BLA 761381/S-002

SUPPLEMENT APPROVAL/
FULFILLMENT OF POSTMARKETING
REQUIREMENTS

Bristol-Myers Squibb Company
Attention: Jateh Major, PharmD
Associate Director
P.O. Box 5326
Princeton, NJ 08543-5326

Dear Dr. Major:

Please refer to your December 27, 2024, supplemental biologics license application (sBLA) and your amendments, submitted under section 351(a) of the Public Health Service Act for Opdivo Qvantig (nivolumab and hyaluronidase-nvhy); subcutaneous injection.

This Prior Approval supplemental biologics license application provides for the following:

1. Updates the Opdivo Qvantig prescribing information with the following new indication:

   OPDIVO QVANTIG, as monotherapy, is indicated for the treatment of adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC) following treatment with intravenous nivolumab and ipilimumab combination therapy.

2. Fulfills postmarketing requirements (PMRs) 4762-2 and 4762-3 and the conversion from accelerated approval to regular approval of the following indication:

   OPDIVO QVANTIG, as monotherapy, is indicated for the treatment of adult patients with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

   There is a limitation of use that OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of unresectable or metastatic MSI-H or dMMR CRC.

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.

[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 ages for pediatric patients <12 years of age because necessary studies are impossible or highly impracticable. This is because of the rarity of pediatric patients with MSI-H/dMMR mCRC in this age group.

We are deferring submission of your pediatric studies for pediatric patients 12 to <17 years of age for this application because this product is ready for approval for use in adults and the pediatric study is currently under review.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. The required study is listed below.

4925-1 Conduct a modeling and simulation study to support dosing of nivolumab and hyaluronidase-nvhy as first-line treatment in pediatric patients 12 years of age and older with unresectable or metastatic microsatellite instability-high or mismatch repair deficient colorectal cancer (MSI-H/dMMR mCRC).

Final Report Submission: 01/2025 (submitted)

Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

SUBPART E FULFILLED

We approved this BLA, on December 27, 2024, 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.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated December 23, 2024, containing the final reports for the following postmarketing requirements listed in the December 27, 2024, approval letter.

4762-2 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.

4762-3 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. You are not required to report on the status of closed (released or fulfilled) PMRs/PMCs in your annual report required under 21.CFR 601.70 of the FD&CA.

We remind you that there is a postmarketing requirement and a postmarketing commitment listed in the December 27, 2024, approval letter 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]

[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

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety-related information [21 CFR 601.12(f)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related 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(f)(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, contact Gina Davis, Senior Regulatory Health Project Manager, at Gina.Davis@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Steven Lemery, M.D., MHS
Director
Division of Oncology 3
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- 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/

STEVEN J LEMERY
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