



NDA 214315

**COMPLETE RESPONSE**

Defender Pharmaceuticals, Inc  
Attention: Lisa McNeil  
Vice President, Quality & Regulatory Affairs  
12935 N Outer Forty Drive  
Suite 212  
St. Louis, MO 63141

Dear Ms. McNeil:

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

or scopolamine nasal gel.

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**

(b) (4)

(b) (4)



(b) (4)



## **HUMAN FACTORS**

- (3) Based on the evaluation of the human factors (HF) validation study results, the user interface does not support the safe and effective use of the proposed product. The results of the HF validation study demonstrated several use errors and close calls with critical tasks that may result in harm to the patient. Specifically, results from your HF validation study demonstrated that several participants used the product inappropriately resulting in use errors (e.g., failure to wipe nozzle tip, administration of a second pump actuation in the same nostril, administration of a single pump actuation in both nostrils). These use errors led to administration of higher than intended doses of drug substance.

As conveyed in the (b) (4) Discipline Review letter, we note that the majority of available nasal products delivered through pump actuation have an associated mental model of a single dose consisting of administration of drug substance into both nostrils. Conversely, scopolamine nasal gel is intended to be administered as a single dose consisting of one pump actuation of drug

substance into a single nostril.

**Information needed to resolve the deficiencies:**

Implement user interface revisions and design modifications to promote the safe and effective use of the proposed product, and provide data demonstrating that, with these mitigations, the product user interface can be used safely and effectively to deliver the intended dose of drug substance.

As the established mental model may limit the impact of measures to mitigate the identified medication errors (e.g., administration of a dose higher than intended), we recommend you consider the potential for a dose of your product to be provided within the existing mental model (i.e., for a dose of product to be delivered as 0.08 mg of scopolamine nasal gel per a single pump actuation in each nostril, to provide a total dose of 0.16 mg of scopolamine nasal gel over 2 actuations of the device).

Prior to conducting an assessment to evaluate the impact of any mitigation strategies (e.g., modifications proposed during the (b) (4) teleconference including changes to the principal display panel of the carton, modifications to the device label, inclusion of a Quick Start guide), we recommend submitting your HF validation study protocol, along with the redesigned user interface, for our review and feedback.

**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 Prescription Drug Labeling Resources<sup>2</sup> and Pregnancy and Lactation Labeling Final Rule<sup>3</sup> 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 FDA.gov.<sup>4</sup>

---

<sup>2</sup> <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

<sup>3</sup> <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

<sup>4</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

**CARTON AND CONTAINER LABELING**

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

**PROPRIETARY NAME**

Please refer to correspondence dated, (b) (4), which addresses the proposed proprietary name, (b) (4). This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

**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 dropouts from the newly completed trials. Describe any new trends or patterns identified.

- (4) 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.
- (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 submitted data are insufficient to support the demonstration of efficacy for scopolamine nasal gel for the prevention of nausea induced by motion. Although statistically significant results were obtained on the evaluation of the key secondary endpoint of subjects with no nausea and no use of rescue medication in Trial MS-33, the results were not highly persuasive ( $p=0.03$ ). Additionally, the results of the analysis for this endpoint (i.e., subjects with no nausea and no use of rescue medication) in Trial MS-29 were not nominally significant ( $p=0.12$ ). Provide additional clinical data to support the demonstration of safety and effectiveness of scopolamine nasal gel for the "prevention of nausea" portion of the proposed indication (i.e., the prevention of nausea induced by motion).
2. We refer to our information request of (b) (4), and the guidance for industry *Naming of Drug Products Containing Salt Drug Substances* (June 2015). In the resubmission, (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 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 any questions, call

(b) (4)

Sincerely,

*{See appended electronic signature page}*

(b) (4)

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/  
-----

(b) (4)

01/25/2024 09:19:18 AM