



BLA 125514/S-125

**SUPPLEMENT APPROVAL/
RELEASE FROM POSTMARKETING REQUIREMENT**

Merck Sharp & Dohme Corp.
Attention: Christopher Cox, Ph.D.
Senior Director, Global Regulatory Affairs
51 North Sumneytown Pike
P.O. Box 1000, UG2D-44
North Wales, PA 19454

Dear Dr. Cox:¹

Please refer to your supplemental biologics license application (sBLA), dated and received January 20, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab) injection.

This Prior Approval supplement biologics application provides for revisions to the Keytruda (pembrolizumab) full Prescribing Information (PI) and medication guide pertaining to the withdrawal of the third line gastric cancer indication; i.e., “Keytruda, as a single agent, for the treatment of patients with recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma whose tumors express PD-L1 (CPS \geq 1) as determined by an FDA-approved test, with disease progression on or after 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu targeted therapy,” originally approved under Accelerated Approval regulations on September 22, 2017, in BLA 125514/Supplement 24.

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.

¹ 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>.

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,² 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*.³

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).

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.

RELEASE FROM POSTMARKETING REQUIREMENTS

We note that the following postmarketing requirement to verify clinical benefit was a condition of the accelerated approval as stated in our September 22, 2017, approval letter (S-024) for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1

² <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

³ 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>.

[Combined Positive Score (CPS) ≥ 1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu targeted therapy:

- 3258-1 Conduct and submit the results of one or more randomized trials to verify and describe the clinical benefit of pembrolizumab over standard therapy based on a clinically meaningful improvement in overall survival in patients with PD-L1 positive, microsatellite stable/mismatch repair (MMR) proficient metastatic gastric or gastroesophageal junction adenocarcinoma.

Trial Completion:	01/2019
Final Report Submission:	07/2019

In addition, we note the following postmarketing requirement to verify clinical benefit was a condition of the accelerated approval as stated in our April 28, 2020, approval letter for the alternate dose and schedule of 400 mg every 6 weeks for the gastric cancer indication (S-064).

- 3850-1 Submit the final analysis of overall response rate, duration of response, and safety from Cohort B of the KEYNOTE-555 trial titled, "*A Phase 1 Randomized Clinical Study of Pembrolizumab (MK-3475) to Evaluate the Relative Bioavailability of Subcutaneous Injection Versus Intravenous Infusion in Participants With Advanced Melanoma*" to verify and describe the anticipated effects of the alternative dosing regimen for pembrolizumab 400 mg every six weeks, that may inform product labeling across indications. All responding patients should be followed for at least 12 months from the onset of response. Provide pharmacokinetic data at first cycle and at steady state from Cohort B and the datasets in the final report.

Final Protocol Submission:	Completed
Trial Completion (Cohort B):	08/2021
Final Report Submission (Cohort B):	02/2022

We have determined that you are released from the above requirements as they are no longer needed because the indication is withdrawn from the label.

This completes all of your postmarketing requirements and postmarketing commitments for S-024 acknowledged in our September 22, 2017, letter.

We remind you that postmarketing requirements listed in the April 28, 2020, approval letter are still open for the other associated supplements and indications.

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*.⁴

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.⁵ Information and Instructions for completing the form can be found at FDA.gov.⁶

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 labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(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).

If you have any questions, call Maryam Khazraee, Regulatory Health Project Manager, at 301-796-7119.

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

⁴ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁶ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

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/

STEVEN J LEMERY
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