DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125377/S-073

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company
Attention: Kruti Patel, R.Ph.
Associate Director
Global Regulatory Affairs, Safety and Biometrics-US Oncology
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. Patel:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received December 29, 2014, submitted under section 351(a) of the Public Health Service Act for Yervoy (ipilimumab), injection, 50 mg and 200 mg.

We acknowledge receipt of your amendments dated April 6, April 9, April 27, June 26, September 1, September 30, 2015, October 8, October 20, October 26, and October 27, and October 28, 2015.

This Prior Approval supplemental biologics application provides for a new indication for the adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm, who have undergone complete resection including total lymphadenectomy

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 and with the minor editorial revisions listed below:

- In the Highlights section under Recent Major Changes added the revised month/year.
- At the end of the Highlights section added the revised month/year.
- At the end of the Medication Guide added the revised month/year.

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 includes 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 this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Yervoy (ipililumab) was approved on March 25, 2011, we have become aware of clinical trial and postmarketing adverse event reports regarding fetal harm. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of fetal harm.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2972-1 A Pregnancy Pharmacovigilance Study to evaluate pregnancy outcomes and infant outcomes following exposure to Yervoy (ipilimumab). This study will include a mechanism to collect, classify, and analyze data on direct exposures (women exposed to ipilimumab as treatment). There will be interim annual reporting of the data collected from the study. The study, at a minimum, will include the following key elements (see the Guidance for Industry Establishing Pregnancy Exposure Registries for a detailed description of these elements):

- Data collection of prospective and retrospective data points, adequate to produce informative, reliable data outcomes.
- Data analysis utilizing descriptive statistics for summarizing data that will fully capture outcomes of concern. Data collected prospectively will be analyzed separately from data collected retrospectively.
- Description of procedures including patient recruitment, along with healthcare provider awareness of the potential safety risk and existence of this study, and the monitoring of pregnancy and infant outcomes.

Each annual interim and the final report should constitute a stand-alone report of cumulative pregnancy and infant outcomes data.

The timetable you submitted on October 8, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	December 2015
Study Initiation:	March 2016
Annual Interim Report:	May 2016
	May 2017
	May 2018
	May 2019
	May 2020
	May 2021
	May 2022
	May 2023
Final Report Submission	May 2024

Submit the protocol(s) to your IND 9186, with a cross-reference letter to this BLA. Submit all interim and final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.
Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70, requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2972-2 Submit the final clinical report and datasets at the time of final analysis for overall survival (OS) of Trial CA184029, entitled "Adjuvant immunotherapy with anti-CTLA-4 monoclonal antibody (ipilimumab) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double-blind Phase 3 trial of the EORTC Melanoma Group," to inform the product label with mature OS data.

Final Report Submission: December 2019

2972-3 Submit the final clinical report and datasets of Trial E1609, entitled "A Phase III Randomized Study of Adjuvant Ipilimumab Anti-CTLA4 Therapy Versus High Dose Interferon a-2b for Resected High Risk Melanoma" to inform any change to the recommended dose of Yervoy (ipilimumab) for adjuvant treatment of resected Stage III melanoma patients, if required, based on the final results of Trial E1609.

Final Report Submission: April 2021

Submit clinical protocols to your IND 9186 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 study completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients 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. 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.

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the address above, by fax to 301-847-8444, or 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).

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 Ruth Maduro, Regulatory Health Project Manager, at (240) 402-4232.

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
10/28/2015