BLA 125514/S-191

CORRECTED SUPPLEMENT APPROVAL/
FULFILLMENT OF POSTMARKETING REQUIREMENT

MSD International Business GmbH
Attention: Lei Zhang, PhD
Senior Director, Global Regulatory Affairs
126 East Lincoln Avenue
P.O. Box 2000, RY34-A2014
Rahway, NJ 07065-0900

Dear Dr. Zhang:

Please refer to your December 17, 2025, supplemental biologics license application (sBLA) and your amendments, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab), for injection.

We also refer to our October 16, 2026, approval letter in which the receipt date of your supplemental application was incorrectly listed as “December 17, 2026” (error in the year). This corrected action letter lists the actual receipt date of the supplemental application as December 17, 2025. This corrected action letter incorporates the correction of the error. The effective action date will remain October 16, 2026, the date of the original letter.

This Prior Approval sBLA provides for updates the Keytruda (pembrolizumab) Prescribing Information and the Medication Guide to:

- Include data supporting the fulfillment of postmarketing requirement (PMR) 3871-1 intended to verify and describe the clinical benefit of pembrolizumab in adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) solid tumors (as determined by an FDA-approved test) that have progressed following prior treatment and who have no satisfactory alternative treatment options.

- Amend the TMB-H indication to define TMB-H as ≥13 mutations/megabase (mut/Mb) as determined by an FDA-approved test.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

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 Medication Guide) 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 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 this sBLA under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses. Approval of this supplement 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.

This product is appropriately labeled for use in all relevant pediatric populations. Therefore, no additional pediatric studies are needed at this time.

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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.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your December 17, 2025, submission, containing the final report for the following postmarketing requirement (PMR) listed in the June 16, 2020, approval letter for BLA 125514/S-071.

3871-1 Submit the final report and datasets from clinical trials evaluating overall response rate and duration of response, to verify and describe the clinical benefit of pembrolizumab in adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors (as determined by an FDA-approved test) that have progressed following prior treatment and who have no satisfactory alternative treatment options. A sufficient number of patients and representation of tumor types (other than lung cancers, MSI-H or dMMR cancers, or melanoma; and including CNS tumors that were determined to be TMB-H based on testing of tissue obtained prior to initiation of temozolomide chemotherapy), and with cancers having a TMB of 10 to < 13 mut/Mb, will be evaluated to characterize response and duration of response. A minimum of 20 pediatric patients will be studied. Overall response rate and duration of response will be assessed by independent central review for patients with cancers having a TMB of ≥10 mut/Mb, ≥10 mut/Mb to < 13 mut/Mb, and ≥13 mut/Mb. All responding patients will be followed for at least 12 months from the onset of response.

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

This closes all of your postmarketing requirements and postmarketing commitments acknowledged in our June 16, 2020, 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

5077-1 Conduct adequate analytical and clinical validation studies to support accurate labeling of pembrolizumab and pembrolizumab berahyaluronidase alfa-pmph to specify the use of an FDA-authorized in vitro companion diagnostic device to accurately and reliably identify patients who have tumor mutational burden (TMB) ≥13 mut/Mb and for whom pembrolizumab or pembrolizumab berahyaluronidase alfa-pmph therapy is indicated.

The timetable you submitted on October 2, 2026, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2027

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/subjects 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 guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*
You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 601.12(f)(4)]. Form FDA 2253 is available at FDA.gov.[3] Information and Instructions for completing the form can be found at FDA.gov.[4]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety-related information [21 CFR 601.12(f)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(f)(4).

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] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, contact Gina Davis, Senior Regulatory Health Project Manager, at Gina.Davis@fda.hhs.gov.

Sincerely,

{*See appended electronic signature page*}

Steven Lemery, M.D., M.H.S.
Director
Division of Oncology 3
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide