



BLA 103705/5332

**SUPPLEMENT BLA APPROVAL**

January 28, 2011

Genentech, Incorporated  
Attention: Michelle H. Rohrer, Ph.D.  
Vice President, Regulatory Affairs  
1 DNA Way, MS# 241B  
South San Francisco, CA 94080-4990

Dear Dr. Rohrer:

Please refer to your Supplemental Biologics License Application (sBLA), dated March 30, 2010, received March 31, 2010, submitted under section 351 of the Public Health Service Act for Rituxan® (rituximab).

We acknowledge receipt of your amendments dated May 28, June 21, July 9, October 19, November 4 and November 29, and December 7, 2010.

This “Prior Approval” efficacy supplement to your biologics license application includes a new indication for use as single-agent maintenance therapy in patients with previously untreated follicular, CD20-positive, B-cell non-Hodgkin’s lymphoma (NHL) who achieve a response to Rituxan in combination with chemotherapy.

We have completed our review of this supplemental 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>, that is identical to the enclosed labeling (text for package insert and Medication Guide) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements. 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>. For administrative purposes, please designate this submission “**Product Correspondence – Final SPL for approved BLA STN 103705/5332.**”

Also within 14 days, amend all pending supplemental applications for this BLA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

The SPL will be accessible via publicly available labeling repositories.

### **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 Rituxan, for the treatment of NHL, has 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.

Since Rituxan® (rituximab) was approved on November 26, 1997 we have become aware of a possible increased risk of cardiac failure from the clinical trial data submitted for approval of this supplemental application. Therefore, we consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of the serious risk of cardiac failure.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet sufficient to assess this serious risk.

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

PMR #1 under sBLA 103705/5332:

A study consisting of an integrated analysis assessing the relative risk of cardiac toxicity based on safety data reported in the following randomized, controlled clinical trials: Protocols M39021, MO18264, E1496, E4494, BO16368, M39045, ML17102, and BO17072. The analysis will include comparative analyses of cardiac adverse events

using MedDRA Preferred Terms and using High Level Terms. The final report will include copies of the clinical protocols and related case report forms, the primary and derived datasets, and all programs used to generate the derived data and the results reported.

The timetable you submitted on November 29, 2010, states that you will conduct this study according to the following schedule:

Final Report Submission: July 31, 2011

Submit the protocol to your IND 8648, with a cross-reference letter to this BLA. Submit the final report 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 Final Report Under 505(o)”**, or **“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 SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitment:

PMC #2 under sBLA 103705/5332:

To submit a final report that includes updated results for overall survival for trial MO18264 (PRIMA), “A Multicenter, Phase III, Open-Label, Randomized Study in Patients with Advanced Follicular Lymphoma Evaluating the Benefit of Maintenance Therapy with Rituxan after Induction of Response with Chemotherapy plus Rituxan in Comparison with No Maintenance Therapy.” The final report should also include the primary and derived datasets and programs used to generate the overall survival results reported.

The original protocol for clinical trial MO18264 (PRIMA) was submitted to FDA on November 2, 2006, and began patient accrual on December 24, 2005. We acknowledge the receipt of protocol amendments on April 4, 2008 and January 1, 2009.

The timetable you submitted on March 30, 2010, states that you will conduct this trial according to the following schedule:

Final Report Submission: December 31, 2013

Submit clinical protocols to your IND 8648 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all 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 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(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
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(s), 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 Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **LETTERS TO HEALTH CARE PROFESSIONALS**

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this BLA to the following address:

MedWatch Program  
Office of Special Health Issues  
Food and Drug Administration  
10903 New Hampshire Ave  
Building 32, Mail Stop 5353  
Silver Spring, MD 20993

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Gina Davis, Regulatory Project Manager, at (301) 796-0704.

Sincerely,

/Patricia Keegan/  
Patricia Keegan, M.D.  
Director  
Division of Biologic Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

ENCLOSURE:  
Content of Labeling