



BLA 125554/S-048, S-049, S-050, S-051,
S-052, S-061, S-062, S-064, S-065, and S-066

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company
Attention: Kathleen O'Donnell
Group Director, US Liaison – Oncology
Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Supplemental Biologics License Applications (sBLAs) and to the amendments, submitted under section 351(a) of the Public Health Service Act for OPDIVO (nivolumab) injection, 40 mg/4 mL, 100 mg/10 mL, and 240 mg/24 mL, dated and received:

- May 5, 2017, for supplements S-048, S-049, S-050, S-051, and S-052;
- January 5, 2018, for supplements S-061 and S-062; and,
- February 13, 2018, for supplements S-064, S-065, and S-066.

These Prior Approval supplemental biologic applications provide for the following updates to the prescribing information:

- For supplements S-048, S-049, S-050, S-051, and S-052: a new dosage regimen of Opdivo 480 mg as an intravenous infusion over 30 minutes every 4 weeks for the following approved indications (S-048):
 - metastatic non-small cell lung cancer with progression on or after platinum-based chemotherapy (S-048);
 - BRAF V600 wild-type unresectable or metastatic melanoma; patients with BRAF V600 mutation-positive unresectable or metastatic melanoma metastatic melanoma; and, in combination with ipilimumab, for unresectable or metastatic melanoma (S-048);
 - advanced renal cell carcinoma in patients who have received prior anti-angiogenic therapy (S-049);
 - adult patients with classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or 3 or more lines of systemic therapy that includes autologous HSCT(S-050);
 - recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-based therapy (S-051); and

- locally advanced or metastatic urothelial carcinoma in patients who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (S-052).
- For supplements S-061 and S-062: a new dosage regimen of Opdivo 480 mg as an intravenous infusion over 30 minutes every 4 weeks for the following approved indications:
 - adjuvant treatment of melanoma with involvement of lymph nodes or metastatic disease following complete resection (S-061); and
 - hepatocellular carcinoma following progression on sorafenib (S-062).
- For supplements S-064, S-065, and S-066: modification of the approved dosage regimens of Opdivo 240 mg every two weeks, to reduce to the infusion time from 60 minutes to 30 minutes, for the following approved indications:
 - adjuvant treatment of melanoma with involvement of lymph nodes or metastatic disease following complete resection (S-064);
 - microsatellite instability-high or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan (S-065); and
 - hepatocellular carcinoma following progression on sorafenib (S-066).

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are 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 prescribing information) 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 the biological product for the following indications, have been granted orphan designation, you are exempt from this requirement for the new dosing regimen for these indications: for the treatment of patients with (b) (4) melanoma; for the treatment of patients with Hodgkin Lymphoma; and hepatocellular carcinoma.

In addition, we are waiving the pediatric study requirement for the new dosing regimen to the following indications because necessary studies are impossible or highly impracticable since the disease/condition does not exist in children: for the treatment of patients with non-small cell lung cancer, advanced renal cell carcinoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, and metastatic colorectal cancer.

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 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
03/05/2018