BLA 761150

BLA APPROVAL

MacroGenics, Inc.
Attention: Maria Petkoski
Director, Regulatory Affairs
9704 Medical Center Drive
Rockville, MD 20850

Dear Ms. Petkoski:

Please refer to your biologics license application (BLA) dated and received December 18, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for Margenza (margetuximab-cmkb) injection.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2139 to MacroGenics Inc., Rockville, Maryland, 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 Margenza (margetuximab-cmkb). Margenza, in combination with chemotherapy, is indicated for the treatment of adult patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Margenza drug substance at (b) (4) (b) (4) The final formulated drug product will be manufactured, filled, labeled, and packaged at (b) (4) (b) (4) You may label your product with the proprietary name, Margenza, and market it at 250 mg/10 mL (25 mg/mL) in a single-dose vial for injection.

DATING PERIOD

The dating period for Margenza shall be 36 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) °C.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Margenza 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 Margenza, or in the manufacturing facilities, will require the submission of information to your biologics license application 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, as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information). 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.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling 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 *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed**

[1] 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.

Carton and Container Labeling for approved BLA 761150." Approval of this submission by the FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Margenza was not referred to a FDA advisory committee because the application did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

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 this application because necessary studies are impossible or highly impracticable. Breast cancer is extremely rare in pediatric patients.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3941-1 Submt the final overall survival analysis and datasets with the final report from clinical Study CP-MGAH22-04 titled; A Phase 3, Randomized Study of Margetuximab Plus Chemotherapy vs Trastuzumab Plus Chemotherapy in the Treatment of Patients With HER2+ Metastatic Breast Cancer Who Have Received Prior Anti-HER2 Therapies and Require Systemic Treatment, to further confirm the clinical benefit of margetuximab. The results from this study may inform product labeling.

The timetable you submitted on December 8, 2020, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2020
Interim Report Submission:	03/2022
Trial Completion:	12/2022
Final Report Submission:	06/2023

3941-2 Provide the final report and dataset containing information pertinent to CD16A (FCGR3A) F158V genotype and patient outcome from clinical trials that correlate CD16A (FCGR3A) F158V genotype with trial efficacy endpoints to further characterize the clinical benefit of margetuximab that may inform product labeling.

The timetable you submitted on December 8, 2020, states that you will conduct this study according to the following schedule:

Interim Report Submission:	03/2022
Study Completion:	12/2022
Final Report Submission:	06/2023

3941-3 Conduct a study to assess neutralizing antibody (nAb) responses against margetuximab in Study CP-MGAH22-04 and the infusion sub-study (CPMGAH22-04) with an adequately validated nAb assay. NAb responses should be evaluated in all confirmed anti-drug antibody positive samples from Study CPMGAH22-04 and the infusion sub-study. Provide the final report and include information on the level of margetuximab in each patient's test sample at each sampling point,an assessment of the effect of nAb development on the anti-tumor activity of margetuximab in individual patients, and the nAb assessment data set.

The timetable you submitted on November 9, 2020, states that you will conduct this study according to the following schedule:

Study Completion:	12/2022
Final Report Submission:	06/2023

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

We remind you of your postmarketing commitments:

3941-4 Provide data from one media fill using the product-specific change parts, (b) (4) and equipment to support (b) (4) the 10 mL vial/20 mm stopper combination that is used for margetuximab DP.

The timetable you submitted on September 18, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission:	06/2021

3941-5 Develop and validate a sensitive, accurate, and reliable assay for the detection of neutralizing antibodies to MARGENZA in the presence of drug levels that are expected to be present in the serum at the time of patient sampling. The neutralizing antibody assay procedure and method validation protocol and report should be submitted to the BLA as a final study report.

The timetable you submitted on November 3, 2020, states that you will conduct this study according to the following schedule:

Study Completion:	10/2021
Final Report Submission:	12/2021

3941-6 Conduct a Drug Product (DP) shipping validation study of commercial DP shipped via commercial lanes to the selected third-party logistics warehouse. The study will include analytical characterization and cell-based potency determination of the DP both pre- and post-shipping. Submit results to the BLA as a final study report.

The timetable you submitted on November 19, 2020, states that you will conduct this study according to the following schedule:

Study Completion:	12/2021
Final Report Submission:	06/2022

3941-7 Conduct a DP leachables study to evaluate the DP container closure system through the end of shelf-life when stored under the recommended conditions of 2-8°C. Analyses will include appropriate methods to detect organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS), semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS), including their chemical identification and quantitation. Testing will be performed at regular intervals throughout the shelf life with study results to be updated annually in the BLA Annual Report. The final report to be submitted to the BLA will include the complete data and risk evaluation for the potential impact of leachables on product safety and quality.

The timetable you submitted on November 19, 2020, states that you will conduct this study according to the following schedule:

Study Results:	Submission in annual report
Study Completion:	09/2024
Final Report Submission:	03/2025

3941-8 Reassess release and stability specifications for margetuximab drug substance and/or drug product, as appropriate, by December 30, 2022 or following manufacture of 30 lots (if earlier) for the following assays: N-glycosylation (DS), residual host cell protein levels (DS), potency by CGI bioassay, HER2 binding ELISA, and FcγRIIIa binding ELISA (DS and DP), visible particles (DP), and protein content (DP). Submit the final report as a Changes Being Effected-30 Supplement (CBE-30).

The timetable you submitted on November 19, 2020, states that you will conduct this study according to the following schedule:

Study Completion:	12/2022
Final Report Submission:	03/2023

3941-9 Conduct studies to optimize the three potency assays (CGI bioassay, HER2 binding ELISA, FcγRIIIa binding ELISA) for IC50 and EC50 reporting; tighten IC50 and EC50 acceptance criteria for reference standard stability assessment based on the study results. Submit the final report as a Prior Approval Supplement (PAS).

The timetable you submitted on November 19, 2020, states that you will conduct this study according to the following schedule:

Study Completion:	06/2022
Final Report Submission:	12/2022

3941-10 Prospectively revalidate the (b) (4) operation as per Agency communications with (b) (4) following the 2020 pre-license inspection of the drug substance manufacturing facility. In addition, confirm (b) (4) Submit the results to the BLA as a Prior Approval Supplement (PAS).

The timetable you submitted on December 8, 2020, states that you will conduct this study according to the following schedule:

Study Completion:	12/2021
Final Report Submission:	03/2022

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 107768 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]

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 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:

[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 molecular entities and 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 Kelly Chiang, Regulatory Project Manager, at Duyen.Mach@fda.hhs.gov or 301-796-5822.

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Deputy Office Director (acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
- 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/

JULIA A BEAVER
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