kloxxado (naloxone HCl, 8 mg) nasal spray than with that of nonprescription Narcan (naloxone HCl, 4 mg) nasal spray.

Regarding efficacy, your comparative bioavailability study demonstrated that the proposed product has comparable or higher systemic exposure and comparable or quicker onset of action than Narcan (naloxone HCl, 4 mg) nasal spray. Therefore, you may rely on the Agency's finding of efficacy for Narcan (naloxone HCl, 4 mg) nasal spray.

To establish the safety of your proposed product, you also submitted analyses of pharmacovigilance safety data related to Kloxxado from three databases and a review of the published medical literature relevant to the clinical safety of multiple doses of intranasal naloxone, as compared to single doses of intranasal naloxone.

Regarding safety, because the systemic exposure of the proposed product is greater than that of Narcan (naloxone HCl, 4 mg) nasal spray, you may not rely on the Agency's finding of safety for Narcan (naloxone HCl, 4 mg) nasal spray. We reviewed the safety data you submitted and conducted a review of the published medical literature to further investigate potential safety issues with the proposed product, and we find that the data submitted are inadequate to address potential increased safety risks of nonprescription use of the proposed product. The higher systemic exposure of the proposed product compared to Narcan (naloxone HCl, 4 mg) nasal spray is a safety concern. We are concerned that higher naloxone doses and exposures may result in increased risk, severity, and duration of precipitated opioid withdrawal, which can result in serious adverse outcomes, including pulmonary edema and cardiovascular events, in opioid-dependent individuals. The higher systemic exposure of the proposed product is a concern in the nonprescription setting, where consumers may access the product without guidance from a health care intermediary.

Furthermore, the higher systemic exposure of the proposed product poses a challenge to effectively communicate to consumers. Conveying the concept that products with the same nominal dose can have different systemic exposures, and therefore different levels of risk for adverse events, in a Drug Facts label (DFL) would be novel and challenging. However, without labeling changes, the proposed product would appear comparable to other 4 mg naloxone nasal spray products in the nonprescription space with regard to nominal dose, directions, and warnings. Consumers would be unaware of the higher exposure and potential increased risk of precipitated withdrawal compared to other marketed nonprescription naloxone nasal spray products.

To support the nonprescription use of this product, you used FDA's model naloxone DFL as the foundation of your proposed DFL. Product-specific instructions were added to the DFL and evaluated in a simulated-use human factors validation study designed to evaluate whether the user interface can be used safely and effectively by intended users for the intended use under the expected environment of use. However, our safety concerns related to the higher naloxone exposure precluded labeling discussions.

### Recommendations to Address Deficiencies

- You may want to consider product reformulation (b) (4) to obtain a lower systemic naloxone exposure consistent with that of approved nonprescription naloxone products.
- To support nonprescription marketing approval of the currently proposed formulation of naloxone HCl, 4 mg, nasal spray, you would need to (1) establish safety of the proposed product's higher systemic exposure for consumers in the nonprescription setting (i.e., by demonstrating that the safety profile of the proposed product, or a formulation with a similar systemic exposure, is comparable to that of an approved nonprescription naloxone product), and to (2) potentially modify labeling and ensure adequate comprehension of your proposed product label.

It is uncertain whether you can establish the safety of the currently proposed product for nonprescription marketing at this time. However, we are open to reviewing your proposals that may include the following:

#### (1) Safety

- a. Published literature that specifically addresses the safety profile of higher-exposure naloxone formulations, especially in opioid-dependent individuals, and/or
- b. Data from adequate clinical safety studies in relevant populations, especially opioid-dependent individuals, to better characterize the risk of precipitated withdrawal with higher-exposure naloxone formulations

#### (2) Labeling

- a. If upon our review you are able to establish safety of your higher exposure 4 mg product comparable to that of an approved nonprescription naloxone product, additional labeling may be unnecessary.

We recommend that you submit protocols for review and feedback prior to the conduct of any studies.

We remain committed to addressing the opioid crisis and are open to further discussions with you to address these concerns and explore potential paths forward for this product.

The development of safe and effective nonprescription naloxone products remains a priority.

## **CARTON AND CONTAINER LABELING**

We reserve further comment on the proposed labeling until the application is otherwise adequate.

## **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 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) 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.
- (3) Provide case report forms and narrative summaries for each subject 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.
- (4) 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.
- (5) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
- (6) Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.
- (7) Provide English translations of current approved foreign labeling not previously submitted.

## **ADDITIONAL COMMENTS**

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

### **Human Factors Development Program and Proposed Product User Interface**

It will be necessary for you to consider how revisions to your proposed product to address the deficiencies outlined above will impact your user interface. If changes are made to the product user interface, device constituent parts, intended users, uses, or

use environments to address the deficiencies outlined above, update your use-related risk analysis (URRA) to determine whether any new risks, including new critical tasks or failure modes are introduced by the changes. If you determine that an additional human factors validation study is not required, we strongly recommend you submit your justification along with a side-by-side comparison of the user interface tested in the human factors study and the intend-to-market user interface for our feedback prior to resubmitting your NDA. The acceptability of your justification will be a matter of review.

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

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

If you have questions, call

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Sincerely,

*{See appended electronic signature page}*

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Center for Drug Evaluation and Research

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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.**  
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/s/  
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