CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208574Orig1s000
208574Orig2s000

OTHER ACTION LETTERS

NDA 208574

COMPLETE RESPONSE

CLASS 2 RESUBMISSION

Teva Pharmaceuticals USA Inc.
Attention: Scott Tomsky
Vice President, Regulatory Affairs, US Generics
425 Privet Road
Horsham, PA 19044

Dear Mr. Tomsky:[1]

Please refer to your new drug application (NDA) dated August 18, 2015, received August 18, 2015 and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Romidepsin Injection solution, 10 mg/2 mL (5 mg/mL).

We acknowledge receipt of your amendment dated May 29, 2019, which constituted a complete response to our June 2, 2017, 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

During a recent inspection of the TEVA PARENTERAL MEDICINES, INC. (FEI 2027158) manufacturing facility 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

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

[1] We update guidance's periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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

FACILITY INSPECTIONS

During a recent inspection of the TEVA PARENTERAL MEDICINES, INC. (FEI 2027158) manufacturing facility 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.

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.

---

[2] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[3] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[4] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

- 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 Kimberly Scott, Regulatory Project Manager, at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Supervisory Associate Deputy Director
Division of Hematology Products
Office of Hematology and Oncology Products
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/

ALBERT B DEISSEROTH
11/04/2019 04:31:36 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208574

COMPLETE RESPONSE

Teva Pharmaceuticals USA Inc.
Joann Stavole
Senior Director, Regulatory Affairs, US Generics
Morris Corporate Center III
400 Interpace Parkway
Parsippany, NJ 07054

Dear Ms. Stavole:

Please refer to your New Drug Application (NDA) dated December 29, 2016, received December 29, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Romidepsin Injection, solution, 10 mg/2 mL (5 mg/mL).

We acknowledge receipt of your amendment dated December 29, 2016, which constituted a complete response to our June 1, 2016, 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 and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

During a recent inspection of the Teva Pharmaceutical Works Private Limited Company, Gödöllő, Hungary (FEI 3002875215) manufacturing facility 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

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* and *Pregnancy and Lactation Labeling Final Rule* 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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm .

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 drugt. 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 FDA Guidance for Industry, *"Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products,"* March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf.

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 Kimberly Scott, Regulatory Project Manager, at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

Edvardas Kaminskas, MD
Deputy Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDVARDAS KAMINSKAS
06/02/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208574

COMPLETE RESPONSE

Teva Pharmaceuticals USA
Attention: Cory Wohlbach
Director, Regulatory Affairs, US Generics
425 Privet Road
Horsham, PA 19044

Dear Mr. Wohlbach:

Please refer to your New Drug Application (NDA) dated August 18, 2015, received August 18, 2015, and your amendments submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Romidepsin Injection, 10 mg/2 mL (5 mg/mL).

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 acknowledge your March 28, 2016 response to the information request dated March 14, 2106. However, the rationale used to support potential extractables/leachables from the (b) (4)

Address this concern as it relates to the proposed manufacturing conditions, taking into consideration any worst case scenario (b) (4) Please include data and/or study results to support your conclusions (b) (4) .

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 "*PLR Requirements for Prescribing Information*" and *"Pregnancy and Lactation Labeling Final Rule"* 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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

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 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.

Submit draft labeling that addresses the proposed revisions below.

1. Romidepsin Prescribing Information:
    a. Section 2 Dosage and Administration
        i. Error-prone symbols that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout this section. In particular, the following symbols appear frequently: ≥ and ≤. Please revise these symbols to reflect their intended meanings and to prevent misinterpretation and confusion.

    b. Section 3 Dosage Forms and Strengths
        i. Revise the phrase [redacted] (b) (4) to "…*single dose vial*."
        We recommend this revision to accurately reflect the package type.

    c. Section 16 How Supplied/Storage and Handling
        i. See recommendation 3.b.i. and revise accordingly.

CARTON AND CONTAINER LABELING

Please submit draft carton and container labeling revised as follows:

1. As per 21CFR 201.100(b)(5), quantitative ingredient information should be provided on the label of the drug if space allows. Alternatively, this information can be included on the carton.

2. Include sterility information for the drug product in the carton container.

3. Romidepsin Carton Labeling:
    a. Consider revising the statement [redacted] (b) (4) to "*For intravenous infusion*
        i. *after dilution*." [redacted] (b) (4) (b) (4)
    b. If space permits, consider relocating the statement "Must be diluted in 500 mL of
        i. 0.9% sodium chloride injection, USP" from the side panel to the principal display panel (PDP). We recommend this revision to increase the visibility of the dilution instructions.

    c. Revise the phrase [redacted] (b) (4) to "*Single Dose Vial*."

4. Romidepsin Container Label:
    a. See recommendations 4.a. through 4.c. and revise accordingly.

FACILITY INSPECTIONS

During a recent inspection of the Teva Pharmaceutical Works Private Limited Company, Gödöllő, Hungary (FEI 3002875215) manufacturing facility 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.

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 the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA 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 NDA 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. 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 FDA Guidance for Industry, *"Formal Meetings Between FDA and Sponsors or Applicants,"* May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

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, please call Kimberly Scott, Regulatory Project Manager, at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

Edvardas Kaminskas, MD
Deputy Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDVARDAS KAMINSKAS
06/01/2016