



BLA 125527

**BLA APPROVAL**

Bristol-Myers Squibb Company  
Attention: Eric Phillips, M.P.H., Sc.D.  
Director, Global Regulatory, Safety and Biometrics, U.S. Oncology  
Route 206 & Province Line Road, Room D1 213  
Princeton, NJ 08543

Dear Dr. Phillips:

Please refer to your Biologics License Application (BLA) for which the first portion was submitted and received on April 30, 2014, and the final portion dated and received December 22, 2014, submitted under section 351(a) of the Public Health Service Act for OPDIVO (nivolumab) Injection.

We also refer to your amendments dated April 30, 2014; June 20, 2014; July 25, 2014; September 26, 2014; October 6 and 10, 2014; November 11, 2014; December 22 and 30, 2014; January 15, 16, 28, 29, and 30, 2015; February 5, 10, 12, 23, 24, 25, 26, 27, 2015; and March 3, 2015.

**LICENSING**

We have approved your BLA for OPDIVO (nivolumab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, OPDIVO under your existing Department of Health and Human Services U.S. License No. 1713. OPDIVO is indicated for treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.

**MANUFACTURING LOCATIONS**

Under this license, you are approved to manufacture OPDIVO drug substance at (b) (4)  
 The final formulated product will be manufactured, filled, labeled, and packaged at Bristol-Myers Squibb Holdings Pharma, Ltd. Liability Company, in Manatí, Puerto Rico. You may label your product with the proprietary name OPDIVO and will market it in 40 mg and 100 mg single-use vials.

### **DATING PERIOD**

The dating period for OPDIVO shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

### **FDA LOT RELEASE**

You are not currently required to submit samples of future lots of OPDIVO to the Center for 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, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

### **APPROVAL & LABELING**

We have completed our review of this application. 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 [21 601.14(b)] in structured product labeling (SPL) format, as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide). 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.

In addition, within 14 days of the date of this letter, amend any pending supplement that includes labeling changes for BLA 125554 with content of labeling in SPL format to include the changes approved in this application.

### **ADVISORY COMMITTEE**

Your application for OPDIVO (nivolumab) was not referred to an FDA advisory committee because: this biologic is not the first in its class; the clinical trial design is acceptable; the application did not raise significant safety or efficacy issues; and the application did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

### **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.

We are waiving the pediatric study requirement for this indication because necessary studies are impossible or highly impracticable since the disease/condition does not exist in children.

### **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.

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 a known serious risk of immune-mediated adverse reactions to include immune-mediated pneumonitis.

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.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of immune-mediated adverse reactions to include immune-mediated pneumonitis.

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

- 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.

The timetable you submitted on February 24, 2015, states that you will conduct this trial according to the following schedule:

Final Report Submission: December 31, 2015

Submit the protocol(s) to your IND 100052, with a cross-reference letter to this BLA. Submit all final report(s) to BLA 125554. 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:

- 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.

The timetable you submitted on February 24, 2015, states that you will conduct this trial according to the following schedule:

Final Report Submission: December 31, 2015

Submit clinical protocols to your IND 100052 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to BLA 125554. 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 BLA 125554. 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. 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 to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, 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**

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (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 4206  
Silver Spring, MD 20903

We have now administratively closed this BLA. Therefore, all 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, promotional materials and other submissions should be addressed to the original **BLA 125554** for this drug product, not to this BLA. In the future, do not make submissions to this BLA except for the final printed labeling requested above.

### **MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

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

ENCLOSURES:  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PATRICIA KEEGAN  
03/04/2015