

BLA 761268

CORRECTED BLA APPROVAL

Celltrion, Incorporated
Attention: Ryan Zettle
Associate Director
Parexel International
2520 Meridian Parkway, Suite 200
Durham, NC 27713

Dear Mr. Zettle:

Please refer to your biologics license application (BLA) dated September 30, 2021, received September 30, 2021, and your amendments, submitted under section 351(k) of the Public Health Service Act for Vegzelma (bevacizumab-adcd) injection, 100 mg/4 mL (25 mg/mL) and 400 mg/16 mL (25 mg/mL).

We also refer to our approval letter dated September 27, 2022, which contained the following error: the 'Initial U.S. Approval' date in the Highlights section of the Prescribing Information (PI) was incomplete. The date was listed as '20XX', and should have been "2022".

This corrected action letter incorporates the correction of the error. The effective action date will remain September 27, 2022, the date of the original letter.

LICENSING

We have approved your BLA for Vegzelma (bevacizumab-adcd) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Vegzelma under your existing Department of Health and Human Services U.S. License **No. 1996**. Vegzelma is indicated for the treatment of patients with:

- Metastatic colorectal cancer
 - in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment.
 - in combination with fluoropyrimidine- irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab product-containing regimen.
- Limitation of Use: not indicated for adjuvant treatment of colon cancer.
- Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel.
- Recurrent glioblastoma in adults.
- Metastatic renal cell carcinoma in combination with interferon alfa.

- Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan.
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer:
 - in combination with carboplatin and paclitaxel, followed by VEGZELMA as a single agent, for stage III or IV disease following initial surgical resection
 - in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens.
 - in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by VEGZELMA as a single agent, for platinum-sensitive recurrent disease.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture bevacizumab-adcd drug substance at Celltrion, Inc. (Plant II) in Incheon, Republic of Korea. The final formulated drug product will be manufactured and filled at Celltrion, Inc. (Plant II), Incheon, Republic of Korea. The final labeling and secondary packaging will be performed at Celltrion Pharm, Inc. in Chungcheongbuk-do, Republic of Korea. You may label your product with the proprietary name, VEGZELMA, and market it in 100 mg/4 mL and 400 mg/16 mL single-dose vials, injection.

DATING PERIOD

The dating period for VEGZELMA 100 mg/4 mL shall be 24 months from the date of manufacture and for VEGZELMA 400 mg/16 mL shall be 48 months from the date of manufacture when stored at $5 \pm 3^{\circ}\text{C}$. 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) $^{\circ}\text{C}$.

We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of VEGZELMA 100 mg/4 mL under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of VEGZELMA 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 VEGZELMA, 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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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). 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.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling and the carton and container labeling submitted on September 7, 2022 (carton), and August 22, 2022 (container), 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 761268.**” Approval of this submission by FDA is not required before the labeling is used.

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>.

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.

The Agency has determined that, at this time, no pediatric study(ies) will be required under PREA for this BLA.

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, call Maryam Khazraee, Regulatory Project Manager, at Maryam.Khazraee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Steven Lemery, M.D., M.H.S.
Director
Division of Oncology 3
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
 - Prescribing Information
- 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/

STEVEN J LEMERY
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