CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212905Orig1s000

OTHER ACTION LETTERS

NDA 212905

COMPLETE RESPONSE

Verrica Pharmaceuticals Inc.
Attention: Misty M. D'Ottavio, RN
Executive Director, Regulatory Affairs
44 West Gay Street, Suite 400
West Chester, PA 19380

Dear Ms. D'Ottavio:

Please refer to your new drug application (NDA) dated and received September 13, 2019, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for cantharidin topical solution.

We acknowledge receipt of your amendment dated November 24, 2021, which constituted a complete response to our September 16, 2021, action letter.

We have completed our review of this application and have determined that we cannot approve this application in its present form. We have described our reasons for this action below.

FACILITY INSPECTIONS

(b) (4)

for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRESCRIBING INFORMATION

(1) 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*1* and Pregnancy and Lactation Labeling Final Rule*2* 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.

CARTON AND CONTAINER LABELING

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

PROPRIETARY NAME

Please refer to correspondence dated, March 23, 2021, which addresses the proposed proprietary name, Ycanth. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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.

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 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 Qianyiren Song, Regulatory Project Manager, at 301-796-2581.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
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/

KENDALL A MARCUS
05/23/2022 08:27:37 AM

NDA 212905

COMPLETE RESPONSE

Verrica Pharmaceuticals Inc.
Attention: Bradley Catalone, PhD, MBA
Head of Drug Development
44 West Gay Street, Suite 400
West Chester, PA 19380

Dear Dr. Catalone:

Please refer to your new drug application (NDA) dated and received September 13, 2019, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for cantharidin topical solution.

We acknowledge receipt of your amendment dated December 23, 2020, which constituted a complete response to our July 13, 2020, action letter.

We acknowledge receipt of your major amendment dated May 13, 2021, which extended the goal date by three months.

We have completed our review of this application, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below.

FACILITY INSPECTIONS

During a recent inspection of the (b) (4) or this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRESCRIBING INFORMATION

(1) 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[1] and Pregnancy and Lactation Labeling Final Rule[2] 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.[3]

CARTON AND CONTAINER LABELING

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

PROPRIETARY NAME

Please refer to correspondence dated, March 23, 2021, which addresses the proposed proprietary name, Ycanth. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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:

---

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

- 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

Labeling and Human Factor comments and recommendations will be conveyed in a separate correspondence.

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 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 Qianyiren Song, Regulatory Project Manager, at 301-796-2581.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
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/

KENDALL A MARCUS
09/16/2021 02:20:43 PM

NDA 212905

COMPLETE RESPONSE

Verrica Pharmaceuticals Inc.
Attention: Patti Neall
Executive Director, Regulatory Affairs
10 N. High Street, Suite 200
West Chester, PA 19380

Dear Ms. Neall:

Please refer to your new drug application (NDA) dated and received September 13, 2019, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for cantharidin topical solution, 7%.

We have completed our review of this application 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 amendments dated May 15 and 29; June 5 and 11, 2020, which were 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.

PRODUCT QUALITY

(1) The proposed drug product specification does not include test to assure the drug product can be safety and accurately expelled onto the lesion area and avoid the adjacent healthy skin. The specification for the final assembled drug product should be revised to include the following:

a. A test for the crushing force of the glass ampule.

b. A leakage test after ampule crushing to assure there is no drug leakage at release and during shelf-life.

c. A droplet test to demonstrate that the users are capable of dispensing various amount of drug product as needed to the affected skin area while avoiding the adjacent healthy skin.

(2) The extraction solutions, (b) (4) used in the extractable/leachable study are considered inadequate because:

(b) (4)

b. Leachable compounds were detected during drug product testing for related substances that were not detected in the extractable studies. Extractable/leachable studies you have committed to in the amendment dated January 23, 2020 should be conducted and the results of these studies should be submitted to the application.

(3) The drug product quality is not assured and the expiration dating period cannot be established because the registration drug product batches provided in the application were not fully assembled (b) (4) In order to assure the drug product quality and established expiration dating period for the drug product, at least 3 months of long-term and accelerated stability data from three batches of fully assembled (b) (4) drug product with at least 3 times-points post manufacture (at initial, 1 months, 2 months, and 3 months) should be submitted to the application.

FACILITIES

(4) Our field investigator could not complete inspection of the manufacturing facility (b) (4) because the facility was not ready for inspection. Satisfactory inspection is required before this NDA can be approved. Please notify us in writing when this facility is ready for inspection.

(5) We have not completed our inspection of your (b) (4) manufacturing facility due to travel restrictions associated with COVID-19 pandemic. An inspection of (b) (4) acility 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 CGMP.

PROCESS

(b) (4)

HUMAN FACTORS

(11) As we previously communicated, our review of the human factors (HF) validation study data noted use errors and difficulties with the critical task- 'Break the Ampule'. We note one use error and three difficulties with the critical task. The use error occurred when the user removed the cap and paperboard sleeve, tipped the applicator upside down and broke the ampule with two hands. Additionally, three other users had difficulty breaking the ampule, which required two hands to break. Of these three use difficulties, one user also tilted the applicator horizontally. Based on your use-related risk analysis (URRA), this task is considered critical because premature cap removal and incorrect applicator orientation can lead to accidental exposure to the patient or healthcare provider's (HCP's) mouth or eyes leading to serious harm. Despite the use error and difficulties with critical task, you did not propose any additional mitigation strategies to address the use issues (e.g., reducing the force required to break the ampule).

We note your heuristic analysis submitted on April 10, 2020 indicates that the average palmar pinch force (grip used to break an ampule) for adult females is 16 lbs. and that the average force to break the ampule with paperboard sleeve on is 19 lbs. From this information you concluded that the force to break the ampule

could increase the potential for use errors - *"there is a potential that users will struggle to break the glass ampule due to the amount of force required. There is risk that some users may remove the paperboard sleeve in order to try and break the glass ampule. There is also potential for users to utilize other means to break the ampule if they are unable to generate enough force with their hands."*

We also reviewed your April 10, 2020 threshold/comparative analyses with Eskata and Levulan Kerastick; products with some similarities to the proposed product in this review. We determined that the Levulan Kerastick has a different user interface than your proposed product because the Levulan Kerastick includes the Kerastick Krusher device as a means of breaking the ampule prior to administration. This difference may impact performance of the critical task of breaking the ampule. Furthermore, with respect to the comparative analyses to the Eskata product, we note postmarketing medication error cases that report accidental exposure to patient and health care professionals when using the product. Given some of the similar design attributes with your proposed product, we are concerned that accidental exposure can occur with cantharidin topical solution, which may present a different risk. As such, we have determined that a leveraging approach for your proposed product is not appropriate and the residual risk with your product is unacceptable.

In summary, we remain concerned that your proposed cantharidin combination product is not safe for use by HCPs. We are concerned that the risk of accidental exposure will outweigh the benefit of the treatment with this combination product. Inherent design issues exist with this product that may contribute to serious harm if accidental exposure occurs during use. Thus, additional mitigation strategies are needed and could include the need for device design changes to optimize applicator use along with other revisions to the product user interface taking into consideration our previously identified concerns and the data collected from your HF validation study. After you implement additional risk mitigation strategies/modifications, we recommend you conduct an additional HF validation study to ensure that these modifications address the observed use errors and use difficulties and do not introduce any new risks.

We recommend you submit your revised HF validation study protocol for feedback from the Agency before commencing the study. Please note we will need 60 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly.

As you further develop your proposed product and prepare your next human factors study protocol to address the above concerns, we have the following additional recommendations:

a. You indicated in your comparative analysis submitted on April 10, 2020 that the Levulan Kerastick product is similar to your proposed product. We note the Kerastick Krusher device has a means of breaking the ampule

prior to administration that differs from your product. The design of the Levulan Kerastick product may inform how you address the break force issues identified during your human factors product development.

b. We noted use errors, difficulties, and subjective feedback indicating concerns with the readability of the Instructions for Use (IFU), but you have not proposed additional risk mitigation strategies to address the use errors and difficulties. Thus, we recommend additional mitigation strategies to address these use errors and difficulties as part of the overall changes to the user interface.

c. We disagree with your characterization of some tasks as non-critical. Tasks that could cause harm to users, as noted in your URRA, should be noted as critical tasks (e.g. Inspect Applicator; (b) (4) Apply Solution; and Allow Solution to Dry). Additionally, we note that the task 'Remove Cap' in your URRA does not assess the risk of incorrect timing of cap removal, which can increase the risk of accidental exposure. Because of the potential for causing harm to the user or patient, these tasks should be re-categorized as critical tasks in your updated URRA.

PRESCRIBING INFORMATION

(12) 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[1] and Pregnancy and Lactation Labeling Final Rule[2] 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.[3]

PROPRIETARY NAME

(13) Please refer to correspondence dated, December 6, 2019 which addresses the proposed proprietary name, Ycanth. This name was found conditionally

[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

acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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.

(14) Describe in detail any significant changes or findings in the safety profile.

(15) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

a. Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.

b. Present tabulations of the new safety data combined with the original application data.

c. Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.

d. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(16) 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.

(17) 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.

(18) 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.

(19) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(20) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(21) 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 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 Qianyiren Song, Regulatory Project Manager, at 301-796-2581.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
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/

KENDALL A MARCUS
07/13/2020 03:54:44 PM