U.S. FOOD & DRUG ADMINISTRATION

BLA 125514/S-151
BLA 125514/S-152

SUPPLEMENT APPROVAL/
FULFILLMENT OF POSTMARKETING REQUIREMENT

Merck Sharp & Dohme, LLC
Attention: Aditi Bhobe, B.Pharm (Sci), RAC
Associate Director - Global Regulatory Affairs
126 E. Lincoln Avenue, RY34-A2014
Rahway, NJ 07065

Dear Aditi Bhobe:

Please refer to your supplemental biologics license applications (sBLAs), dated November 9, 2023, and your amendments, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab) Injection.

We also refer to your sBLA 125514/S-136, approved April 3, 2023, under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses.

Prior Approval sBLA 152 (S-152) provides for regular approval, following prior Accelerated Approval, for Keytruda in combination with enfortumab vedotin-ejfv for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.

Prior Approval sBLA 151 (S-151) provides for expansion of the indication to the following: Keytruda in combination with enfortumab vedotin-ejfv for the treatment of adult patients with locally advanced or metastatic urothelial cancer.

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information, and Patient Package Insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

SUBPART E FULFILLED

We approved BLA 125514/S-136 under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses. Approval of supplement 152 (S-152) fulfills your commitments made under 21 CFR 601.41.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

We are waiving the pediatric study requirement for S-151 because necessary studies are impossible or highly impracticable. Additionally, we note that none of the above PREA criteria applies to S-152, therefore you are exempt from this requirement for S-152.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated November 9, 2023, containing the final report for the following post marketing requirement listed in the April 3, 2023, approval letter for BLA 125514 supplement 136 (S-136).

4429-1 Conduct clinical trial EV-302, "Enfortumab Vedotin and Pembrolizumab vs. Chemotherapy Alone in Untreated Locally Advanced or Metastatic Urothelial Cancer" and submit the final OS, PFS, ORR and DoR results, intended to verify and describe the clinical benefit of enfortumab vedotin in combination with pembrolizumab in patients with untreated locally advanced or metastatic urothelial cancer.

We have reviewed your submission and conclude that the above requirement was fulfilled.

This completes all of your postmarketing requirements and postmarketing commitments acknowledged in our April 3, 2023, letter. You are not required to report on the status of closed (released or fulfilled) PMRs/PMC in your annual report required under 21 CFR 601.70 of the FD&CA.

POSTMARKETING COMMITMENT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment under BLA 125514/S-151:

4563-1 Complete clinical trial KEYNOTE-A39, titled "An open-label, randomized, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab versus chemotherapy alone in previously untreated locally advanced or metastatic urothelial cancer," to obtain the final overall survival analysis based on the prespecified final number of events.

The timetable you submitted on December 4, 2023, states that you will conduct this study according to the following schedule:

Trial Completion: 10/2024
Final Report Submission: 04/2025

Submit the datasets with the final report submission.

Submit clinical protocols to your IND 122753 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

[3] For the most recent version of a guidance, check the FDA guidance web page athttps://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, call Jeannette Dinin, Regulatory Project Manager, at 240-402-4978 or email: Jeannette.Dinin@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Daniel Suzman, MD
Deputy Director
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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/

DANIEL L SUZMAN
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