CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125547Orig1s000

Trade Name: Portrazza Injection, 800 mg/50 mL

Generic Name: (necitumumab)

Sponsor: Eli Lilly and Company

Approval Date: November 24, 2015

Indications: PORTRAZZA™ is an epidermal growth factor receptor (EGFR) antagonist indicated, in combination with gemcitabine and cisplatin, for first-line treatment of patients with metastatic squamous non-small cell lung cancer.

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125547

BLA APPROVAL

Eli Lilly and Company
Attention: Deborah Lynch
Associate Vice President, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Ms. Lynch:

Please refer to your Biologics License Application (BLA) dated December 2, 2014, received December 2, 2014, submitted under section 351(a) of the Public Health Service Act for PORTRAZZA (necitumumab) injection, 800 mg/50 mL.

We acknowledge receipt of your amendments dated October 22, 2014, November 25, 2014; January 20 and 28; February 6 (2), 13, and 27; April 1, 14, 15, 21, and 22; May 4, 12, 14, 18, 29 (2); June 10 (2), 11 (2), 17, and 25; July 8 and 28; August 3, 13 (2), 19, and 31 (2); September 8, 11, and 17; October 8 (2), and 13 (3), 27, 30, 2015; November 9, 10, 11, 12, 18, 19, 20, and 23, 2015.

LICENSING

We have approved your BLA for PORTRAZZA (necitumumab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, PORTRAZZA under your existing Department of Health and Human Services U.S. License No. 1891. PORTRAZZA is indicated, in combination with gemcitabine and cisplatin, for first-line treatment of patients with metastatic, squamous, non-small cell lung cancer. PORTRAZZA is not indicated for treatment of non-squamous, non-small cell lung cancer.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture necitumumab drug substance at ImClone Systems LLC Building 50, Suite 1, in Branchburg, NJ, USA.

The vialed drug product will be manufactured, filled, labeled, and packaged at Eli Lilly and Company in Indianapolis, Indiana, USA (Lilly) and tested for release at Lilly and at ImClone Systems LLC, Branchburg, NJ, USA.

You may label your product with the proprietary name, PORTRAZZA™, and will market it as an 800 mg/50 mL injection in a single-dose vial.

DATING PERIOD

The dating period for PORTRAZZA shall be 24 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 necitumumab drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

Results of ongoing stability should be submitted to the annual report.

We have approved the annual 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 PORTRAZZA 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 PORTRAZZA, 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 text.

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels **and/or** carton and immediate container labels submitted on August 31, 2015, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved BLA 125547**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2987-1 Conduct endotoxin and sterility test method qualification study using two additional batches of Necitumumab Drug Product manufactured according to the commercial drug substance and drug product manufacturing processes and submit the results in accordance with 21 CFR 601.12.

The timetable you submitted on November 23, 2015, states that you will conduct this study according to the following schedule:

Study Completion:	06/16
Final Report Submission:	09/16

2987-2 Complete endotoxin (LPS) recovery study using three batches of drug substance manufactured during a recent campaign and submit the study report in accordance

with 21 CFR 601.12. If the results do not meet acceptance criteria, develop an alternative method to detect endotoxin in the drug substance.

The timetable you submitted on November 23, 2015, states that you will conduct this study according to the following schedule:

Study Completion: 09/16
Final Report Submission: 11/16

2987-3 Re-evaluate all necitumumab drug substance lot release and stability data after availability of IEC and CE-SDS release data from 30 lots of drug substance manufactured by (b) (4) Submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

The timetable you submitted on November 23, 2015, states that you will conduct this study according to the following schedule:

Study Completion: 12/20
Final Report Submission: 02/21

2987-4 Re-evaluate all necitumumab drug product lot release and stability data after availability of IEC and CE-SDS release data from at least 20 lots of drug product manufactured by the commercial manufacturing process. Submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications, based on the available drug substance and drug product data.

The timetable you submitted on November 23, 2015, states that you will conduct this study according to the following schedule:

Study Completion: 12/20
Final Report Submission: 02/21

2987-5 Further characterize the molecular changes that are associated with changes in ADCC activity of necitumumab, and update the necitumumab control strategy accordingly.

The timetable you submitted on November 23, 2015, states that you will conduct this study according to the following schedule:

Study Completion: 12/17
Final Report Submission: 06/18

Submit clinical protocols to your IND 102512 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 study 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 package insert 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 package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

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:

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 4206
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 http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics 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 within two weeks of receipt of this communication.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals,

complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, please call Ms. Missiratch (Mimi) Biable, Senior Regulatory Health Project Manager, at (301) 796-0154.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA KEEGAN on behalf of RICHARD PAZDUR
11/24/2015