CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125486Orig1s000

Trade Name: Gazyva

Generic Name: obinutuzumab

Sponsor: Genentech, Inc.

Approval Date: October 3, 2013

Indications: GAZYVA (obinutuzumab) is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia in combination with chlorambucil.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125486/0

BLA APPROVAL

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Rohrer:

Please refer to your Biologics License Application (BLA) dated April 22, 2013 received on April 22, 2013 submitted under section 351(a) of the Public Health Service Act for GAZYVA (obinutuzumab).

We acknowledge receipt of your amendments dated April 25, May 15, June 3, 28, July 3, 8, 16, 18, 19, 25, 31, August 1, 2, 6, 12, 14, 15, 19, 22, 27, 30, September 3, 10, 12, 13, 17, 18, 20, 23, 24, 25, 27, October 7, 9, 15, 17, 21, 22, 23, 24, 29, 30, and 31, 2013.

LICENSING

We have approved your BLA for GAZYVA (obinutuzumab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, GAZYVA (obinutuzumab) under your existing Department of Health and Human Services U.S. License No. 1048. GAZYVA (obinutuzumab) is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia in combination with chlorambucil.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture obinutuzumab drug substance at Roche Diagnostics GmbH in Penzberg, Germany, and obinutuzumab drug product at Roche Diagnostics GmbH in Mannheim, Germany. Drug product will be labeled and packaged at F. Hoffmann-La Roche Ltd, in Kaiseraugst, Switzerland.

You may label your product with the proprietary name, GAZYVA, and will market it in 1000 mg/40 mL (25 mg/mL) liquid single use vials.

DATING PERIOD

The dating period for GAZYVA (obinutuzumab) shall be 36 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as (b) (4)

(b) (4). The dating period for your obinutuzumab drug substance shall be (b) (4) from the date of manufacture when stored at (b) (4)

FDA LOT RELEASE

You are not currently required to submit samples of future lots of GAZYVA (obinutuzumab) 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.

Upon review of the supporting data, the design space as proposed in BLA 125486 was found to be acceptable. The Agency would like to reiterate that in addition to the information described in the application, it is our expectation that plans for implementation of the design space for the commercial process are documented within the firm's Quality System. Such quality systems may include plans for handling movements within the design space (e.g., change control procedures, plans for updating batch records). In accordance with ICH Q8(R2), while the Agency does not expect any regulatory notification for movements within the design space, any other changes in the manufacturing, testing, packaging, or labeling or manufacturing facilities for GAZYVA (obinutuzumab) 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.

We note that your October 31, 2013 submission includes final printed labeling (FPL) for your package insert. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

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 [21 601.14(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

We acknowledge your October 18, 2013 submission containing final printed carton and container labels.

ADVISORY COMMITTEE

Your application for GAZYVA (obinutuzumab) was not referred to an FDA advisory committee because this biologic is not the first in its class, the clinical trial design is acceptable, the application did not raise significant safety or efficacy issues that were unexpected for a drug/biologic of this class, and there were no controversial issues that would benefit from advisory committee discussion.

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:

PMC #1 Perform a formal verification study of the (b) (4) hold time for (b) (4) Submit the final report to the Agency as a CBE-30 by February 28, 2014.

The timetable you submitted on October 16, 2013 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	Complete
Study Completion:	12/2013
Final Report Submission:	02/2014

PMC #2 Submit a protocol for (b) (4) The protocol should include bioburden and endotoxin limits to demonstrate continued microbial control over (b) (4) lifetime. The protocol should be submitted as a CBE-30 by December 2013.

Execute the approved protocol concurrently throughout the respective lifetime of the [redacted] (b) (4) until the claimed or planned lifetimes are reached. Provide available results in the first annual report following the approval of the CBE-30 and concurrently with subsequent annual reports.

The timetable you submitted on October 30, 2013 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2013
Study Completion:	concurrently throughout respective lifecycle
Final Report Submission:	Annual report 2014 and subsequent Annual reports until end of one full lifecycle for each of the included items

Submit clinical protocols to your IND 104405 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 post marketing 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 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. For instruction on completing the Form FDA 2253, see page 2 of the Form. 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.

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, call Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):
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/

RICHARD PAZDUR
11/01/2013