CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208419Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208419

COMPLETE RESPONSE

Actavis LLC, an indirect, wholly-owned subsidiary of Teva Pharmaceuticals U.S.A. Inc.
Attention: Cory Wohlbach
Senior Director, Regulatory Affairs
400 Interpace Parkway
Morris Corporate Center III
Parsippany, NJ 07054

Dear Mr. Wohlbach:

Please refer to your New Drug Application (NDA) dated and received December 23, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pemetrexed Injection (b) (4) 25 mg/mL.

We acknowledge receipt of your amendment dated January 24, 2018, which constituted a complete response to our September 26, 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.

CHEMISTRY, MANUFACTURING, AND CONTROLS

Drug Product

1. Provide updated drug product release and stability specifications for all three presentations of Pemetrexed Injection, to reflect the change of (b) (4) in the formulation and the addition of a new presentation. We recommend that you add an assay test for the (b) (4) in the drug product specifications.

2. Provide updated stability data for three batches for each presentation of Pemetrexed Injection from both Sindan and Actavis Italy sites. Provide A minimum of 12- months long- term and 6-months accelerated stability data on at least three primary batches for each presentation at the time of the NDA submission for one facility. For an alternate facility, three- months data under accelerated storage conditions for three batches of each presentation may be provided if the drug products are of comparable quality.

MICROBIOLOGY

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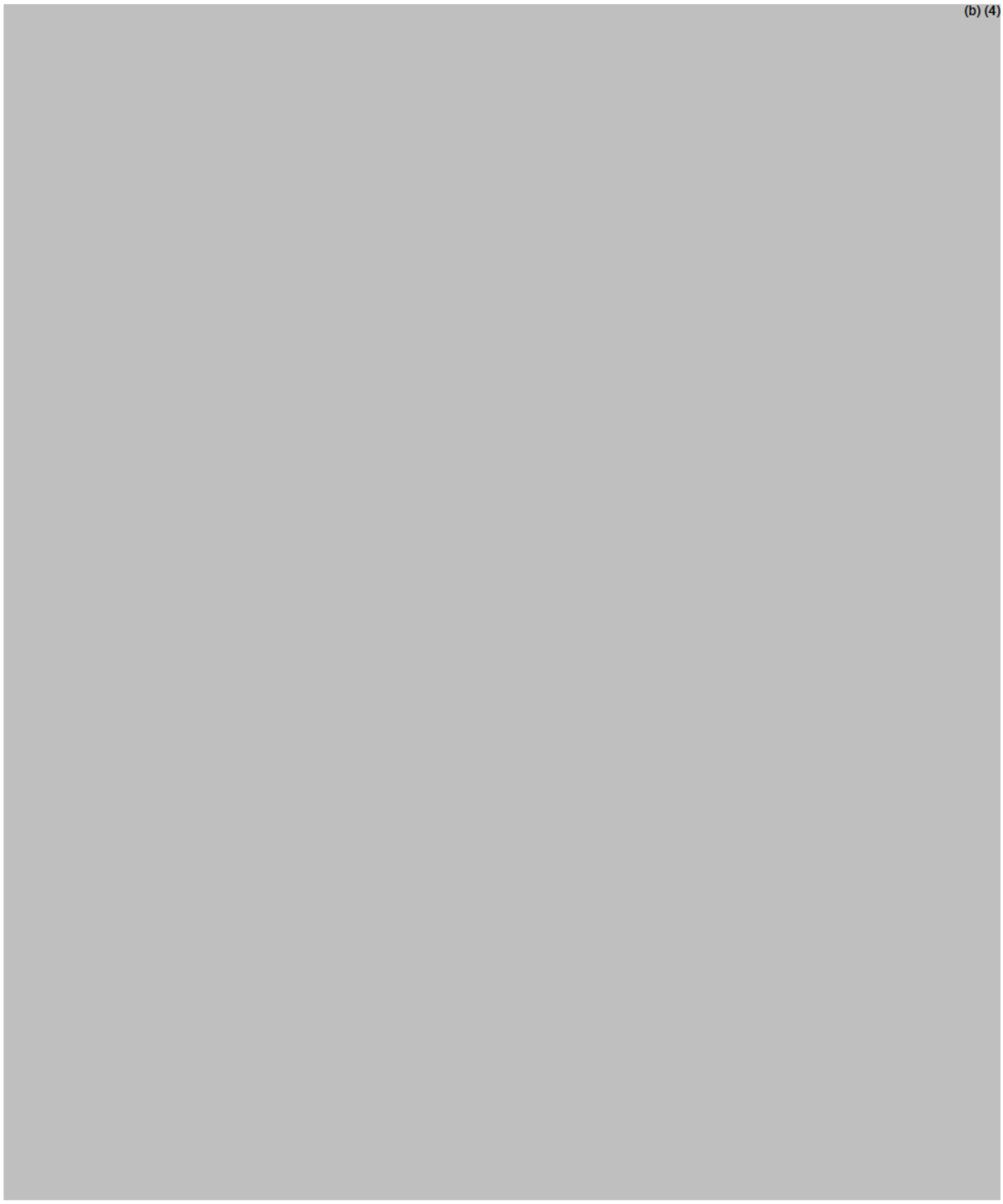

7. The method suitability report NV/TR00385 version 1 for the bacterial endotoxins test performed by the kinetic-turbidimetric method at the Actavis Italy S.p.A. facility is acknowledged. It is noted that at the S.C. Sindan-Pharma S.R.L. facility the bacterial endotoxins test is performed by a kinetic-chromogenic method. Demonstration of the

suitability of the kinetic-chromogenic method for the new drug product formulation proposed in the unsolicited amendment dated October 4, 2017, has not been provided. Provide a summary of the study performed to demonstrate the suitability of the bacterial endotoxins test method performed at the S.C. Sindan-Pharma S.R.L. facility for the new formulation. The summary should include: a description of the preparation of samples; a description of the sample dilutions tested; and the actual results. Also indicate the dilution of the drug product that is proposed for routine bacterial endotoxins testing at the S.C. Sindan-Pharma S.R.L. facility.

8. Demonstration of the suitability of the sterility tests performed at Actavis Italy S.p.A. and S.C. Sindan-Pharma S.R.L. facilities for the new drug product formulation proposed in the unsolicited amendment dated October 4, 2017, has not been provided. Provide a description of the sterility test method suitability studies performed at the Actavis Italy S.P.A. and S.C. Sindan-Pharma S.R.L facilities and provide the actual results of the studies.

9. Comment on the risk for growth of adventitious microbial contamination under the specified storage conditions (not more than 14 days in the refrigerated conditions 2°C - 8°C [36° to 46°F] and not more than (b) (4) hours at the room temperature) after dilution with the specified diluents (5% Dextrose Injection, USP) given the reformulation of the drug product. In the absence of a scientific rationale for the safety of the specified storage conditions with the reformulated drug product, a new microbiological study will be requested.

PRESCRIBING INFORMATION

10. 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. Describe in detail any significant changes or findings in the safety profile.

11. 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.

12. 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.

13. 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.

14. 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.

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

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

17. 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," December 2017 at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues; however, we recommend the following be implemented prior to approval of this NDA:

General Container & Carton Labeling Comments:

18. Consider revising the statement on the principal display panel "(b) (4)" and "(b) (4)" to read "Must dilute before intravenous infusion". We recommend this to minimize the risk of administering the drug as an intravenous bolus.

19. Increase the prominence of the storage condition statement, "Refrigerate at 2°- 8°C…", located on the side panel by using bold font to highlight the important storage information.

Container Labels:

20. The barcode should be surrounded by adequate white space to allow scanners to read the barcode properly in accordance with 21 CFR 201.25(c)(1)(i). For the product made in Italy, consider increasing the white space around the barcode while retaining the vertical orientation of the barcode.

Carton Labeling:

21. As proposed, the barcode is located on the bottom panel for products made in Romania and on the side panel for products made in Italy. Consider revising the carton labeling so the location of the barcode is consistent between the different manufacturing sites.

22. Remove the statement "(b) (4)". We recommend this revision due to post-marketing reports that negative statements (e.g. "(b) (4)") may have the opposite of the intended meaning because the word "(b) (4)" can be overlooked and the warning can be misinterpreted as an affirmative action.

23. Revise the warning statements on the principal display panel to include the statement "Store refrigerated". We recommend this revision because this storage condition is

distinct from other currently marketed pemetrexed products stored at room temperature, and thus should be emphasized to promote the safe and effective use of this product.

24. Include the following statement on the side panel of the carton labeling: "**To Dilute**: dilute with 5% Dextrose Injection, USP to achieve a total volume of 100 mL for intravenous infusion."

If you have any questions, call Rebecca Cohen, Regulatory Health Project Manager, at (240) 402-4998.

Sincerely,

{See appended electronic signature page}

Joseph Gootenberg, M.D.
Deputy Director
Division of Oncology Products 2
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/

JOSEPH E GOOTENBERG
06/26/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208419

COMPLETE RESPONSE

Actavis, L.L.C.
Attention: Joann Stavole, M.S., R.A.C.
Senior Director, Regulatory Affairs
400 Interpace Parkway
Morris Corporate Center III
Parsippany, NJ 07054

Dear Ms. Stavole:

Please refer to your New Drug Application (NDA) dated and received on December 23, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pemetrexed Injection (b) (4) 25 mg/mL.

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 recent inspection of Sindan-Pharma S.R.L (FEI: 3005566806) manufacturing facility for this application, our field investigators conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

MICROBIOLOGY

(b) (4)

PRESCRIBING INFORMATION

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SAFETY UPDATE

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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:

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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.

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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 Rebecca Cohen, Regulatory Health Project Manager, at (240) 402-4998.

Sincerely,

{See appended electronic signature page}

Joseph Gootenberg, M.D.
Deputy Director
Division of Oncology Products 2
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/

JOSEPH E GOOTENBERG
09/26/2017