DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125085/91

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

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

December 16, 2010

Re: Docket No. FDA-2010-N-0621
PROPOSAL TO WITHDRAW MARKETING APPROVAL; NOTICE OF OPPORTUNITY FOR A HEARING

Dear Dr. Rohrer:

The Food and Drug Administration (FDA or Agency) is proposing to withdraw approval of the breast cancer indication for bevacizumab (Avastin). This indication was approved on February 22, 2008, as a supplement (BL 125085/91) to your biologics license. The approval allows Genentech to label and market Avastin for use in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer.

This proposal is necessary because postmarketing trials required as a condition of this approval have failed to verify the clinical benefit.

I. Background

The Agency approved Genentech's biologics license application (BLA) 125085 for Avastin on February 26, 2004. The initial approval allowed Genentech to market Avastin for use in combination with intravenous 5-fluorouracil-based chemotherapy for the first-line treatment of patients with metastatic carcinoma of the colon and rectum. In addition to this original indication, the Agency subsequently approved the following indications for Avastin (with the submission tracking number of the efficacy supplement containing the data that served as the basis for the approval):

- As an adjunct to chemotherapy for the second-line treatment of patients with metastatic colorectal cancer (BL 125085/74, June 20, 2006)
- For first-line treatment of patients with unresectable, locally advanced, recurrent, or metastatic non-squamous, non-small cell lung cancer, in combination with carboplatin and paclitaxel (BL 125085/85, October 11, 2006)
- For the treatment of metastatic renal cell carcinoma in combination with interferon alfa (BL 125085/168, July 31, 2009)
- For the treatment of glioblastoma with progressive disease following prior therapy as a single agent (BL 125085/169, May 5, 2009) under accelerated approval
- For use in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer (BL 125085/91, February 22, 2008) under accelerated approval

A. Basis for Approval Under 21 CFR 601.41

We granted marketing approval for Avastin's breast cancer and glioblastoma indications under our regulations governing accelerated approval of biological products, 21 CFR 601.40 through 46 (part 601, subpart E). These regulations, specifically § 601.41, allow FDA to grant marketing approval for biological products intended to treat serious or life-threatening conditions based on clinical trials showing an effect on a clinical endpoint other than survival or irreversible morbidity.

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Approval of Avastin's breast cancer indication was granted under § 601.41. The approval was based on evidence of longer progression-free survival (PFS) among patients receiving bevacizumab based on the results of a single randomized, open-label trial (designated E2100) comparing the safety and efficacy of paclitaxel alone or with bevacizumab. This study, which was not sponsored or conducted by Genentech, utilized a prespecified primary endpoint of PFS as determined by investigators with overall response rate and overall survival as secondary endpoints. PFS is the time from initiation of therapy until measurable growth of tumor(s) and/or death from any cause. It is primarily determined by radiographic measurement of tumor(s), and may not correlate with symptomatic improvement or improved overall survival. The supplement also contained the results of another trial, AVF2119g, which is a Genentech-sponsored, randomized, open-label trial of capecitabine with or without bevacizumab in patients with disease progression after both anthracycline- and taxane-based regimens. The AVF2119g trial failed to demonstrate statistically significant effects on PFS, based on independent review, or on overall survival.

Because of the subjective nature of the PFS endpoint and the lack of replication of the treatment effect on PFS in the AVF2119g trial, an independent radiology review committee conducted a review to confirm the interim analysis PFS results obtained by the E2100 trial investigators. The results of the independent review demonstrated a reduction in the risk of disease progression (hazard ratio (HR) 0.48) for patients receiving bevacizumab plus paclitaxel compared to paclitaxel alone. Although all patients experienced disease progression or death, the estimated median PFS occurred later (11.4 months) in the bevacizumab arm as compared to the control arm (5.8 months). There was no evidence that the addition of bevacizumab to paclitaxel resulted in longer overall survival.

Results from the E2100 trial were presented to the Oncologic Drugs Advisory Committee (ODAC) on December 5, 2007. The ODAC expressed concern that the E2100 trial had shortcomings in design and conduct and voted 5 to 4 against approval. FDA subsequently granted accelerated approval of the breast cancer indication based on the reported effect on PFS in the E2100 trial. This approval reflected the Agency's desire to make a potentially promising new therapy available pending confirmatory trials, consistent with the objectives of the subpart E regulations.

B. Obligation to Complete Postmarketing Trials

Section 601.41 states that approvals under this section will be subject to the requirement that the applicant study the product further "to verify and describe its clinical benefit, where there is uncertainty as to the relation . . . of the observed clinical benefit to ultimate outcome." In the case of Avastin's breast cancer indication, approval was contingent upon successful completion of the following two clinical trials and submission of efficacy supplements containing the final reports and revised labeling based on the trial results:

- Trial BO17708, "A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Bevacizumab in Combination with Docetaxel in Comparison with Docetaxel Plus Placebo as First-Line Treatment for Patients with HER2-Negative Metastatic Breast Cancer" (AVADO trial).

- Trial AVF 3694g, "A Multicenter, Phase 3, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination with Chemotherapy Regimens in Subjects with Previously Untreated Metastatic Breast Cancer" (RIBBON1 trial). Eligible patients were randomized to receive bevacizumab or placebo in combination with either an anthracycline- or taxane-based chemotherapy or in combination with capecitabine.

C. Withdrawal Provisions

As set forth in § 601.43, the Agency may withdraw approvals granted under subpart E if, among other reasons, a postmarketing clinical study fails to verify clinical benefit (§ 601.43(a)(1)), or other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use (§ 601.43(a)(6)). The Agency proposes to withdraw approval of Avastin's breast cancer indication for both of these reasons: both of the postmarketing clinical trials identified above failed to verify clinical benefit, and all available data confirm that the risk of serious adverse events associated with Avastin is significant. This information demonstrates that Avastin is not shown to be safe or effective when used for its breast cancer indication.

The addition of Avastin to docetaxel (AVADO trial) and to taxane/anthracycline-based chemotherapy or to capecitabine (RIBBON1 trial) showed a statistically significant improvement in PFS. The magnitude of the PFS

improvement, however, was not clinically meaningful. In AVADO, the addition of Avastin 15 mg/kg to docetaxel yielded a reduction in the risk of disease progression (HR 0.62) compared to docetaxel alone with a difference of 0.9 months in estimated median PFS between the two arms. In the RIBBON1 trial, the addition of Avastin 15 mg/kg to taxane/anthracycline chemotherapy yielded a reduction in the risk of disease progression (HR 0.64) compared to docetaxel alone, with a difference of 1.2 months in the estimated median PFS between the two arms. In the capecitabine cohort of the RIBBON1 trial, the addition of Avastin 15 mg/kg to capecitabine yielded a reduction in the risk of disease progression (HR 0.69) compared to docetaxel alone, with a difference of 2.9 months in the estimated median PFS between the two arms. The differences in PFS observed in these trials, as measured by the hazard ratio or median PFS differences, failed to confirm the magnitude of the PFS treatment effect observed in the E2100 trial, which was the basis for the accelerated approval.

In addition, the results of the AVADO and RIBBON1 trials are consistent with the results of the E2100 and AVF2119g trials presented to the ODAC in 2007 in that all of them demonstrate that the addition of bevacizumab does not extend survival in women with metastatic breast cancer. The addition of bevacizumab to standard chemotherapy regimens resulted in an overall increase in serious adverse events, grade 3 through 5 adverse events (serious or life-threatening events or death), and adverse events related to bevacizumab.

On July 20, 2010, the ODAC reviewed the results of the AVADO and RIBBON1 trials and voted 12 to 1 to recommend against the use of bevacizumab in combination with chemotherapy for the first-line treatment of metastatic breast cancer.

We conclude that the AVADO and RIBBON1 trials have failed to verify Avastin's clinical benefit when used in accordance with its approved breast cancer indication
(§ 601.43(a)(1)). More specifically, the AVADO and RIBBON1 trials (1) failed to confirm the magnitude of PFS improvement suggested by the E2100 trial, (2) confirmed the absence of a beneficial effect on survival, and (3) confirmed the risk profile (incidence and severity of adverse events) of bevacizumab when administered to women with metastatic breast cancer. This information changes our assessment of the relative risks and benefits associated with Avastin's use to treat metastatic breast cancer. We conclude that clinical benefit for patients is lacking, and the two trials have therefore failed to verify clinical benefit. We further conclude these trials demonstrate that Avastin is not shown to be safe or effective when used in accordance with its approved breast cancer indication (§ 601.43(a)(6)). Accordingly, we propose to withdraw approval of Avastin's breast cancer indication pursuant to § 601.43.

II. Grounds for Withdrawal Under Both the FD&C Act and Implementing Regulations

Section 506 of the Food Drug & Cosmetic Act (the FD&C Act) (21 U.S.C. 356), added to the statute with the passage of the Food and Drug Administration Modernization Act of 1997 (FDAMA), describes the accelerated approval and expedited withdrawal procedures. Under section 506(b)(2), such an approval may be subject to the requirement that the sponsor conduct appropriate postapproval studies. Section 506(b)(3) provides explicit authority for the Agency to use an expedited withdrawal procedure to withdraw approval of a product that has received an accelerated approval. Under this section, FDA can undertake an expedited withdrawal proceeding if, among other reasons, a postapproval study fails to verify clinical benefit, or evidence demonstrates that the product is not safe or effective under its conditions of use. This provision allows the Agency to withdraw approval using expedited procedures as described in FDA regulations.

FDA's implementing regulations at 21 CFR part 601, subpart E, describe the procedures for accelerated approval and expedited withdrawal of biological products for serious or life-threatening illnesses. They provide that FDA may grant marketing approval "on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity." When an approval is issued under the accelerated approval mechanism described in subpart E of the regulations, approval is based on a weighing of the clinical benefit suggested by and expected based on the existing data against known and potential risks of the product. As a condition of such approval, the application holder is required to submit additional postapproval clinical studies that verify and describe the clinical benefit.

If a meaningful clinical benefit cannot be verified, the risk/benefit assessment that supported initial approval of the product changes significantly, and FDA may conclude that the product no longer meets the safety and efficacy requirements for continued marketing. When this occurs, expedited withdrawal is generally in the public interest. Accordingly, the regulations provide that FDA may withdraw an approval issued under subpart E when "[a] postmarketing clinical study fails to verify clinical benefit[,]" or "[o]ther evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use" (§ 601.43(a)(1) and (a)(6)).

The postapproval clinical trials required to support continued approval of Avastin's breast cancer indication have failed to verify and describe Avastin's clinical benefit for this indication. Accordingly, we are hereby notifying Genentech, pursuant to section 506 of the Act and under § 601.43(a)(1) and (a)(6) of our regulations, that FDA's Center for Drug Evaluation and Research (CDER) is proposing to withdraw the approval of BL 125085/91. We are hereby notifying Genentech of an opportunity for a hearing on the withdrawal of BL 125085/91.

III. Notice of Opportunity for a Hearing and Submission of Written Comments

In accordance with § 601.43(b), the Director of CDER hereby provides Genentech with notice of an opportunity for a hearing on CDER's proposal to withdraw approval of BL 125085/91, the grounds for which are described in section II of this letter. Genentech may file a written request for a hearing within 15 days of receipt of this letter. If Genentech fails to file a written request for a hearing within 15 days, Genentech will thereby waive its opportunity for a hearing (§ 601.43(c)(2)). The failure of an applicant to file a timely request for a hearing constitutes an election by that applicant not to avail itself of the opportunity to request a hearing concerning the action proposed and constitutes a waiver of any contentions concerning the legal status of that applicant's drug product. If the hearing process is waived, then FDA may proceed to withdraw approval of the affected application and to take other appropriate action. Any biological product marketed outside the scope of an approved BLA or an approved new drug application (NDA) is subject to regulatory action at any time.

If Genentech files a timely request for a hearing, the company must, within 30 days of receipt of this letter, submit data, information, and analyses to demonstrate that there is a genuine and substantial issue of material fact that requires a hearing. A request for a hearing may not rest upon mere allegations or denials, but must present specific facts showing that there is a genuine and substantial issue of material fact that requires a hearing. If it conclusively appears on the face of the data, information, and analyses submitted that there is no genuine and substantial issue of material fact, or if the required data, information, and analyses are not provided, the hearing request will not be granted. If a hearing is granted, it will be conducted according to the procedures outlined in part 15 of FDA regulations (21 CFR part 15), as modified by § 601.43(e), and the Commissioner's decision will constitute final Agency action subject to judicial review
(§ 601.43(f)).

If you choose to make a paper submission under this notice of opportunity for a hearing, it must be filed in four copies. Please submit written requests for a hearing; any data, information, and analyses justifying a hearing; and any other comments identified with Docket No. FDA-2010-N-0621 to:

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

If you choose to make an electronic submission, please submit any requests for a hearing; any data, information, and analyses justifying a hearing; and any other comments identified with Docket No. FDA-2010-N-0621 to *http://www.regulations.gov*.

Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, submissions may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and on the Internet at *http://www.regulations.gov*.

IV. Authority and Contact Information

This notice is issued under § 601.43(b) and under authority delegated to the Director of CDER at FDA. If you have questions regarding this notice, please contac

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research