



BLA 125514/S-121
BLA 125514/S-122

**SUPPLEMENT APPROVAL/
FULFILLMENT OF POSTMARKETING
REQUIREMENTS**

Merck Sharp & Dohme Corp.
a subsidiary of Merck & Co., Inc.
Attention: Lynn May Brown, PhD
Director, Global Regulatory Affairs
1 Merck Dr., PO Box 100
Whitehouse Station, NJ 08889

Dear Dr. Brown:

Please refer to your supplemental biologics license applications (sBLA), dated August 20, 2021, and your amendments, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab) Injection.

We also refer to your supplemental biologics license application 034 (S-034), approved on June 12, 2018, under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses.

Prior Approval supplemental biologics application 121 (S-121) provides for the use of Keytruda, in combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS \geq 1) as determined by an FDA-approved test.

Prior Approval supplemental biologics application 122 (S-122) provides for regular approval of Keytruda, as a single agent, for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS \geq 1) as determined by an FDA-approved test.

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 Medication Guide) and include the labeling changes proposed in any pending “Changes Being Effectuated” (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 Effectuated” (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 S-034 of this BLA 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.

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-121 because necessary studies are impossible or highly impracticable. Additionally, we note that none of the above PREA criteria applies to S-122, therefore you are exempt from this requirement for S-122.

FULFILLMENT OF POSTMARKETING REQUIREMENT(S)/COMMITMENT(S)

We refer to your supplemental biologics license application (sBLA) under section 351 of the Public Health Service Act for Keytruda (pembrolizumab) Injection.

We have received your submission dated August 20, 2021, containing the final report for the following post marketing requirement listed in the June 12, 2018, Approval letter for BLA 125514 supplement 034 (S-034).

3427-1 Conduct clinical trial KEYNOTE-826 (KN-826) in cervical cancer for Progression Free Survival (PFS)-Overall Survival (OS), entitled “A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Pembrolizumab Plus Chemotherapy vs. Chemotherapy Plus Placebo for the First-line Treatment of Persistent, Recurrent, or Metastatic Cervical Cancer”.
Submit analyses and datasets with final report for PFS and OS.

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 June 12, 2018, Approval letter for S-034.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment under BLA 125514/S-121:

4164-1 Conduct clinical trial, KEYNOTE-826, titled “A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Pembrolizumab Plus Chemotherapy vs. Chemotherapy Plus Placebo for the First-line Treatment of Persistent, Recurrent, or Metastatic Cervical Cancer” and provide the final overall survival analysis with the final report.

The timetable you submitted on October 7, 2021, states that you will conduct this study according to the following schedule:

Trial Completion: 11/2022
Final Report Submission: 05/2023

Submit the datasets with the final report. Submit clinical protocols to your IND 126191 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 at <https://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>

BLA 125514/S-121

BLA 125514/S-122

Page 5

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}

Laleh Amiri-Kordestani, MD
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/

LALEH AMIRI KORDESTANI
10/13/2021 07:18:01 AM