BLA 125514/S-085

SUPPLEMENT APPROVAL
POST MARKETING REQUIREMENTS FULFILLMENT

Merck Sharp & Dohme Corp
Attention: Vinay Girijavallabhan, PhD
Director, Global Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 200
RY34-B293
Rahway, NJ 07065-0900

Dear Dr. Girijavallabhan:

Please refer to your supplemental biologics license application (sBLA), dated April 30, 2020, received April 30, 2020 and your amendments, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab) injection for intravenous use.

This Prior Approval supplemental biologics application provides for traditional approval of the following indications:

- for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL)
- for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy
- for the treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy.
  Limitations of use: Keytruda is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

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.

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.

MERCK EX1196
Merck Sharp & Dohme LLC v. The Johns Hopkins University
IPR2024-00625

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 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 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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

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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.

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

FULFILLMENT OF POSTMARKETING REQUIREMENTS

We have received your submission dated April 30, 2020 containing the progression-free survival analysis from KEYNOTE-204 for the following postmarketing requirements listed in the March 14, 2017 approval for BLA 125514/S-015 and June 13, 2018 approval for BLA 125514/S-030.

3188-1 Complete the trial and submit the final report and data to verify and describe the clinical benefit of pembrolizumab, including efficacy and safety, from Trial KN204, a Phase 3 randomized, open-label, active-controlled trial comparing pembrolizumab to brentuximab vedotin for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma. Enroll approximately 300 patients. The primary endpoint should include progression-free survival.

3389-1 Complete the trial and submit the final report and data to verify and describe the clinical benefit of pembrolizumab, including efficacy and safety, from Trial KN204, a Phase 3 randomized, open-label, active-controlled trial comparing pembrolizumab to brentuximab vedotin for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma. Enroll approximately 300 patients. The primary endpoint should include progression-free survival.

We have received your submission dated September 23, 2020, containing the final study report for KEYNOTE-170 for the following postmarketing requirement listed in the June 13, 2018, approval letter for BLA 125514/S-030.

3389-2 Characterize the safety of long-term use in patients with primary mediastinal large B-cell lymphoma. Submit a final report and data sets with safety and efficacy outcomes of trial KEYNOTE-170 with at least 3 years of follow-up data.

We have reviewed your submissions and conclude that the above requirements were fulfilled.

We remind you that there are postmarketing requirements listed in the March 14, 2017 approval letter that are still open.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct

postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Keytruda was approved on September 4, 2014, we have become aware of a higher incidence of immune-mediated adverse reactions in pediatric patients with cHL compared to pediatric patients with solid tumors. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risk of higher incidence of immune-mediated adverse reactions observed in pediatric patients with cHL.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3938-1 Submit the final results and datasets characterizing the risk of immune-mediated or potentially immune-mediated toxicities, serious adverse events, and long-term safety for pediatric patients with lymphoma enrolled in KEYNOTE-051 who receive pembrolizumab. All patients with Hodgkin lymphoma should be followed for safety for a minimum of 6 months on pembrolizumab.

The timetable you submitted on October 1, 2020 states that you will conduct this study according to the following schedule:

Trial Completion:	03/2024
Final Report Submission:	09/2024

FDA considers the term final to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

Submit the protocol(s) to your IND 118604, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required**

Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)".

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

3938-2	Submit the final results and datasets for response rate and duration of response as assessed by an independent review committee in all pediatric patients who received pembrolizumab for Hodgkin lymphoma in KEYNOTE-051, to further characterize the clinical benefit of pembrolizumab. All patients who achieve an objective response should be followed for duration of response for a minimum of 6 months. The results from this trial may inform product labeling.

The timetable you submitted on October 1, 2020, states that you will conduct this study according to the following schedule:

Trial Completion:	03/2024
Final Report Submission:	09/2024

Submit clinical protocols to your IND 118604 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).

If you have any questions, call Kimberly Scott, Regulatory Project Manager, at 240 402-4560.

Sincerely,

{See appended electronic signature page}

Nicole Gormley, MD
Director (Acting)
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[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

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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/

NICOLE J GORMLEY
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