BLA 125554/S-132

SUPPLEMENT APPROVAL/
FULFILLMENT OF POSTMARKETING
REQUIREMENT

Bristol-Myers Squibb Company
Attention: Bahar Demirdirek, Ph.D.
Director, Global Regulatory Lead
P.O. Box 5326
Princeton, NJ 08543-5326

Dear Dr. Demirdirek:

Please refer to your December 23, 2024, supplemental biologics license application (sBLA) and your amendments, submitted under section 351(a) of the Public Health Service Act for OPDIVO (nivolumab) injection.

This Prior Approval supplemental biologics license application provides for updates to the OPDIVO (nivolumab) Prescribing Information (PI) and Medication Guide (MG) by updating the following indications based on results from Study CA2098HW supporting postmarketing requirements (PMRs) 3243-1 and PMR 3449-1 and the conversion from accelerated approval to full approval:

- *OPDIVO, in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC).*

- *OPDIVO, as a single agent, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.*

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 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).

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.

We are waiving the pediatric study requirement from birth to less than 12 years of age because the necessary studies are impossible or highly impracticable. Colorectal cancer rarely occurs in this pediatric age group.

We note that you have fulfilled the requirement for a pediatric assessment in patients 12 to less than 17 years of age for this application.

[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.

SUBPART E FULFILLED

We approved BLA 125554 Supplement 34 and BLA 125554 Supplement 63 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.

FULFILLMENT OF POSTMARKETING REQUIREMENTS

We have received your submission dated December 23, 2024, containing the final reports for the following postmarketing requirements listed in the July 31, 2017, approval letter for BLA 125554/S-034 and the July 10, 2018, approval letter for BLA 125554/S-063.

3243-1 Submit the final report, including datasets, from trials conducted to verify and describe the clinical benefit of nivolumab 240 mg intravenously every two weeks in patients with microsatellite instability high or mismatch repair deficient metastatic colorectal cancer who have progressed following treatment with fluoropyrimidine, oxaliplatin and irinotecan, including at least 150 patients enrolled in BMS-initiated trials. In order to characterize response rate and duration, patients will be followed for at least 12 months from the onset of response.

3449-1 Submit the final report, including datasets, from a randomized trial conducted to verify and describe the clinical benefit of nivolumab, administered in combination with ipilimumab, in patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer. The trial will be designed to demonstrate a clinically meaningful improvement in progression-free survival in patients randomized to receive nivolumab and ipilimumab as compared to patients randomized to receive nivolumab alone. In addition, the trial should evaluate for differences in overall survival between arms based on a pre-specified analysis. The analysis plan should describe the power for the overall survival analysis, as well as all assumptions made in determining the power.

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

We remind you that there are postmarketing commitments listed in the July 31, 2017, and July 10, 2018, approval letters that are still open.

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]

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.[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 Amy Allen, Senior Regulatory Health Project Manager, at (301) 796-8416.

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

ENCLOSURE:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[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

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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/

STEVEN J LEMERY
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