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April 8, 2011

BY EMAIL AND U.S. MAIL

Karen Midthun, M.D.
Presiding Officer
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20854

Re: Docket No. FDA-2010-N-0621; Avastin®

Dear Dr. Midthun:

I am writing on behalf of Genentech, Inc. ("Genentech") in response to your February 23, 2011 letter requesting, in part, a joint statement by the Center for Drug Evaluation and Research ("CDER") and Genentech of those issues that are disputed in the matter referenced above. As noted in the parties' April 7, 2011 Joint Statement of Undisputed Facts and Select Issues, CDER and Genentech did not reach full agreement on how to characterize the issues to be addressed in this matter. Accordingly, CDER and Genentech indicated that they would submit separate supplemental documents summarizing each party's understanding of the central questions to be resolved.

We see the core issue presented in this proceeding as whether FDA should maintain or withdraw the accelerated approval of Avastin for use with paclitaxel to treat first-line HER2-negative metastatic breast cancer ("MBC"), subject to Genentech's conduct of a new confirmatory study of Avastin with paclitaxel. The accelerated approval provisions of the Federal Food, Drug, and Cosmetic Act and FDA regulations provide that FDA *may* withdraw an accelerated approval if a postmarketing study fails to verify clinical benefit.[1] The ultimate question here is whether FDA *should* withdraw approval of Avastin's MBC indication in light of the facts presented. In particular, the question is whether FDA should withdraw approval when the studies consistently show an efficacy benefit, the benefit is

[1] Federal Food, Drug, and Cosmetic Act § 506(b)(3); 21 C.F.R. § 601.43(a).

greatest when Avastin is combined with paclitaxel, and it is agreed that the safety profile is well-characterized with no new safety signals in the subsequent MBC studies.

To answer this question, we believe FDA should consider whether the data supporting Avastin in combination with paclitaxel continue to meet the standard for accelerated approval. This inquiry includes the proper interpretation of the efficacy data on Avastin in first-line MBC with paclitaxel versus with other chemotherapy agents and how to evaluate the benefit-risk profile of Avastin relative to comparable therapeutic options. It is also important to consider whether withdrawal here would be consistent with other pertinent FDA approval and withdrawal actions. Whereas these questions turn on science, law, and public health policy, we believe their ultimate resolution should be based on what is in the best interests of MBC patients.

Genentech would enumerate the specific questions to be presented at the hearing as follows:

1. Does the benefit-risk profile of Avastin in combination with paclitaxel for first-line metastatic breast cancer support maintaining the availability of Avastin with paclitaxel as an approved treatment option for physicians and patients to elect based on appropriate prescribing information?

2. Do the data supporting Avastin plus paclitaxel continue to meet the standard for accelerated approval because they establish a reasonable likelihood of clinical benefit with the paclitaxel combination and can be characterized further through an additional study?

3. Do the observed differences in PFS results in the E2100, AVADO, and RIBBON1 studies suggest that the choice of chemotherapy partner may be important in the efficacy of Avastin?

4. Is withdrawal of Avastin's metastatic breast cancer indication consistent with FDA's approval of other treatments for first-line metastatic breast cancer?

5. Is withdrawal of Avastin's metastatic breast cancer indication consistent with available precedent from the withdrawal of other products under FDA's accelerated approval program?

6. Are FDA's actions on Avastin likely to facilitate or deter the future development of treatments for first-line metastatic breast cancer?

* * *

Thank you for your consideration of this submission.

Respectfully submitted,

Michael S. Labson

Covington & Burling LLP
Counsel for Genentech, Inc.

cc: Donald Beers, Office of the Chief Counsel, Food and Drug Administration
Laurie Lenkel, Office of the Ombudsman, Food and Drug Administration
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