DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125554/S-016

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT
FULFILLMENT OF POSTMARKETING COMMITMENT

Bristol-Myers Squibb Company
Attention: Linda Gambone, Ph.D.
Director, U.S., Regulatory Global Regulatory Sciences
Route 206 & Province Line Rd., Mail Stop D32-01
Princeton, NJ 08543

Dear Dr. Gambone:

Please refer to your Supplemental Biologics License Application (sBLA), dated December 7, 2015, submitted under section 351(a) of the Public Health Service Act for OPDIVO (nivolumab) Injection for Intravenous Infusion, 40 mg/4 mL (10 mg/mL) and 100 mg/10 mL (10 mg/mL) single-dose vial.

This Prior Approval supplemental biologics application provides for updates to the Clinical Studies section 14.2 of the package insert, titled Metastatic Non-Small Cell Lung Cancer (NSCLC), to incorporate demographic data and supportive efficacy results for progression-free survival, overall response rate, and response duration from Study CA209017.

This supplement also includes labeling revisions to the package insert to:

- Update the Dose Modifications table in the Dosage and Administration section to include suspected or confirmed Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necroysis (TEN) under Grade3 or 4 immune-mediated skin reactions.
- Pool the data in the Adverse Reaction subsection for squamous and non-squamous NSCLC.
- Modify the Warnings and Precautions sections 5.1 through 5.8 to replace disease-specific information with the results of pooled analysis across multiple randomized trials conducted in patients with metastatic NSCLC, melanoma, renal cell cancer, or classical Hodgkin's lymphoma to describe the risks of serious immune-mediated adverse reactions with nivolumab, administered either as a single agent or with ipilumumab.
- Modify the Warnings and Precautions sections 5.6 and 5.8 to include the following new adverse reactions identified through BMS' pharmacovigilance program or in Study CA209017: SJS, TEN, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), myositis, myocarditis, and rhabdomyolysis.

In addition, the Medication Guide was updated to reflect revisions made in the package insert.

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 SECTION

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 package insert, 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 MS Word format that includes the changes approved in this supplemental application.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated December 7, 2015, containing the final report for the following postmarketing requirement listed in the March 4, 2015, approval letter for BLA 125527.

2877-1 Conduct a randomized trial that will characterize the incidence, severity and response to treatment of nivolumab induced immune-mediated adverse reactions to include immune-mediated pneumonitis.

We have reviewed your submission and conclude that the above requirement was fulfilled.

FULFILLMENT OF POSTMARKETING COMMITMENT

We have received your submission dated December 7, 2015, containing the final report for the following postmarketing commitment listed in the March 4, 2015, approval letter for BLA 125527.

2877-2 Submit the final report and efficacy datasets for the open-label randomized trial of nivolumab versus docetaxel in patients with previously treated advanced squamous non-small cell lung cancer.

We have reviewed your submission and conclude that the above commitment was fulfilled.

This completes all of your postmarketing requirements and postmarketing commitments acknowledged in our March 4, 2015, approval letter for BLA 125527. However, we remind you that there are postmarketing requirements and postmarketing commitments still open under BLA 125554.

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 package insert(s) 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 package insert(s), 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 Meredith Libeg, Senior Regulatory Health Project Manager, at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
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 and this page is the manifestation of the electronic signature.

/s/

PATRICIA KEEGAN
10/04/2016