BLA 761365

BLA APPROVAL

Astellas Pharma US, Inc.
Attention: Sarah Groenendal, M.S., RAC
Director, Regulatory Affairs
2375 Waterview Drive
Northbrook, IL 60062

Dear Sarah Groenendal:

Please refer to your biologics license application (BLA) dated May 12, 2023, and your amendments, submitted under section 351(a) of the Public Health Service Act for Vyloy (zolbetuximab-clzb) for injection.

We acknowledge receipt of your May 9, 2024, resubmission which constituted a complete response to our January 4, 2024, action letter.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2124 to Astellas Pharma US Inc., Northbrook, Illinois, 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 Vyloy (zolbetuximab-clzb). Vyloy is a claudin 18.2-directed cytolytic antibody and is indicated in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adults with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction adenocarcinoma whose tumors are claudin (CLDN) 18.2 positive as determined by an FDA-approved test.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture zolbetuximab-clzb drug substance at (b) (4) The final formulated drug product will be manufactured, filled and primary packaged at (b) (4) (b) (4) The final formulated drug product will be labeled and secondary packaged at (b) (4) You may label your product with the proprietary name, Vyloy, and market it in 100 mg/vial for injection.

DATING PERIOD

The dating period for Vyloy shall be 48 months from the date of manufacture when stored at 2°C to 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 (b) (4) months from the date of manufacture when stored at (b) (4) (b) (4)°C.

Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your 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 Vyloy 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 Vyloy, 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, Patient Package Insert). Information on submitting SPL files using eLIST may be found in the

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

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

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling **and** carton and container labeling submitted on October 14, 2024, 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 761365** Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for zolbetuximab-clzb was not referred to an FDA advisory committee because no review issues were identified that raised significant public health questions regarding the risk:benefit assessment of zolbetuximab-clzb for the proposed indication.

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 and the molecular target of your drug is not relevant to the growth or progression of a pediatric cancer, you are exempt from this requirement.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

[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.

4723-1 Conduct a clinical trial to further characterize the clinical effects of zolbetuximab-clzb, including pharmacokinetics (PK), activity, and safety in the underrepresented racial and ethnic minority populations. The analysis should support an evaluation of comparative efficacy and safety between the aforementioned population and the population primarily represented in your trial.

The timetable you submitted on October 10, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2025
Final Protocol Submission:	05/2025
Trial Completion:	12/2030
Final Report Submission:	06/2031

4723-2 Conduct an analysis of the incidence of anti-drug antibodies in clinical samples from pivotal clinical studies of zolbetuximab-clzb (i.e., SPOTLIGHT and GLOW) using a validated immunogenicity assay (e.g., 8951-ME-0006) and evaluate the potential clinical impact of the anti-drug antibodies on pharmacokinetics, efficacy, and safety of zolbetuximab-clzb.

The timetable you submitted on October 10, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission:	12/2024

4723-3 Conduct an analysis of the incidence of neutralizing antibodies against zolbetuximab-clzb, using a validated neutralization assay, in patients enrolled in the pivotal clinical studies of zolbetuximab-clzb (i.e., SPOTLIGHT and GLOW), and evaluate the potential clinical impact of the neutralizing antibodies on the pharmacokinetics, pharmacodynamics, safety, and efficacy of zolbetuximab-clzb.

The timetable you submitted on October 10, 2024, states that you will conduct this study according to the following schedule:

Study Completion:	09/2025
Final Report Submission:	11/2025

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 129598 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*.[3]

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

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.

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:

[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

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 call Nataliya Fesenko, Pharm.D., Senior Regulatory Health Project Manager, at (240) 402-6376.

Sincerely,

{See appended electronic signature page}

Paul G. Kluetz, M.D.
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation & Research

ENCLOSURES:

- Content of Labeling
    - Prescribing Information
    - Patient Package Insert
- 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
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