BLA 761467/S-009

SUPPLEMENT APPROVAL

Merck Sharp & Dohme LLC
Attention: June Ancona
Associate Director, Global Regulatory Affairs
351 North Sumneytown Pike, PO Box 1000
North Wales, PA 19454-2505

Dear June Ancona:

Please refer to your supplemental Biologics License Application (sBLA) received December 19, 2025, and your amendments, submitted under section 351(a) of the Public Health Service Act for Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph) solution for injection.

This Prior Approval sBLA provides for the addition of the following indication based on Interim Analysis 1 (IA1) of MK-6482-022/LITESPARK-022, entitled, *"A Multicenter, Double-blind, Randomized Phase 3 Study to Compare the Efficacy and Safety of Belzutifan (MK-6482) Plus Pembrolizumab (MK-3475) Versus Placebo Plus Pembrolizumab, in the Adjuvant Treatment of Clear Cell Renal Cell Carcinoma (ccRCC) Post Nephrectomy (MK-6482-022)":*

> Pembrolizumab and berahyaluronidase alfa-pmph, in combination with belzutifan, is indicated for the adjuvant treatment of adult patients with ccRCC at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions.

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.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable to conduct in the pediatric population.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

5012-1 Complete the ongoing clinical trial, LITESPARK-022 (NCT05239728), titled "A Multicenter, Double-blind, Randomized Phase 3 Study to Compare the Efficacy and Safety of Belzutifan (MK-6482) Plus Pembrolizumab (MK-3475) Versus Placebo Plus Pembrolizumab, in the Adjuvant Treatment of Clear Cell Renal Cell Carcinoma (ccRCC) Post Nephrectomy (MK-6482-022)," and provide all pre-planned interim and final analyses of disease-free survival (DFS) and overall survival (OS), including those from the second interim analysis (IA2 [interim OS analysis]), the third interim analysis (IA3 [interim OS analysis]), and the final OS analysis, to further characterize the clinical benefit of pembrolizumab in combination with belzutifan as adjuvant treatment of adult patients with renal cell carcinoma with a clear cell component (ccRCC) at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

The timetable you submitted on June 5, 2026, states that you will conduct this study according to the following schedule:

Interim Report Submission (Analysis 2 (IA2)):	03/2028
Interim Report Submission (Analysis 3 (IA3)):	03/2030
Trial Completion:	07/2031
Final Report Submission (Final OS analysis):	01/2032

Submit the datasets for OS with the final report submission.

Submit clinical protocols to your IND 161465 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/subjects 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.*[1]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[2] Information and Instructions for completing the form can be found at FDA.gov.[3]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

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).

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

If you have any questions, contact Dana Kappel, Regulatory Project Manager, at (301) 796-8768 or at Dana.Kappel@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Daniel Suzman, 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/

DANIEL L SUZMAN
06/12/2026 11:34:06 AM