



BLA 125554/S-019

ACCELERATED APPROVAL

Bristol-Myers Squibb Company
Attention: Alexandra Park
Director, Global Regulatory, Safety & Biometrics-Oncology
Route 206 & Province Lane
Princeton, NJ 08543

Dear Ms. Park:

Please refer to your Supplemental Biologics License Application (sBLA), dated March 1, 2016, received March 1, 2016, and your amendments, submitted under section 351 of the Public Health Service Act for OPDIVO[®] (nivolumab) injection, 100 mg/10 mL and 40 mg/4 mL.

This Prior Approval supplemental biologics application provides for OPDIVO[®] (nivolumab) injection for the treatment of patients with classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin.

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.

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, 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.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated May 12, 2016. This requirement, along with required completion dates, is listed below.

This postmarketing clinical trial is subject to the reporting requirements of 21 CFR 601.70:

PMR 3089-1 Conduct a randomized phase 3 clinical trial in classical Hodgkin lymphoma that verifies and isolates the clinical benefit of nivolumab for patients with classical Hodgkin lymphoma. The primary endpoint would be progression-free survival as determined by an independent review committee. Overall survival would be a key secondary endpoint.

Draft Protocol Submission:	09/2016
Final Protocol Submission:	02/2017
Trial Completion:	06/2021
Primary Progression-Free Survival Analysis:	09/2024
Final Report Submission:	12/2026

Submit clinical protocols to your IND 119380 for this product. In addition, under 21 CFR 601.70 you should include a status summary of each requirement in your annual report 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 entered into each study/trial.

Submit final reports to this BLA as a supplemental application. For administrative purposes, 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, 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 biologic 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 OPDIVO[®] (nivolumab) was approved on December 22, 2014, we have become aware of higher than expected occurrences of serious complications in patients who receive allogeneic hematopoietic stem cell transplantation after OPDIVO (nivolumab). These complications include severe graft-versus-host disease (GVHD), steroid-requiring febrile syndromes, hepatic veno-occlusive disease, and transplant-related mortality. Potential complications also include serious immune mediated adverse events and pulmonary complications. 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 signals of serious risk and to identify unexpected serious risk when available data indicate the potential for serious risk of complications after allogeneic hematopoietic stem cell transplantation.

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:

- PMR 3089-2 Characterize complications after allogeneic hematopoietic stem cell transplantation (HSCT) following nivolumab in at least 90 patients with classical Hodgkin lymphoma, of which at least 50% had received nivolumab alone or in combination as the regimen immediately prior to the allogeneic HSCT conditioning regimen. Evaluate toxicities at least through transplant Day 180, and include details of prior nivolumab treatment and the transplant regimen. Characterize toxicities including hyperacute graft-versus-host disease (GVHD), severe (grade III-IV) acute GVHD, febrile syndromes treated with steroids, immune mediated adverse events, pulmonary complications, hepatic veno-occlusive disease, critical illness, and transplant-related mortality. Toxicities may be characterized prospectively, or through a combination of prospective and retrospective data analysis.

The timetable you submitted on May 12, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2016
Final Protocol Submission:	12/2016
Study Completion:	12/2021
Interim Report Submission:	06/2019
Final Report Submission:	12/2022

Submit the protocols to your IND 119380, with a cross-reference letter to this BLA. Submit all final reports 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) 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.

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products 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 Natasha Kormanik, Regulatory Project Manager, at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
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/

ANN T FARRELL
05/17/2016