



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 103792/5175

Genentech, Incorporated
Attention: Todd Rich, M.D.
Senior Director, Regulatory Affairs
1 DNA Way, MS #242
South San Francisco, CA 94080-4990

JAN 18 2008

Dear Dr. Rich:

Your request to supplement your biologics license application for trastuzumab (Herceptin) to revise the indication for use as a single agent, for the adjuvant treatment of HER2-overexpressing node-negative (ER/PR negative or with one high-risk feature) or node-positive breast cancer, following multi-modality anthracycline based therapy has been approved.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

We acknowledge that the Highlights section of the package insert currently meets the half page requirement so a waiver of this requirement is not needed at this time.

We acknowledge your written commitments to provide additional information on ongoing studies and to conduct postmarketing studies as described in your letters of January 18, 2008, as outlined below:

Postmarketing Study Commitments subject to reporting requirements of 21 CFR 601.70.

1. To provide a final clinical study report (CSR) of the safety and efficacy of 2-years of trastuzumab treatment in Study BO16348 (HERA) in order to provide a final analysis of cardiac toxicity based on serial ejection fraction monitoring, characterizing the cumulative incidence, severity, duration and reversibility. The final study report will include the primary datasets and programs for generation of analyses; analyses will include, but not be limited to the analyses described in the statistical analysis plan. The final CSR will be submitted by December 31, 2013. If the results from the 2-year trastuzumab arm are released by the IDMC at the interim analysis, then the final CSR will be submitted by December 31, 2009.

2. To provide updated safety information of the observation and 1-year trastuzumab arms in Study BO16348 (HERA). Interim cardiac safety updates (narratives of new primary or secondary cardiac events) will be provided on an annual basis beginning in December 2008 and continuing until the time of the final CSR, which will be submitted by December 31, 2013. If the results from the 2-year trastuzumab arm are released by the IDMC at the interim analysis, then the CSR will be submitted by December 31, 2009.
3. To submit a protocol for review for a prospectively and actively enrolled pregnancy registry that will collect information assessing pregnancy complications and birth outcomes in women with breast cancer exposed to a Herceptin-containing regimen prior to conception or during pregnancy. Notice of a pregnancy registry and the telephone contact number will be included in the package insert. A proposal, including a prospective protocol for FDA review will be submitted to FDA by June 30, 2008. The registry will become active by December 31, 2008, and interim reports of all data collected will be submitted on an annual basis to FDA through December 31, 2019.
4. To conduct a QT protocol according to the principles of ICH E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (Section IID) in a minimum of 50 subjects receiving trastuzumab. A detailed protocol for this study will be submitted by September 30, 2008. The study will be initiated by March 31, 2009, and will be completed by 31 March, 2013. A final study report will be submitted by September 30, 2013. A supplement with revised labeling, if applicable, will be submitted by March 31, 2014.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 103792. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA STN BL 103792. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- Postmarketing Study Commitment Protocol
- Postmarketing Study Commitment - Final Study Report
- Postmarketing Study Correspondence
- Annual Status Report of Postmarketing Study Commitments

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and

- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (<http://www.fda.gov/cder/pmc/default.htm>). Please refer to the February 2006 Guidance for Industry: Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see <http://www.fda.gov/cder/guidance/5569fnl.htm>) for further information.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "Product Correspondence – Final SPL for approved STN BL 103792/5175." In addition, within 21 days of the date of this letter, amend any pending supplement(s) for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

You may submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Amundson Road, Beltsville, MD 20705-1266. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

This information will be included in your biologics license application file.

Sincerely,



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

Enclosure: Package Insert Labeling