



DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration  
Silver Spring MD 20993

BLA 125514/S-035

**SUPPLEMENT APPROVAL  
FULFILLMENT OF POSTMARKETING REQUIREMENT**

Merck Sharp & Dohme Corp.  
Attention: Robert Kester  
Director, Global Regulatory Affairs  
126 E. Lincoln Avenue  
RY34-B293  
Rahway, NJ 07065-0900

Dear Mr. Kester:

Please refer to your supplemental Biologics License Application (sBLA) dated March 23, 2018, received March 23, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab), for injection 50 mg, and Keytruda (pembrolizumab), injection 100 mg/4 mL (25 mg/mL).

This Prior Approval supplemental biologics application provides for modifications to the product labeling for the approved indication of pembrolizumab, in combination with pemetrexed and carboplatin, for the first-line treatment of patients with metastatic non-squamous, non-small cell lung cancer approved on May 10, 2017, under the provisions of 21 CFR 601.41, to add the following language (*italicized*) *with no EGFR or ALK genomic tumor aberrations*, to replace “carboplatin” with “platinum chemotherapy” and to remove the following statement:

*This indication is approved under accelerated approval based on tumor response rate and progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.*

In addition, the WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, and CLNICAL STUDIES sections of the product labeling has been updated with the results from Study KEYNOTE-189.

**APPROVAL & LABELING**

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

## **WAIVER OF HIGHLIGHTS SECTION**

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 <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, 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 titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

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 MS Word format that includes the changes approved in this supplemental application.

## **SUBPART E FULFILLED**

We approved 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 the below postmarketing requirement (PMR 3197-1) 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 none of these criteria apply to your application, you are exempt from this requirement.

## **FULFILLMENT OF POSTMARKETING REQUIREMENT**

Approval of this supplement fulfills the following postmarketing requirement listed in the May 10, 2017, approval letter for BLA 125514/S-016:

- 3197-1 Conduct and submit the results of a multicenter, randomized trial or trials to verify and escribe the clinical benefit of pembrolizumab, in combination with pemetrexed-platinum therapy, over pemetrexed-platinum therapy in patients with non-squamous non-small cell lung cancer as determined by an improvement in overall survival or a large improvement in progression-free survival that is clinically meaningful.

Trial Completion: December 2019  
Final Report Submission: June 2020

We have reviewed your submission and conclude that the above requirement was fulfilled. You are no longer required to report on this commitment.

**POSTMARKETING COMMITMENT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitment:

- 3433-1 Submit the clinical trial report and datasets for the updated survival results for KEYNOTE-189, entitled “A Randomized, Double-Blind, Phase III Study of Platinum plus Pemetrexed Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Non-squamous Non-small Cell Lung Cancer Subjects,” in order to inform the label with mature overall survival data in accordance with the pre-specified final analysis of KEYNOTE-189.

The timetable you submitted on March 30, 2018 and August 10, 2018, states that you will conduct this trial according to the following schedule:

Final Report Submission: June 2021

Submit all postmarketing final reports to this BLA. 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 Final Report**” or “**Postmarketing Commitment Correspondence**.”

**PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

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

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

## **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 questions, call Leah Her, Senior Regulatory Health Project Manager, at (240) 402-6611.

Sincerely,

*{See appended electronic signature page}*

Patricia Keegan, M.D.  
Director  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

ENCLOSURE:  
Content of Labeling

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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.**  
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/s/  
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PATRICIA KEEGAN  
08/20/2018