BLA 761467/Original 2

BLA ACCELERATED APPROVAL

Merck Sharp & Dohme LLC
Attention: Janice Kim, PharmD, MS
Director, Global Regulatory Affairs
126 East Lincoln Avenue, P.O. Box 2000
RY34-A2014
Rahway, NJ 07065

Dear Dr. Kim:

Please refer to your biologics license application (BLA) dated and received January 23, 2025, and your amendments, under section 351(a) of the Public Health Service Act for Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph) injection.

BLA 761467/Original 2 provides for the use of Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph) for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

As communicated to you on September 18, 2025, all future submissions to BLA 761467/Original 2 should specify the BLA number and the Original number to which each submission pertains.

A separate action letter will be issued for BLA 761467/Original 1 which provides for the use of Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph) for indications under traditional approval.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 0002 to Merck Sharp & Dohme LLC, Rahway, New Jersey, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph) injection. Keytruda Qlex is indicated

for accelerated approval for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Keytruda Qlex (pembrolizumab 165 mg/ml) drug substance at (b) (4) (b) (4) and Berahyaluronidase alfa drug substance at (b) (4) The final formulated drug product will be manufactured, filled, labeled at BSP Pharmaceuticals S.p.A, Latina Scalo, Italy (FEI: 3007255826), and packaged at Merck Sharp & Dohme LLC, Wilson, North Carolina (FEI: 1036761), and Merck Sharp & Dohme B.V., Haarlem, Netherlands (FEI: 3002807658). You may label your product with the proprietary name, Keytruda Qlex, and market it in 2.4 mL (395 mg pembrolizumab and 4800 units berahyaluronidase alfa) and 4.8 mL (790 mg pembrolizumab and 9600 units berahyaluronidase alfa) Type (b) (4) glass vials as solution for injection for subcutaneous administration.

DATING PERIOD

The dating period for Keytruda Qlex shall be 24 months from the date of manufacture when stored at 5 ± 3 °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 pembrolizumab 165 mg/ml drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C (b) (4) The dating period for your berahyaluronidase alfa drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C (b) (4)

We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your berahyaluronidase alfa drug substance **and** drug product under 21 CFR 601.12.

FDA LOT RELEASE

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

APPROVAL AND LABELING

We have completed our review of this application, as amended. It is approved under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 601.41, effective on the date of this letter, for use as recommended in the enclosed agreed-upon approved labeling. This BLA provides for the use of Keytruda Qlex for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Marketing of this drug product and related activities must adhere to the substance and procedures of the accelerated approval statutory provisions and regulations.

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] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide). Information on submitting SPL files using eLIST may be found in the draft guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* (October 2009).[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

We acknowledge your September 15, 2025, submission containing final printed carton and container labeling.

ADVISORY COMMITTEE

Your application for pembrolizumab and berahyaluronidase alfa-pmph was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

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

[2] When final, this guidance will represent FDA's current thinking on this topic. 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.

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 601.41, you are required to conduct further adequate and well-controlled clinical trials intended to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If required postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated September 18, 2025. This requirement is listed below.

4904-1 Submit the final report and datasets from clinical trials evaluating overall response rate and duration of response, to verify and describe the clinical benefit of pembrolizumab in adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors (as determined by an FDA-approved test) that have progressed following prior treatment and who have no satisfactory alternative treatment options. A sufficient number of patients and representation of tumor types (other than lung cancers, MSI-H or dMMR cancers, or melanoma; and including CNS tumors that were determined to be TMB-H based on testing of tissue obtained prior to initiation of temozolomide chemotherapy), and with cancers having a TMB of 10 to <13 mut/Mb, will be evaluated to characterize response and duration of response. A minimum of 20 pediatric patients will be studied. Overall response rate and duration of response will be assessed by independent central review for patients with cancers having a TMB of ≥10 mut/Mb, ≥10 mut/Mb to <13 mut/Mb, and ≥13 mut/Mb. All responding patients will be followed for at least 12 months from the onset of response.

The timetable you submitted on September 18, 2025, states that you will conduct this trial according to the following schedule:

Final Report Submission: 12/2025

Submit clinical protocols to your IND 127548 for this product. FDA considers the term final to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

You must submit reports of the progress of each clinical trial required under section 506(c) (listed above) to this BLA 180 days after the date of approval of this BLA and approximately every 180 days thereafter (see section 506B(a)(2) of the FDCA) (hereinafter “180-day reports”).

You are required to submit two 180-day reports per year for each open study or clinical trial required under 506(c). The initial report will be a standalone submission and the

subsequent report will be combined with your application's annual status report (ASR) required under section 506B(a)(1) of the FDCA and 21 CFR 601.70. The standalone 180-day report will be due 180 days after the date of approval (with a 60-day grace period). Submit the subsequent 180-day report with your application's ASR. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted[3].

Your 180-day reports must include the information listed in 21 CFR 601.70(b). FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics,* to submit your 180-day reports.[4]

180-day reports must be clearly designated "**BLA 761467 180-Day AA PMR Progress Report**."

FDA will consider the submission of your application's ASR under section 506B(a)(1) and 21 CFR 601.70, in addition to the submission of reports 180 days after the date of approval each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

Submit final reports to this BLA as a supplemental application. For administrative purposes, the cover page of all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(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.

We are waiving the pediatric study requirement for patients < 12 years of age because necessary studies are impossible or highly impracticable. This is due to the rarity of the disease in this population.

[3] You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.
[4] FORM FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

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*.[5]

REPORTING REQUIREMENTS

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

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:

[5] https://www.fda.gov/media/128163/download

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 4207
Silver Spring, MD 20903

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, contact Ashley Lane, Senior Regulatory Project Manager, at Ashley.Lane@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Deputy Director (Acting)
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

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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