CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214520Orig1s000

OTHER ACTION LETTERS

NDA 214520

COMPLETE RESPONSE

CorMedix Inc.
Attention: Phoebe Mounts, PhD, Esq.
Executive Vice President and General Counsel
5825 Bellanca Drive
Elkridge, MD 21075

Dear Dr. Mounts:

Please refer to your new drug application (NDA) dated and received June 30, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for taurolidine 67.5 mg/5 mL (13.5 mg/mL) and heparin 5,000 USP Units/5 mL (1,000 Units/mL) catheter lock solution.

We acknowledge receipt of your amendment dated February 25, 2022, which constituted a complete response to our February 26, 2021, action 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 / FACILITY INSPECTIONS

(1) During a recent inspection of the (b) (4) and Rovi Pharma Industrial Services S.A (FEI 3016688535) manufacturing facilities for this application, our field investigators conveyed deficiencies to the representatives of the facilities. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRESCRIBING INFORMATION

(2) Draft labeling will be provided in a separate communication. Upon resubmission of your application, submit draft labeling that is responsive to that communication. Do not submit draft labeling prior to your official resubmission.

Prior to resubmitting the draft labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling

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

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, 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, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.
- Additional resources for the PI, patient labeling, and carton/container labeling.

CARTON AND CONTAINER LABELING

(3) Draft carton and container labeling will be provided in a separate communication. Upon resubmission of your application, submit draft carton and container labeling that is responsive to that communication. Do not submit draft carton and container labeling prior to your official resubmission.

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

PROPRIETARY NAME

(4) Please refer to correspondence dated July 20, 2022, which addresses the proposed proprietary name, Defencath. This proposed name is unacceptable due to confusion with another product that is also under review. Therefore, the ultimate acceptability of your proposed proprietary name, Defencath, is dependent upon which application is approved first.

We note that you proposed an alternate proprietary name in your submission dated March 3, 2022. In order to initiate the review of the alternate proprietary name, (b) (4), submit a new request for proprietary name review when you respond to the application deficiencies. If Defencath is still your preferred proprietary name, you may indicate in the cover letter narrative that Defencath remains your preferred name. We will provide additional administrative guidance pertaining to your proprietary name, as appropriate.

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 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:

Product Quality / Facilities:

There are facilities (e.g., release/stability testing sites) included in DMF (b) (4) for HEPARIN SODIUM ((b) (4)) that were not listed in your application (i.e., Form FDA 356h and/or in Section 3.2.S.2.1). Please note that the FDA cannot provide to you the status of facilities not listed in your application. Please contact the DMF holder to identify and resolve any discrepancies and clarify which facilities listed in the DMF support your application. We recommend that the DMF related facilities supporting your application be added to your Form FDA 356h and in Section 3.2.S.2.1. If only a subset of the facilities listed in the DMF will be referenced in your application to support commercial manufacturing and/or testing, the letter of authorization (LOA) should specify those facilities. Absent this specificity, the FDA intends to assume that all facilities listed in a referenced DMF support your application.

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 Kristine Park, PhD, RAC, Senior Regulatory Health Project Manager, at (301) 796-0471.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Director
Office of Infectious Diseases
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/

JOHN J FARLEY
08/04/2022 05:18:45 PM

NDA 214520

COMPLETE RESPONSE

CorMedix Inc.
Attention: Phoebe Mounts, PhD, Esq.
Executive Vice President and General Counsel
5825 Bellanca Drive
Elkridge, MD 21075

Dear Dr. Mounts:

Please refer to your new drug application (NDA) dated June 30, 2020, received June 30, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Defencath (taurolidine 67.5 mg/5 mL (13.5 mg/mL) and heparin 5,000 USP Units/5 mL (1,000 Units/mL)) catheter lock solution.

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

Facility:

(1) During a review of records requested under Federal Food, Drug, and Cosmetic Act section 704(a)(4), provided by Rovi Pharma Industrial Services S.A. (FEI 3016688535) manufacturing facility, the FDA noted objectionable conditions. These objectionable conditions will be conveyed to the representative of the facility within 10 business days of issuance of this Complete Response letter. Satisfactory resolution of these objectionable conditions is required (e.g., preapproval inspection and/or adequate facility responses addressing these conditions) before this application may be approved. If it is determined that an inspection is needed to approve your application, please note that FDA continues to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

For more information, please see the FDA guidance related to COVID-19.[1]

[1] https://www.fda.gov/emergency-preparedness-and-/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders

Process:

(2) You have not demonstrated that the currently proposed in-process control for the [redacted] (b) (4) ([redacted] (b) (4) mL± [redacted] (b) (4) mL) in the drug product manufacturing process is appropriate. As previously communicated to you, conduct and provide results of an extraction study to demonstrate that the labeled volume of the drug product solution (5 mL) can be consistently withdrawn from vials, including vials that are [redacted] (b) (4). Revise the [redacted] (b) (4) based on the results of the extraction study conducted.

PRESCRIBING INFORMATION

(3) Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] and Pregnancy and Lactation Labeling Final Rule[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Submit draft labeling that addresses our proposed revisions in the attached labeling.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[4]

[2] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm08415 9.htm
[3] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm09330 7.htm
[4] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling revised as follows:

As currently presented, the National Drug Code (NDC) is denoted by a placeholder (NDC XXXXX-XXX-XX) on both the proposed container label and carton labeling dated February 12, 2021. However, we note that Section 16, *How Supplied/Storage and Handling* of your proposed PI includes the NDC 72990-(b) (4). Therefore, replace the current placeholders (NDC XXXXX-XXX-XX) with the intended NDCs on the container label and carton labeling and submit for our review.

PROPRIETARY NAME

Please refer to correspondence dated August 28, 2020, which addresses the proposed proprietary name, Defencath. 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 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.

ADDITIONAL COMMENT

We have the following comment that is not an approvability issue:

Product Quality:

We acknowledge the updates made in Module 3.2.P.3.4 with the revised in-process control (IPC) and (b) (4). However, the (b) (4) could not be located. Please include the (b) (4) with appropriate acceptance criteria as part of the IPC for (b) (4). Submit the testing method and update Module 3.2.P.3.4 and the proposed Master Batch Record (MBR), accordingly.

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 Kristine Park, PhD, RAC, Senior Regulatory Health Project Manager, at (301) 796-0471.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Director
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Labeling
    - Prescribing Information

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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.

/s/

JOHN J FARLEY
02/26/2021 12:46:05 PM