U.S. FOOD & DRUG ADMINISTRATION

BLA 761136, Original 1

BLA APPROVAL

Celgene Corporation
Attention: Mary Vandekauter, MS, RAC
Director, Regulatory Affairs
86 Morris Avenue
Summit, NJ 07901

Dear Ms. Vandekauter:

Please refer to your biologics license application (BLA) dated April 4, 2019, received April 4, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for REBLOZYL (luspatercept – aamt), subcutaneous injection.

We also refer to our approval letter dated November 8, 2019 which contained the following error: in the Manufacturing Locations section, the labeling site (b) (4) (b) (4) was not included.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain November 8, 2019, the date of the original approval letter.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2114 to Celgene Corporation, Summit, 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 REBLOZYL (luspatercept – aamt). REBLOZYL is indicated for the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture luspatercept drug substance at (b) (4) The final formulated drug product will be manufactured, filled, and primary packaged at (b) (4) You may label your product with the

proprietary name, REBLOZYL, and market it in the 25 mg lyophilized powder in a single (b) (4) 2.0 mL vial to be reconstituted with 0.68 mL sterile water for injection and 75 mg lyophilized powder in a single (b) (4) 2.0 mL vial to be reconstituted with 1.6 mL sterile water for injection.

DATING PERIOD

The dating period for REBLOZYL shall be 18 months from the date of manufacture when stored at 2 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.

We have approved the stability protocol(s) 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 REBLOZYL 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 REBLOZYL, 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 with minor editorial revisions listed below and reflected in the enclosed labeling.

- Added license number

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

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

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 carton and container labeling submitted on November 5, 2019, 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 Carton and Container Labeling for approved BLA 761136, Original 1**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for REBLOZYL was not referred to an FDA advisory committee because evaluation of the safety data for the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions did not raise significant safety or efficacy issues that were unexpected in the intended population.

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, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

[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.

We have determined that an analysis of spontaneous post-marketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of thrombosis and to assess signals of serious risks of secondary malignancies (including acute myeloid leukemia (AML)), hepatotoxicity and renal toxicity associated with luspatercept.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of thrombosis and to assess signals of serious risks of secondary malignancies (including AML), hepatic toxicity, and renal toxicity.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

3709-1 Complete Study A536-06: An Open-Label Extension Study to Evaluate the Effects of ACE-536 in Patients with Beta-Thalassemia. Include all the patients from Study A536-04 who enrolled into the open-label extension study (A536-06). Include summary analysis and updated safety summary to include safety data on thrombosis, all malignancies (including AML), hepatic toxicity, and renal toxicity. Include updated assessments of ferritin levels, liver iron concentrations and use of chelators evaluations in the reports. Include updated safety and efficacy analysis and submit datasets at the time of final clinical study report submission.

The timetable you submitted on November 7, 2019 states that you will conduct this trial according to the following schedule:

Trial Completion:	04/2020
Final Report Submission:	10/2020

3709-2 Complete Trial ACE-536-B-THAL-001: Phase 3, Randomized, Placebo-controlled, Multicenter Study to Determine the Efficacy and Safety of Luspatercept (ACE-536) in Adults who Require Regular Blood Transfusions. Evaluate safety and efficacy data for the patients who enrolled in the open-label treatment for up to five years. Include summary analysis and updated safety summary to include safety data on thrombosis, all malignancies (including AML), hepatic toxicity, and renal toxicity. Include updated assessments of ferritin levels, liver iron concentrations and use of chelators and any cardiac iron evaluations in the reports. Include updated safety and efficacy analysis and submit datasets at the time of final clinical study report submission.

The timetable you submitted on November 7, 2019 states that you will conduct this trial according to the following schedule:

Trial Completion:	06/2020
Final Report Submission:	12/2020

3709-3 Complete Trial ACE-536-B-THAL-002: A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Determine the Efficacy and Safety of Luspatercept (ACE-536) versus Placebo in Adults with non-Transfusion Dependent Beta (B) Thalassemia. Include summary analysis and updated safety summary to include safety data on thrombosis, all malignancies (including AML), hepatic toxicity, and renal toxicity. Include updated assessments of ferritin levels, liver iron concentrations and use of chelators and any cardiac iron evaluations in the reports. Include updated safety and efficacy analysis and submit datasets at the time of final clinical study report submission.

The timetable you submitted on November 7, 2019 states that you will conduct this trial according to the following schedule:

Interim Report (Preliminary Study Report):	09/2021
Trial Completion:	03/2023
Final Report Submission:	09/2023

3709-4 Conduct an assessment of cases of secondary primary malignancies (and malignancies for B-thalassemia), to include hematological malignancies (AML, de-novo AML, transformation to AML), and solid tumors identified in sponsor-initiated and investigator-initiated clinical trials across the entire luspatercept development program for 5 years post approval.

The timetable you submitted on November 8, 2019 states that you will conduct this trial according to the following schedule:

Interim Report #1 (Annual Summary Safety Report) Submission:	12/2020
Interim Report #2 (Annual Summary Safety Report) Submission:	12/2021
Interim Report #3 (Annual Summary Safety Report) Submission:	12/2022
Interim Report #4 (Annual Summary Safety Report) Submission:	12/2023
Trial Completion:	12/2023
Final Report Submission:	12/2024

Submit clinical protocol(s) to your IND 112562 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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

We remind you of your postmarketing commitments:

3709-5 Implement a test monitoring (b) (4) oxidation and (b) (4) (b) (4) isomerization into the luspatercept drug substance release and stability specification and drug product release specification. Submit the proposed release specification and supporting validation results following 21 CFR 601.12 (b).

The timetable you submitted on October 31, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2020

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. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Patient Package Insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[3] Information and Instructions for completing the form can be found at FDA.gov.[4] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see 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] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[5] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.[6]

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, call Rosa Lee-Alonzo, Senior Regulatory Health Project Manager, at (301) 348-3004.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, MD
Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

[6] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

ENCLOSURE(S):

- Content of Labeling
    - Prescribing Information

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/

RICHARD PAZDUR
11/08/2019 12:00:00 AM