DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125554/S-042

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING
REQUIREMENT(S)/COMMITMENT

Bristol-Myers Squibb Company
Attention: Marie Hildebrandt, Ph.D.
Associate Director, US Regulatory-Oncology
P.O. Box 4000
Princeton, NJ 08543

Dear Dr. Hildebrandt:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received on April 13, 2017, and your amendments, submitted under section 351(a) of the Public Health Service Act for OPDIVO (nivolumab) injection, 100 mg/10 mL, 40 mg/4 mL and 240 mg/24 mL.

We acknowledge receipt of your amendment dated September 7, 2018, which constituted a complete response to our October 13, 2017, action letter.

This Prior Approval supplemental biologics application provides for modifications to the product labeling for the approved indications of OPDIVO, as a single agent, for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, and of OPDIVO, in combination with ipilimumab, for the treatment of patients with unresectable or metastatic melanoma to remove the following statement:

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

In addition, this Prior Approval supplemental biologics application provides for the simplification of the following approved indications:

- OPDIVO, as a single agent, for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma
- OPDIVO, as a single agent, for the treatment of patients with BRAF V600 mutation positive unresectable or metastatic melanoma
- OPDIVO, in combination with ipilimumab, for the treatment of patients with unresectable or metastatic melanoma

into a single approved indication: OPDIVO, as a single agent or administered with ipilimumab, for the treatment of patients with unresectable or metastatic melanoma.

Furthermore, the Adverse Reactions and Clinical Studies sections of the product labeling have been updated with the results of the final analysis of Study CHECKMATE-067, and the Clinical Studies section has been updated with the results of the final analysis of Study CHECKMATE-037.

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 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.

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 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).

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 requirements (PMR 2838-1 and 2959-1) 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 this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENTS

Approval of this supplement fulfills the following postmarketing requirements listed in the December 22, 2014, approval letter for BLA 125554 and the September 30, 2015, approval letter for BLA 125554/S-002.

2838-1 Conduct and submit the results of a multicenter, randomized trial or trials establishing the superiority of nivolumab over standard therapy in adult patients with unresectable or metastatic melanoma who are refractory to ipilimumab or who have not been previously treated with ipilimumab,

2959-1 Conduct and submit the results of a multicenter, randomized trial or trials to verify and describe the clinical benefit of nivolumab in combination with ipilimumab in previously untreated adult patients with unresectable or metastatic, BRAF V600 wild-type melanoma.

We have reviewed your submission and conclude that the above requirements were fulfilled. You are no longer required to report on these requirements.

FULFILLMENT OF POSTMARKETING COMMITMENT

Approval of this supplement fulfills the following postmarketing commitment listed in the November 23, 2015, approval letter for BLA 125554/S-001.

2960-1 Submit the final overall survival (OS) data from Trial CA209037, a randomized, open-label, Phase 3 Trial of Nivolumab Versus Investigator's Choice in Advanced (Unresectable or Metastatic) Melanoma Patients Progressing Post Anti-CTLA-4 Therapy, to provide long-term data that will inform the label on the

efficacy of nivolumab as a treatment for patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

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

We remind you that there are postmarketing requirement(s) **AND** postmarketing commitment(s) that are still open.

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.

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 Kwadwo Korsah, Regulatory Health Project Manager, at (301) 796-6630.

Sincerely,

{See appended electronic signature page}

Ashley Ward, M.D.
Acting Associate Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of 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/

ASHLEY F WARD
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