

February 27, 2008

Oncology Drug Advisory Committee
Food and Drug Administration
Via email to Nicole Vesely, Pharm.D. nicole.vesely@fda.hhs.gov

These comments are submitted on behalf of C3: Colorectal Cancer Coalition (C3), a non-profit, nonpartisan advocacy organization that is committed to the fight against colon and rectal cancer. We appreciate the opportunity to comment on the Food and Drug Administration (FDA) Oncology Drug Advisory Committee (ODAC) consideration of Erythropoiesis Stimulating Agents (ESAs) for non-renal disease applications.

C3 pushes for research to improve screening, diagnosis, and treatment of colorectal cancer; for policy decisions that make the most effective colorectal cancer prevention and treatment available to all; and for increased awareness that colorectal cancer is preventable, treatable, and beatable. C3 believes in fully disclosing sources of financial support, per our disclosure policy which can be viewed at www.FightColorectalCancer.org/funding.htm. In 2006 and 2007, C3 received funding from Amgen in the form of a charitable donation. Since the May 2007 Oncology Drug Advisory Committee (ODAC) meeting, C3 has met with Amgen and Johnson & Johnson (J&J) to increase our understanding of these issues and express our concerns. J&J held a meeting on February 19, 2008 in Washington, DC, and paid the travel expenses of a C3 Board member so that she could attend the meeting.

Neither these companies nor any of our other corporate supporters have influenced our comments on this issue.

As oncology patient advocates we are used to looking at complex risk/benefit situations, but in this case, there are an inordinate number of frustrating and concerning issues:

- There is a systemic inability to find and pull together all of the relevant data – who has it, who owns it, who can see it?
- The possibility exists that a supportive care drug could actually cause a patient's cancer to grow faster, and increase mortality.
- There is mistrust of the manufacturers and the oncology professional associations due to their large financial conflicts of interest.
- Leadership is unclear. Whose job is it to look out for the patient? Who can and will take charge of this situation and bring it to a quick resolution?
- There is a perceived lack of progress. ESAs have been on the market for many years, billions of dollars have been spent by insurers, millions of patients have been treated, and yet we still have many of the same unanswered questions we had at the 2004 ODAC.

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After reviewing the publicly-available information, we have more questions than answers. These can be grouped into three areas:

1. What is the plan for answering the question of whether ESAs have a tumor-promoting effect?
2. What is the plan for answering the question of whether ESAs provide patient benefit when dosed according to the FDA label?
3. What is the appropriate clinical use of ESAs pending the answers to these questions?

We also hope that lessons learned from the past will be applied to future trials. A search of clinicaltrials.gov shows that 382 trials have been or are being conducted looking at epoetin alfa or darbepoetin alfa. Approximately 115 trials can be identified as occurring in oncology. These 115 trials intended to enroll over 30,000 patients, although an unknown number of trials were terminated early due to poor accrual. Our understanding is that most of these trials were conducted at higher doses than are currently acceptable, which limits the applicability of data to situations involving a lower dose. In discussions with the manufacturers, we learned that FDA has not had easy access to data generated overseas or data generated by independent investigators. We have also learned that a comprehensive list of all ESA trials does not seem to exist. We urge FDA to work closely with the manufacturers to ensure that future trial designs and locations result in accessible, meaningful data.

1. What is the plan for answering the question of whether ESAs have a tumor-promoting effect?

The possibility that ESAs may have a tumor-promoting effect is frightening. We urge FDA and the manufacturers to focus not only on the possible presence of erythropoietin receptors (EpoR) on cancer cells, but also areas such as:

- Cancer cell proliferation or growth due to EpoR signaling;
- Cancer cell resistance to chemotherapy due to EpoR signaling; and
- Tumor microenvironment changes due to promotion of angiogenesis.

Is there a plan in place to review all existing information and the areas where new research is going forward? Who is responsible for execution of the plan? Where will the results be published? The December 2007 National Cancer Institute meeting provided a platform for such a discussion; however, the results of the meeting have not yet been made public, and we are not aware of follow-up plans. In order to generate confidence in the quality of research being done, meetings such as this should be open to the public and provide timely communication of progress. We feel strongly that the ESA issue needs to be laid out clearly, in a public way.

2. What is the plan for answering the question of whether ESAs provide patient benefit when dosed according to the FDA label?

In a meeting with Amgen, we were told that a phase III trial was being designed to answer the question of whether ESAs provide patient benefit when dosed according to the current label (November 2007 version). As described to us, the trial will enroll

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6000+ lung, breast and colorectal cancer patients over eight years in an international setting.

We have many questions and concerns about this trial:

- Will trial sites be overseas, in the US or both?
 - If overseas, what changes will be made to ensure that the data will be easily accessible to FDA?
 - The risks associated with blood transfusion vary widely throughout the world; how will that risk be leveled across all trial sites?
- Will the trial accrue?
 - Will patients and physicians be willing to participate?
 - Supportive care trials are historically difficult to accrue; for example, the current EPO-ANE-3010 trial is accruing slowly. What changes are being made to ensure that this trial will actually accrue on schedule?
- Will the results be meaningful?
 - Can results in three disease sites (breast, colorectal and lung) be extrapolated to the 200+ forms of cancer?

There is an old quote that says, *“Insanity is doing the same thing over and over, and expecting different results.”* We are concerned that this phase III trial proposal is ‘the same thing’, and that after eight years of waiting, we will end up where we are today, without a definitive answer to our questions. Again, we feel strongly that the clinical research plan must be laid out clearly and publicly.

3. What is the appropriate clinical use of ESAs pending the answers to these questions?

The goal of every clinical intervention is increasing patient benefit while decreasing patient risk. J&J presented an overview of their RiskMAP program. As described, the program minimizes the risk of thrombovascular events by reducing exposure of patients to ESAs, especially patients with high risk of thrombovascular events. A key component of the program is the patient medication guide, which will help patients and physicians have a full discussion of the risks and benefits of ESA use.

We feel that this is a good start; however, we are not sure that patients and doctors will actually interact as planned. Many ODAC appointees are practicing oncologists, and have colleagues who practice in academic and community settings. Do you feel that community oncologists will have the time to spend reviewing this information with patients – people who are already ill and dealing with side effects of treatment?

In addition, we wonder if FDA could provide additional guidance about use in specific disease sites where risk is elevated above an acceptable level, or about concomitant medications which increase risk of thrombovascular events, such as bevacizumab.

Finally, we urge FDA and the manufacturers to consider capturing data from the ongoing use of ESAs through a patient registry.

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One Alternative: Patient Registry

We feel that development of a patient registry to evaluate use of ESAs when patients are dosed according to the current FDA label could provide great value. There is precedent for such a registry:

- FDA implemented a patient registry and informed consent process for drugs such as thalidomide and natalizumab through the Special Restricted Distribution Program.
- CMS has used patient registries to evaluate use of devices such as the implantable cardioverter defibrillator and diagnostic use of PET scans for a variety of cancers.

We understand that designing such a registry would be complex, and that multiple barriers would need to be overcome. At the same time, we feel that a registry such as this could provide more robust data across all tumor types, perhaps even in a more timely way.

We greatly appreciate the opportunity to comment on the critical issues in front of ODAC and FDA, and look forward to listening to your discussion on March 13. Thank you very much for your consideration of our comments.

Sincerely,



Carlea Bauman, President
C3: Colorectal Cancer Coalition