DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable Fortney Pete Stark
Chairman
Subcommittee on Health
Committee on Ways and Means
House of Representatives
Washington, D.C. 20515-6143

OCT 12 2007

Dear Mr. Chairman:

Thank you for your letter of October 2, 2007, co-signed by Representative Henry A. Waxman, Chairman, Committee on Oversight and Government Reform, regarding erythropoiesis-stimulating agents (ESAs) in the treatment of anemia for use in patients with certain cancers.

We have restated your questions in bold followed by our answers.

1. What are the health risks associated with use of ESAs for cancer patients?

Health risks associated with the use of ESAs for cancer patients include:

- *Promotion of tumor growth and decreased survival* – ESAs shortened overall survival and/or time-to-tumor progression in clinical studies in patients with advanced breast, head and neck, lymphoid, and non-small cell lung malignancies. These studies administered ESAs to target a hemoglobin of > 12 g/dL; the risks of tumor promotion and shortened survival have not been excluded with lower target hemoglobin levels.
- *Increased Mortality and Cardiovascular Events* – an increased incidence of thrombotic events (e.g. heart attack, stroke, heart failure, blood clots, death) has been observed in clinical trials in patients with chronic renal failure, cancer patients on chemotherapy, and surgical candidates.
- *Pure Red Cell Aplasia* – a potential risk of rare anti-ESA antibody-associated anemia.

2a. What is FDA's assessment of the risks and benefits of ESA use for cancer patients?

See response to Question 3.

2b. Are there benefits in terms of quality of life or better tumor outcomes associated with higher hemoglobin levels?

No. There is no evidence that ESAs result in improved survival, tumor control, health-related quality of life at any hemoglobin level in cancer patients undergoing chemotherapy. Indeed, studies targeting higher hemoglobin levels have shown adverse effects as noted in response to Question 1. ESAs were approved based on their effectiveness in reducing the need for red blood cell transfusions in cancer patients undergoing concomitant chemotherapy.

3. Can you explain the FDA label's recommendation for ESA use for cancer patients?

The labeling of epoetin alfa and darbepoetin alfa are based on results of studies that have been submitted to and reviewed by the Food and Drug Administration (FDA). These studies included randomized controlled studies demonstrating a reduction in need for red blood cell transfusion in patients undergoing chemotherapy. The ESA labeling was updated in March 2007, to include a boxed warning and the results of studies showing the new safety information described in response to Question 1. Specifically, several studies targeting higher hemoglobin levels have recently shown more deaths and faster tumor growth.

FDA's approved labeling for ESAs in cancer patients undergoing chemotherapy recommends use of the lowest dose necessary to avoid the need for blood transfusions. This recommendation is based on the evidence of serious safety concerns with ESAs observed in controlled clinical trials while recognizing the role these agents may play in some patients as part of the supportive care regimen to avoid blood transfusions in patients with cancer undergoing chemotherapy. The current labeling advises that the hemoglobin not exceed 12 g/dl in cancer patients. FDA considers this to be an upper safety limit for ESA dosing, not a target for the therapy. FDA is aware that there has been some confusion about the dosing recommendations in the current approved labeling and will work to clarify that confusion as we complete labeling changes that we are currently discussing with Amgen in follow-up to the May 2007 Oncology Drugs Advisory Committee (ODAC) meeting.

4a. Does the CMS NCD conflict with the FDA label for dosing of ESAs in treating cancer patients?

FDA believes that the approved labeling and the Centers for Medicaid and Medicare Service (CMS) National Coverage Decision (NCD) are generally consistent in their recommendations regarding the use of ESAs in patients with cancer undergoing chemotherapy. As noted above, FDA's approved labeling recommends use of the lowest dose necessary to avoid the need for blood transfusions and transfusions are not normally given to patients whose hemoglobin is 10 g/dl or higher. Also, as noted above, the recommendation in the approved labeling that the hemoglobin not exceed 12 g/dl in cancer patients is intended as an upper safety limit, not a target for therapy.

4b. Is the NCD consistent with the scientific literature on this issue?

Yes, FDA believes that the NCD is generally consistent with the available data and the published scientific literature.

Thank you for your interest in this matter. If you have further questions, please let us know. A similar letter has been sent to Chairman Waxman.

Sincerely,

Stephen R. Mason
Acting Assistant Commissioner
for Legislation