BLA 125554/S-092

GENERAL ADVICE

Bristol-Myers Squibb Company
Attention: Dana Grimaldi, B.A., M.B.A.
Director, US Regulatory Lead
Global Regulatory Strategy and Policy
P.O Box 5326
Princeton, NJ 08543-5326

Dear Ms. Grimaldi:

Please refer to your supplemental Biologics License Application (BLA) under section 351(a) of the Public Health Service Act for Opdivo (nivolumab) injection.

We also refer to our May 20, 2021, approval letter issued for BLA Supplement 125554/S-092. This letter contained an error in the first paragraph incorrectly noting the date of submission for the supplement as November 20, 2021. The correct date of submission for Supplement 092 is **November 20, 2020**.

This General Advice letter acknowledges the error described above and incorporates the correction of the error. The remainder of the May 20, 2021, Supplement Approval letter remains as issued and there is no change in the approval date of May 20, 2021, for BLA Supplement 125554/S-092.

If you have any questions, contact Gina Mehta, PharmD, Regulatory Project Manager, at (301) 796-7910.

Sincerely,

{See appended electronic signature page}

Lola Fashoyin-Aje, M.D., M.P.H
Deputy Director
Division of Oncology 3
Office of Oncologic Diseases
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

IBILOLA A FASHOYIN-AJE
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BLA 125554/S-092

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company
Attention: Dana Grimaldi B.A., M.B.A.
Director, US Regulatory Lead
Global Regulatory Strategy and Policy
P.O Box 5326
Princeton, NJ 08543-5326

Dear Ms. Grimaldi:

Please refer to your supplemental biologics license application (sBLA), dated and received November 20, 2021, submitted under section 351(a) of the Public Health Service Act for Opdivo (nivolumab) injection, for intravenous use.

This Prior Approval supplemental biologics application provides for the following new indication for OPDIVO:

- *For the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease, in patients who have received neoadjuvant chemoradiotherapy (CRT)*

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.

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

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 FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

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 Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

POSTMARKETING COMMITMENT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4065-1 Submit the final overall survival analyses and datasets for the ongoing clinical trial CA209577 "A Randomized, Multicenter, Double Blind, Phase III Study of Adjuvant Nivolumab or Placebo in Subjects With Resected Esophageal, or Gastroesophageal Junction Cancer," to further characterize the clinical benefit of nivolumab as adjuvant therapy following neoadjuvant concurrent chemotherapy and radiation in patients with residual disease following complete resection of esophageal or gastroesophageal junction cancer.

The timetable you submitted on April 28, 2021, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2019 (completed)
Trial Completion:	06/2024
Final Report Submission:	12/2024

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 126406 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 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. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

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 FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

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, contact Gina Mehta, PharmD, Regulatory Health Project Manager, at (301) 796-7910 or via email.

Sincerely,

{See appended electronic signature page}

Lola Fashoyin-Aje, M.D., M.P.H
Deputy Director
Division of Oncology 3
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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/s/

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