BLA 761289

CORRECTED BLA APPROVAL

AstraZeneca AB
c/o AstraZeneca Pharmaceuticals LP
Attention: Lynn Kerr
Director, US Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Kerr:

Please refer to your biologics license application (BLA) dated February 23, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Imjudo (tremelimumab-actl) injection for intravenous infusion.

We also refer to our approval letter dated October 21, 2022, which contained the following error: reference to "section 351(k) of the Public Health Service Act", which should have been "section 351(a) of the Public Health Service Act."

This corrected action letter incorporates the correction of the error. The effective action date will remain October 21, 2022, the date of the original letter.

LICENSING

We have approved your BLA for Imjudo (tremelimumab-actl) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Imjudo under your existing Department of Health and Human Services U.S. License No. 2059. Imjudo is indicated in combination with durvalumab, for the treatment of adult patients with unresectable hepatocellular carcinoma.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Imjudo drug substance at [redacted] (b) (4) The final formulated drug product will be manufactured, filled, labeled, and packaged [redacted] (b) (4) You may label your product with the proprietary name, Imjudo, and market it in 25 mg/1.25 mL (20 mg/mL) solution in a single-dose vial or 300 mg/15 mL (20mg/mL) solution in a single-dose vial.

DATING PERIOD

The dating period for Imjudo shall be 48 months from the date of manufacture when stored at 2-8°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 drug substance shall be a total of (b) (4) months from the date of manufacture (b) (4)

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Imjudo 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 Imjudo, 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 & 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.[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 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.

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

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling which were submitted on October 21, 2022, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761289**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Imjudo 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.

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 deferring submission of your pediatric study until December 31, 2024, because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

4333-1 Conduct Study D419EC00001 (A Phase I/II, open-label, multicenter study to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of tremelimumab in combination with durvalumab in pediatric patients) to further characterize the safety, pharmacokinetics, and efficacy of tremelimumab in combination with durvalumab in patients from birth to <18 years of age with relapsed/refractory malignant solid tumors or a relapsed/refractory hematological malignancy including lymphomas for whom no standard treatment is available. Include at least 12 patients in the dose escalation cohort and at least 45 evaluable patients in the dose expansion cohort.

Trial Completion: 02/2024
Final Report Submission: 12/2024

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.[3]

Submit the protocol to your IND 141756 with a cross-reference letter to this BLA. Reports of this required pediatric postmarketing study must be submitted as a biologics license application (BLA) or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission **"SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS"** in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4333-2 Conduct a study, Study 2, to evaluate the efficacy and safety of tremelimumab used in combination with durvalumab in children from birth to less than 18 years of age with a pediatric solid tumor, to further characterize the efficacy and safety of tremelimumab in combination with durvalumab in pediatric solid tumors.

The timetable you submitted on September 30, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 12/2024
Final Protocol Submission: 06/2025
Trial Completion: 06/2030
Final Report Submission: 04/2031

4333-3 Conduct a study, Study 3, to evaluate the efficacy and safety of tremelimumab in combination with durvalumab in children from birth to less than 18 years of age with a pediatric hematological malignancy, to further characterize the efficacy and safety of tremelimumab in combination with durvalumab in pediatric hematologic malignancies.

The timetable you submitted on September 30, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 12/2024
Final Protocol Submission: 06/2025
Trial Completion: 06/2030
Final Report Submission: 04/2031

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.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4333-4 To perform a shipping validation study under real time shipping conditions (i.e., temperature, mode of transport, shipping duration, and shipping containers and packing representative of the minimum and maximum load) using a representative commercial tremelimumab drug product lot in the final commercial container closure and packaging systems to evaluate the ability of the shipping containers to maintain the recommended temperature and to evaluate the impact of shipping from the AstraZeneca Sweden labeling and packaging site to the US Distribution Center on the physical integrity and product quality of tremelimumab drug product. The shipping validation data will be submitted in accordance with 21 CFR 601.12.

The timetable you submitted on August 9, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/31/2023

4333-5 Implement (b) (4) monitoring (b) (4) (b) (4) validated by the microbial retention study.

The timetable you submitted on May 31, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/31/2023

Submit clinical protocols for PMC 4333-2 and 4333-3 your IND 141756 for this product with a cross-reference letter to the BLA. 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*.[4]

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.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements at 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 at 21 CFR 600.81.

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

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:

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 biological products 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 Christina Leach, Regulatory Health Project Manager, at Christina.Leach@fda.hhs.gov or 240-402-6571.

Sincerely,

{See appended electronic signature page}

Paul Kluetz, MD
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

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

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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/

PAUL G KLUETZ
10/31/2022 03:36:23 PM