BLA 761381

BLA APPROVAL/
BLA ACCELERATED APPROVAL

Bristol Myers Squibb, Company
Attention: Jateh Major, PharmD
Associate Director, Global Regulatory Sciences and Policy, Oncology
P.O. Box 5326
Princeton, NJ 08543-5326

Dear Dr. Major:

Please refer to your February 29, 2024, biologics license application (BLA) and your amendments, submitted under section 351(a) of the Public Health Service Act for Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) subcutaneous injection.

LICENSING

We have approved your BLA for Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Opdivo Qvantig under your existing Department of Health and Human Services U.S. License No. 1713. Opdivo Qvantig is indicated for the following indications:

Renal Cell Carcinoma (RCC)

- adult patients with intermediate or poor risk advanced RCC, as a first-line treatment following combination treatment with intravenous nivolumab and ipilimumab.

  Limitations of Use: OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of renal cell carcinoma.
- adult patients with advanced RCC, as a first-line treatment in combination with cabozantinib.
- adult patients with advanced RCC who have received prior anti-angiogenic therapy.

Melanoma

- adult patients with unresectable or metastatic melanoma.
- adult patients with unresectable or metastatic melanoma following combination treatment with intravenous nivolumab and ipilimumab.

Halozyme EX2023
Merck v. Halozyme
IPR2026-00314

Limitations of Use: OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of unresectable or metastatic melanoma.

- for the adjuvant treatment of adult patients with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma.

Non-Small Cell Lung Cancer (NSCLC)

- adult patients with resectable (tumors ≥4 cm or node positive) NSCLC in the neoadjuvant setting, in combination with platinum-doublet chemotherapy.
- adult patients with metastatic NSCLC and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO QVANTIG.

  Limitations of Use: OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of metastatic NSCLC.

Squamous Cell Carcinoma of the Head and Neck (SCCHN)

- adult patients with recurrent or metastatic SCCHN with disease progression on or after a platinum-based therapy.

Urothelial Carcinoma (UC)

- adjuvant treatment of adult patients with UC who are at high risk of recurrence after undergoing radical resection of UC.
- adult patients with locally advanced or metastatic UC who:
  - have disease progression during or following platinum-containing chemotherapy.
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Esophageal Cancer

- adult patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy (CRT).
- adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma as first-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy.

  Limitations of Use: OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of patients with unresectable advanced or metastatic ESCC

- adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

- adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy.

Colorectal Cancer

- adult patients with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as monotherapy or as monotherapy following combination treatment with intravenous nivolumab and ipilimumab.

  Limitations of Use: OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of MSI-H or dMMR metastatic CRC.

Hepatocellular Carcinoma (HCC)

- adult patients with HCC previously treated with sorafenib and following combination treatment with intravenous nivolumab and ipilimumab.

  Limitations of Use: OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of HCC.

The colorectal cancer and hepatocellular cancer indications are approved under accelerated approval. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture nivolumab drug substance at Bristol-Myers Squibb Company in Devens, Massachusetts. The final formulated drug product will be manufactured and filled at Catalent Indiana, LLC, Bloomington, Indiana. The final formulated nivolumab and hyaluronidase-nvhy drug product will be secondary packaged and labeled at Packaging Coordinators, LLC, Philadelphia, Pennsylvania. You may label your product with the proprietary name, Opdivo Qvantig, and market it in 600 mg nivolumab and 10,000 units hyaluronidase per 5 mL injection in a single-dose vial.

DATING PERIOD

The dating period for Opdivo Qvantig shall be 36 months from the date of manufacture when stored at 2 - 8 °C, protected from light. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product.

The dating period for your nivolumab drug substance shall be 48 months from the date of manufacture when stored at ≤ -35 ˚C, protected from light. We have approved the stability protocol in your license application for the purpose of extending the expiration dating period of your nivolumab drug substance under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Opdivo Qvantig to the Center of Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Opdivo Qvantig, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

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 ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide). 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 (October 2009)*.[2]

The SPL will be accessible via publicly available labeling repositories.

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[1] See 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 at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling submitted on December 17, 2024, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761381**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Opdivo Qvantig was not referred to an FDA advisory committee as no significant review issues were identified during the review of this application.

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 601.41, you are required to conduct further adequate and well-controlled clinical trials intended to verify and describe clinical benefit. You are required to conduct such clinical trial(s) with due diligence. If required postmarketing clinical trial(s) fail to verify clinical benefit or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirements specified in your submission dated December 26, 2024. These requirements are listed below.

4762-1 Submit the final report demonstrating an improvement in overall survival from a multicenter, randomized trial to confirm the clinical benefit of nivolumab in combination with ipilimumab over standard therapy in patients with advanced hepatocellular carcinoma, that may inform product labeling. Submit the datasets with the final report.

Final Report Submission: 01/2025

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.

Final Report Submission: 11/2026

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.

Final Report Submission: 11/2026

Submit clinical protocols to your IND 138302 for this product. FDA considers the term final to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

You must submit reports of the progress of each clinical trial required under section 506(c) (listed above) to this BLA 180 days after the date of approval of this BLA and approximately every 180 days thereafter (see section 506B(a)(2) of the FDCA) (hereinafter "180-day reports").

You are required to submit two 180-day reports per year for each open study or clinical trial required under 506(c). The initial report will be a standalone submission and the subsequent report will be combined with your application's annual status report (ASR) required under section 506B(a)(1) of the FDCA and 21 CFR 601.70. The standalone 180-day report will be due 180 days after the date of approval (with a 60-day grace period). Submit the subsequent 180-day report with your application's ASR. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted[3].

Your 180-day reports must include the information listed in 21 CFR 601.70(b). FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics,* to submit your 180-day reports.[4] 180-day reports must be clearly designated "BLA 761352 180-Day AA PMR Progress Report."

[3] You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.
[4] FORM FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

FDA will consider the submission of your application's ASR under section 506B(a)(1) and 21 CFR 601.70, in addition to the submission of reports 180 days after the date of approval each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

Submit final reports to this BLA as a supplemental application. For administrative purposes, the cover page of all submissions relating to this postmarketing requirement must be clearly designated "Subpart E Postmarketing Requirement(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 for ages < 12 years of age because there is evidence strongly suggesting that the drug product would be ineffective in this pediatric group.

We are deferring submission of your pediatric study for ages 12 years to < 17 years of age for this application because this product is ready for approval for use in adults and the pediatric study have not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are 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. This required study is listed below.

4762-4 Conduct a molecularly targeted pediatric cancer investigation using an age-appropriate formulation of nivolumab and hyaluronidase-nvhy in pediatric patients 12 years of age and older.

Final Report Submission: 01/2025

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[5]

[5] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Submit the protocol(s) to your IND 150904, with a cross-reference letter to this BLA. 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.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4762-5 Establish and validate/qualify an appropriate method (existing or new), for determining the number and size of product-related visible particles in nivolumab subcutaneous injection drug product and implement the method for evaluation of visible particles in nivolumab subcutaneous injection drug product stability testing.

Final Report Submission: December 19, 2025

Submit clinical protocols to your IND 150904 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/subjects 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*.[6]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication

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

[21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[7] Information and Instructions for completing the form can be found at FDA.gov.[8]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements at 21 CFR 600.80. Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements at 21 CFR 600.81.

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution.

If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[8] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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, MD, MHS
Director
Division of Oncology 3
Office of Oncologic Disease
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

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
12/27/2024 10:02:10 AM