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RESEARCH**

APPLICATION NUMBER:

125427Orig1s000

APPROVAL LETTER



BLA 125427/0

BLA APPROVAL

Genentech, Inc.
Attention: Erica J. Evans, Ph.D.
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Evans:

Please refer to your Biologics License Application (BLA) dated August 24, 2012, received August 27, 2012, submitted under section 351(a) of the Public Health Service Act for Kadcyła (ado-trastuzumab emtansine).

We acknowledge receipt of your amendments dated June 12, and 25; July 11 and 31; August 24, and 27; September 12, 18(2), 21, 25(2), 26(2), and 28(2); October 8(2), 9(2), 11(2), 17(2), 18(2), 23(2), 24, 25, 29, 30, and 31; November 1, 2(3), 5, 6, 8(2), 12(3), 13(3), 14(2), 16, 20(2), 26, and 30(2); December 5(2), 6, 7(6), 13, 14, 19, 20, 21(2) and January 2, 3, 4, 7, 11, 15(2), 17(2), 18, 22, 23, 24,(3), 25(3), 28(2), 30(2) and February 5, 6, 7, 8, 12, and 15, 2013.

LICENSING

We have approved your BLA for Kadcyła (ado-trastuzumab emtansine) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Kadcyła (ado-trastuzumab emtansine) under your existing Department of Health and Human Services U.S. License No. 1048. Kadcyła (ado-trastuzumab emtansine) is indicated, as a single agent, for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture ado-trastuzumab emtansine bulk drug substance at [REDACTED] ^{(b) (4)}, and ado-trastuzumab emtansine final drug product at [REDACTED] ^{(b) (4)}. Drug product labeling and packaging will be done at Genentech Hillsboro Fill Finish Facility in Hillsboro, Oregon.

You may label your product with the proprietary name, Kadcyła, and will market it as a lyophilized product in two single-use presentations of 100 mg per 15 mL vial and 160 mg per 20 mL vial.

Trastuzumab intermediate will be manufactured at Genentech, Inc., Vacaville, CA and Roche Singapore Technical Operations Pte. Ltd, Singapore. DM1 intermediate will be manufactured at [REDACTED] (b) (4).

DATING PERIOD

The dating period for ado-trastuzumab emtansine drug product (160 mg/vial) shall be 36 months from the date of manufacture when stored at 2°C to 8°C. The dating period for ado-trastuzumab emtansine drug product (100 mg/vial) shall be 24 months from the date of manufacture when stored at 2°C to 8°C. The date of manufacture shall be defined as the date of [REDACTED] (b) (4) the formulated drug product. The dating period for your trastuzumab intermediate shall be [REDACTED] (b) (4). The dating period for your ado-trastuzumab emtansine drug substance shall be [REDACTED] (b) (4).

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of the drug substance and drug product under 21 CFR 601.12. Data supporting extension of the expiration dating period should be submitted to the BLA Annual Report.

Consistent with 21 CFR 601.12, Genentech must inform FDA about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved application.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of ado-trastuzumab emtansine 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 Kadcyla (ado-trastuzumab emtansine), 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.

We note that your February 13, 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, text for the patient package insert, Medication Guide). 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.

In addition, within 14 days of the date of this letter, amend any pending supplement that includes labeling changes for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your January 30, 2013, submission containing final printed carton and container labels.

ADVISORY COMMITTEE

Your application for Kadcyla (ado-trastuzumab emtansine) was not referred to an FDA advisory committee because outside expertise was not necessary; 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.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. Breast cancer is on the list of conditions that do not occur in pediatric patients and qualify for a full waiver.

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.

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 signals of serious risks of embryo-fetal toxicity and of increased toxicity due to a variable antibody drug ratio and to identify unexpected serious risks of increased toxicity due to (b) (4)

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

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

1. Establish a Pregnancy Registry to collect and analyze information for 10 years on pregnancy complications and birth outcomes in women with breast cancer exposed to ado-trastuzumab-emtansine within 6 months of conception or during pregnancy. Submit yearly interim reports, which may be included in your annual reports, on the cumulative findings and analyses from the Pregnancy Registry.

The timetable you submitted on February 15, 2013, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/13
Final Protocol Submission:	05/13
Interim Report #1:	05/14
Interim Report #2:	05/15
Interim Report #3:	05/16
Interim Report #4:	05/17
Interim Report #5:	05/18
Interim Report #6:	05/19
Interim Report #7:	05/20
Interim Report #8:	05/21
Interim Report #9:	05/22
Study Completion:	05/23
Final Report Submission:	05/24

2. Perform a multivariate characterization study to support the implementation of *trans*-succinimidyl 4-(*N*-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) during manufacture of T-DM1. (b) (4)

The timetable you submitted on February 15, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 03/13
Study Completion: 05/13
Final Report Submission: 06/13

3. Develop and validate an iCIEF method to use as a drug substance and drug product regulatory method for monitoring the unconjugated antibody content and propose a specification limit for the unconjugated antibody content based on clinical and commercial batch data.

The timetable you submitted on February 15, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 05/13
Study Completion: 11/13
Final Report Submission: 12/13

4. Provide quarterly reports on the status of any (b) (4). These reports should include, at a minimum, a summary of the root cause analyses, associated corrective actions, and disposition of all affected DM1 batches. Also, provide the disposition of any potentially affected finished product batches using these affected DM1 batches. Submit an interim report documenting that the manufacturing processes have been appropriately controlled at the manufacturing facilities according to Genentech's evaluation. The interim report should include a request for follow-up inspection(s). Submit a final report with a statement concerning the follow-up performed on the (b) (4) issues during the course of the FDA inspection(s), an update on whether there have been any further instances of (b) (4), and a proposal to prevent (b) (4) managed by each site's quality system.

The timetable you submitted on February 15, 2013, states that you will conduct this study according to the following schedule:

Quarterly Report #1: 05/13
Quarterly Report #2: 08/13
Quarterly Report #3: 11/13
Quarterly Report #4: 02/14
Interim Report: 04/14

Quarterly Report #5: 05/14
Quarterly Report #6: 08/14
Quarterly Report #7: 11/14
Quarterly Report #8: 02/15
Final Report Submission: 04/15

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of increased toxicity in patients with hepatic impairment.

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

5. Conduct a clinical trial to evaluate the impact of hepatic impairment on the pharmacokinetics of Kadcyla (ado-trastuzumab emtansine), total trastuzumab, and DM1-containing catabolites. Based on the results of this trial, update the approved Kadcyla labeling with recommendations for appropriate use of Kadcyla in patients with hepatic impairment.

The timetable you submitted on February 15, 2013, states that you will conduct this trial according to the following schedule:

Trial Completion: 06/14
Final Report Submission: 06/15

Submit the protocol(s) to your IND 071072, with a cross-reference letter to this BLA. Submit all final report(s) 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 Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“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 NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

6. Transfer the methodology for validated dye ingress testing developed by Genentech to (b) (4). Conduct a study to confirm filling and crimping conditions for container closure integrity using the validated transferred dye ingress method and provide a final report in the 2014 annual report.

The timetable you submitted on February 15, 2013, states that you will conduct this study according to the following schedule:

Study Completion: 03/13
Final Report Submission: 04/14

7. Conduct a study to assess the risk of endotoxin masking (b) (4) using endotoxin spiked ado-trastuzumab emtansine drug product (b) (4). Submit a final report that includes updated specifications as a Prior Approval Supplement.

The timetable you submitted on February 15, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/13

8. If endotoxin masking is observed in the drug product (b) (4), develop an alternative method to quantitate endotoxin in the finished ado-trastuzumab emtansine drug product (b) (4) using routine production conditions. Submit a final report on any changes in the analytical methods as a Prior Approval Supplement.

The timetable you submitted on February 15, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 09/13
Final Report Submission: 12/13

9. Dedicate (b) (4) for ado-trastuzumab emtansine drug product manufacture and submit a final report of the results from sterilization validation and 3 media fill simulations as a Changes Being Effected Supplement (CBE-0).

The timetable you submitted on February 15, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/13

10. Conduct cleaning verification [REDACTED] (b) (4) until use of [REDACTED] (b) (4) is implemented and report the updated [REDACTED] (b) (4) procedures in the 2014 Annual Report.

The timetable you submitted on February 15, 2013, states that you will conduct this study according to the following schedule:

Study completion: 06/13
Final Report Submission: 04/14

11. Conduct endotoxin spiking and recovery studies [REDACTED] (b) (4)

Submit the final report as a Changes Being Effected in 30 days Supplement (CBE-30).

The timetable you submitted on February 15, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/13

12. Develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ado-trastuzumab emtansine, including procedures for accurate detection of neutralizing antibodies to ado-trastuzumab emtansine in the presence of ado-trastuzumab emtansine levels that are expected to be present in the serum or plasma at the time of patient sampling. The assay final report will be submitted as a Prior Approval Supplement by June, 2015.

The timetable you submitted on February 15, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission (Assay and Methodology) Date: 06/15

13. Reassess release and stability specifications for ado-trastuzumab emtansine drug substance and drug product through the end of February 2015. Submit the final report as a Changes Being Effected-30 Supplement (CBE-30).

The timetable you submitted on February 15, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/15

14. Provide a material compatibility assessment [REDACTED] (b) (4)

(b) (4)

Provide a toxicological risk assessment (b) (4)

If significant (b) (4) are identified during these assessments, initiate action to mitigate the source(s) of risk to product quality.

The timetable you submitted on February 15, 2013, states that you will conduct this study according to the following schedule:

Material Compatibility Assessment Completion:	04/13
(b) (4) Assessment and Toxicological Risk Assessment:	05/13
Final Report Submission:	06/13

15. Conduct ado-trastuzumab emtansine exposure-response analyses for progression-free survival, final overall survival, and safety utilizing data from trial BO25734/TDM4997 (TH3RESA). The results of the exposure-response analyses from both TH3RESA and BO21977/TDM4370g (EMILIA) will be used to determine whether a postmarketing trial is needed to optimize the dose in patients with metastatic breast cancer who have lower exposure to ado-trastuzumab emtansine conjugate at the approved dose (3.6 mg/kg q3w). Submit a final report of the exposure-response analyses based on TH3RESA and EMILIA.

The timetable you submitted on February 15, 2013, states that you will conduct this study according to the following schedule:

Trial Completion:	06/16
Final Report Submission:	12/16

Submit clinical protocols to your IND 071072 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 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-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action 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.

If you have any questions, call Lisa Skarupa, Regulatory Project Manager, at (301) 796-2219.

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
02/22/2013