DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

December 16, 2010

Dear Breast Cancer Community:

I am writing to explain why and how FDA made today's decision to request removal of the metastatic breast cancer indication for Avastin (bevacizumab). I also wanted to tell you about the next steps in this process so that you can stay involved.

I assure you that we understand how hard it is to cope with breast cancer – especially metastatic breast cancer. We know that there are not enough effective treatments for this cancer. We also know that many patients are willing to accept the risk of serious side effects if there is a chance that a drug might help them live longer. FDA includes this acceptance of risk in the drug review assessment.

But even with these considerations, we are required by law to approve a drug for a use only if the drug's benefits are shown to outweigh its risks. Additional studies of Avastin in metastatic breast cancer failed to meet this standard. In these studies, Avastin did not help patients live longer. At the same time, the rate of severe or life-threatening side effects was 14-20% higher in patients who were on Avastin plus chemotherapy as compared to patients on chemotherapy alone. Also, no direct patient benefit was shown. Based upon these results, the benefit of treatment with Avastin did not outweigh its risks. While it has been reported to us that some individual patients have benefited, without a test to select likely responders, there is no way to identify a group for whom benefits outweigh the risks. These results formed the scientific basis for our decision today. Lowering the approval standard for this drug would undermine efforts to keep more effective and safer drugs available for patients.

Many patients with breast cancer, patient advocacy organizations, and health professionals have expressed varying opinions about Avastin. Some patients were concerned that our decision would be affected by factors other than science – including issues of cost and reimbursement. FDA regulations specifically prohibit us from taking cost and reimbursement into account when approving or withdrawing a drug. I want to assure you that our decision was based solely on the scientific risk/benefit analysis and on the best treatment options for patients.

What scientific evidence did FDA rely on to make its recommendation? FDA worked closely with Genentech, the manufacturer of Avastin, throughout the regulatory process for the drug's use in metastatic breast cancer. Avastin's use in metastatic breast cancer was first publicly discussed at a 2007 Oncologic Drugs Advisory Committee Meeting (ODAC). Committee members included independent experts in the field of oncology, as well as a patient, a consumer, and an industry representative. ODAC was asked whether Avastin should be given accelerated approval, a mechanism which allows a product to be marketed temporarily, on the basis of promising early results from clinical trial E2100. In trial E2100, patients with HER2-negative breast cancer on Avastin and chemotherapy did not have an improvement in overall survival (OS), which is considered the gold standard for cancer drug approval. But, patients did have evidence of delayed tumor growth on x-rays, known as progression-free survival (PFS). ODAC voted 5 to 4 against accelerated approval for metastatic breast cancer. At that time, FDA went against the advice of ODAC and granted accelerated approval based on the early findings of an improvement in PFS, with the provision that Genentech provide additional data to confirm and describe Avastin's clinical benefit. Provision of additional data is a condition of accelerated approval. FDA was hopeful that the confirmatory studies of Avastin in combination with chemotherapy would show it prolonged the life of patients with this fatal disease.

We discussed Avastin again with ODAC on July 20, 2010. Genentech showed data from two recent studies (AVADO and RIBBON1) intended to support changing the accelerated approval to a regular approval. The study results indicated that:

- Adding Avastin to chemotherapy did not prolong the lives of women with breast cancer (OS).
- Adding Avastin to chemotherapy resulted in a temporary and shorter than expected delay in tumor growth as seen on x-rays (PFS). The delay was much shorter than seen in the earlier trial (E2100) that led to accelerated approval.

Based upon those trials, ODAC unanimously recommended against changing the accelerated approval to a regular approval. ODAC also recommended, by a vote of 12 to 1, that FDA remove the indication for use in metastatic breast cancer. The Committee said the data did not show a meaningful survival benefit to patients and, further, exposed them to dangerous toxicities. You can read more about the July 20, 2010, ODAC meeting here.

After listening to the advice from ODAC and reviewing all of the data submitted for Avastin, FDA had to determine whether the benefits of Avastin outweighed the risks. A consistent finding across all three trials was the chance of suffering serious side effects that are unique to Avastin, as well as a greater chance of suffering serious side effects from chemotherapy, when Avastin was added to chemotherapy. Side effects observed included kidney damage, development of holes in parts of the body (for example, nose, stomach, intestines), massive bleeding requiring blood transfusions, and various cardiovascular problems (for example, heart attack, stroke, clotting in arteries, chest pain, and reduced blood flow to the brain).

Taking into consideration all of the information from these three clinical studies, FDA concluded that the serious risks outweigh the limited benefits for treatment of patients with metastatic breast cancer.

You can read a more in-depth discussion of the scientific information on Avastin in the published Decision Memo located on FDA's Avastin web page here. The web page contains several additional resources and provides instructions if you are interested in commenting on this action.

What does this recommendation mean for you? Until a final decision is made, the indication for metastatic breast cancer will remain. Avastin will continue to be available to patients with breast cancer. This recommendation does not affect Avastin's other approved indications to treat advanced colon, lung, kidney, and brain cancers. As long as Avastin is on the market, the law allows doctors to prescribe it for any use – even if the use is not formally FDA-approved. A patient and her physician or prescriber, working together, should decide on the right treatment. We respect this process and a doctor's professional judgment about a patient's needs.

What are the next steps? FDA started the process of removing Avastin's metastatic breast cancer indication by issuing a formal announcement today called a Notice of Opportunity for a Hearing. This hearing gives Genentech the chance to defend the breast cancer use approval. A final decision about the breast cancer indication will not be made until after the hearing. In addition, FDA remains open to proposals for additional clinical studies of Avastin in breast cancer to identify and confirm a specific group of women for whom the drug may be effective. Such studies could lead to a new indication for Avastin in breast cancer.

I want to assure everyone that FDA remains committed to working with pharmaceutical companies to facilitate the development and availability of safe and effective treatment options for patients with breast cancer. Ultimately, the goal of drug development is to make meaningful progress towards finding cures and saving patients' lives while minimizing toxicities and protecting the quality of their lives.

Sincerely,

/S/

Janet Woodcock, M.D.