DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 103976/S-5224

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING COMMITMENT

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080

Attention: Cindy Wilson
Regulatory Program Management

Dear Ms. Wilson:

Please refer to your Supplemental Biologics License Application (sBLA), dated October 30, 2015, submitted under section 351(a) of the Public Health Service Act for Xolair (omalizumab) Powder for Injection, 150 mg.

We also refer to our letter dated September 30, 2015, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Xolair (omalizumab). This information pertains to the results from a case controlled study, which showed that patients with a history of anaphylaxis to food or medications are at increased risk of anaphylaxis with the use of Xolair (omalizumab).

This supplemental biologics application provides for revisions to the labeling for Xolair (omalizumab). The agreed upon changes to the language included in our September 30, 2015, letter are as follows (additions are noted by underline and deletion are noted by ~~strikethrough~~). The final labeling includes modifications to the description of the case control study and available data on the incidence of anaphylaxis with Xolair.

5.1 Anaphylaxis

Anaphylaxis has been reported to occur after administration of Xolair in premarketing clinical trials and in postmarketing spontaneous reports [see *Boxed Warning and Adverse Reactions* (6.3)]. Signs and symptoms in these reported cases have included bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Some of these events have been life-threatening. In premarketing clinical trials in patients with asthma, anaphylaxis was reported in 3 of 3507 (0.1%) patients. Anaphylaxis occurred with the first dose of Xolair in two patients and with the fourth dose in one patient. The time to onset of anaphylaxis was 90 minutes after administration in two patients and 2 hours after administration in one patient.

A case control (b) (4) study showed that, among Xolair users, patients with a history of anaphylaxis to foods, medications, or other causes (b) (4) were at increased risk of anaphylaxis associated with ~~to~~ Xolair, compared to those with no prior history of anaphylaxis [see *Adverse Reactions* (6.1)].

In postmarketing spontaneous reports, the frequency of anaphylaxis attributed to Xolair use was estimated to be at least 0.2% of patients based on an estimated exposure of about 57,300 patients from June 2003 through December 2006. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond one year after beginning regularly scheduled treatment.

Administer Xolair only in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening. Observe patients closely for an appropriate period of time after administration of Xolair, taking into account the time to onset of anaphylaxis seen in premarketing clinical trials and postmarketing spontaneous reports [see *Adverse Reactions* (6)]. Inform patients of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs or symptoms occur.

Discontinue Xolair in patients who experience a severe hypersensitivity reaction [see *Contraindications* (4)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Anaphylaxis Case Control Study

A retrospective case-control study investigated risk factors for anaphylaxis to Xolair among patients treated with Xolair for asthma. Cases with an adjudicated history of anaphylaxis to Xolair were compared to controls with no such history. The study found that a self-reported history of anaphylaxis to foods, medications or other causes was more common among patients with Xolair anaphylaxis (57% of 30 cases) compared to controls (23% of 88 controls) [OR 8.1, 95% CI 2.7 to 24.3]. Because this is a case control study, the study cannot provide the incidence of anaphylaxis among Xolair users. From other sources, anaphylaxis to Xolair was observed in 0.1% of patients in clinical trials and at least 0.2% of patients based upon postmarketing reports [see *Warnings and Precautions* (5.1), *Adverse Reactions (*6.3)].

(b) (4)

(b) (4)

APPROVAL & LABELING

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 the package insert and text for the 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.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes 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.

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 none of these criteria apply to your application, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated June 26, 2014, containing the final report for the following postmarketing commitment listed in the July 2, 2007, approval letter.

2722-2 To establish an observational repository of cases of severe hypersensitivity reactions associated with Omalizumab administration and appropriate control cases. This repository will be a prerequisite for the conduct of a subsequent case-controlled study that will assess the risk of severe hypersensitivity reactions associated with Omalizumab use. For each identified case, up to four control subjects will be enrolled. Data collected will include clinical histories, serum for reactive antibody tests and allergy skin test results. The repository will remain active until 30 identified cases have serum available for testing or until the repository has been active for 4 years, whichever occurs first.

We have reviewed your submission and conclude that the above commitment was fulfilled.

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 Carol F. Hill, Senior Regulatory Health Project Manager for Safety, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Sally Seymour, MD
Deputy Director for Safety
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

SALLY M SEYMOUR
12/03/2015