BLA 761049/S-009

**SUPPLEMENT APPROVAL/
FULFILLMENT OF POSTMARKETING
REQUIREMENT**

EMD Serono, Inc.
Attention: Jennifer L. Stevens, JD
Executive Director
US Hub Lead/Global Regulatory Program Lead
45A Middlesex Turnpike
Billerica, MA 01821

Dear Ms. Stevens:

Please refer to your supplemental biologics license application dated April 7, 2020, received April 7, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for Bavencio (avelumab) Injection.

This Prior Approval supplemental biologics application provides for a new indication for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy.

We also refer to your biologics license application (BLA) 761078, approved May 9, 2017, under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

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).

SUBPART E FULFILLED

As noted above, we approved BLA 761078 under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses (21 CFR 601.41) and required further adequate and well-controlled clinical trials to verify and describe the clinical benefit of avelumab. Therefore, you were required to conduct postmarketing requirement 3201-1. Because BLA 761078 was administratively closed on the date of its approval, all submissions and reports for BLA 761078 were addressed to BLA 761049.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated April 7, 2020, containing the final report for the following postmarketing requirement listed in the May 17, 2019, approval letter for BLA 761078.

3201-1	Conduct "Javelin Bladder 100: A Phase 3, Multicenter, Multinational, Randomized, Open-label Parallel-arm Study of Avelumab Plus Best Supportive Care Versus Best Supportive Care Alone as a Maintenance Treatment in patients with Locally Advanced or Metastatic Urothelial Cancer Whose Disease Did Not Progress After Completion of First-line Platinum-containing Chemotherapy" and provide a final report, datasets, and revised labeling.

We have reviewed your submission and conclude that the above requirement was fulfilled.

[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.

Approval of this supplement fulfills your requirement made under 21 CFR 601.41 for BLA 761078.

We remind you that there is a postmarketing commitment listed in the May 9, 2017, approval letter for BLA 761078 that is still open.

In addition, we remind you that the required postmarketing study (PMR 3185-1) for BLA 761049, under the accelerated approval regulations (21 CFR 601.41), remains open.

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.

We are waiving the pediatric studies requirement for this application because necessary studies are impossible or highly impracticable in children. Urothelial carcinoma occurs, for the most part, in the adult population. The incidence of this cancer type in pediatric patients is extremely rare and as such, clinical pediatric studies are impossible or highly impracticable.

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 avelumab was approved on March 23, 2017, we have become aware of a signal of increased incidence of adverse events in patients with treatment-induced anti-drug antibodies leading to dose reduction and discontinuation of avelumab, and infusion related reactions observed in clinical trials. 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 this signal of serious risk of increased adverse events.

Furthermore, the active postmarket risk identification and analysis system as available 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:

3882 -1 Reanalyze anti-drug antibodies (ADA) in the stored samples from 249 avelumab-treated patients with urothelial cancer (UC) (Study EMR100070-001) and 88 avelumab-treated patients with Merkel cell carcinoma (MCC) (Study EMR100070-003 Part A) that are evaluable for treatment-emergent ADA with the new ADA method. Using the updated treatment-emergent ADA data from the above two studies and emerging treatment-emergent ADA data from approximately 350 patients with UC in Study B9991001, assess the effect of treatment-emergent ADA on safety endpoints in patients with metastatic MCC or locally advanced or metastatic UC. The final report should include the following analyses and datasets:

a) Individual trial analyses assessing the effects of ADA on safety as the numbers of treatment-emergent adverse events (TEAEs), Grade 3-4 TEAEs, serious TEAEs, TEAEs leading to discontinuation, and infusion-related reactions (IRRs).

b) The ADA rate; median time to detection of ADA; median duration of ADA positivity in months, and the numbers of doses (before/after first detection of ADA and total) received in patients with treatment-emergent ADA.

c) Effect of “early” ADA (e.g., based on ADA at Week 5 or at another early visit with adequate justification) on safety outcome measures (TEAEs), Grade 3-4 TEAEs, serious TEAEs, TEAEs leading to discontinuation, and IRRs) in individual trials.

For all analyses performed, include the following information in the final study report: the model codes and output listings; all datasets as a SAS transport files (*.xpt); and a description of each data item in a define.xml file.

The timetable you submitted on June 17, 2020, states that you will conduct this study according to the following schedule:

Study Completion:	09/2020
Final Report Submission:	03/2021

REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)

Submit the protocols to Pfizer's IND 126217, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing 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) 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 commitment:

3882 - 2 Submit the final overall survival analysis and datasets from clinical trial JAVELIN Bladder 100 titled; *A phase 3 Multicenter, Multinational, Randomized, Open Label, Parallel-Arm Study of Avelumab Plus Best Supportive Care Versus Best Supportive Care Alone As a Maintenance Treatment in Patients With Locally Advanced or Metastatic Urothelial Cancer Whose Disease Did Not Progress After Completion of First-Line Platinum-Containing Chemotherapy,* to provide additional efficacy data for avelumab as maintenance treatment in patients with advanced or metastatic urothelial cancer that may inform product labeling.

The timetable you submitted on June 17, 2020, states that you will conduct this study according to the following schedule:

Study Completion:	06/2021
Final Report Submission:	12/2021

Submit clinical protocols to Pfizer's IND 126217 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]

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).

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, contact Rajesh Venugopal, Senior Regulatory Project Manager, at (301) 796-4730.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, MD
Deputy Director
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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/

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