

March 13, 2008
Oncologic Drugs Advisory Committee Meeting
Background Information and Questions to the Committee

Current Oncology Indications:

Procrit (epoetin alfa) is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.

Aranesp (darbepoetin alfa) is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.

The basis for approval of both Procrit and ARANESP® was a reduction in proportion of patients on chemotherapy receiving red blood cell transfusions.

This is the third ODAC convened by FDA since the 1993 approval of Procrit for the treatment of chemotherapy-induced anemia. The first ODAC was held in May 2004 to discuss adverse findings of increased tumor promotion and/or decreased survival in patients receiving ESAs in the ENHANCE (head and neck cancer) and BEST (breast cancer) trials. Further trial information led to a second ODAC in May 2007 when information from four additional trials [CAN-20 (non-small cell lung cancer), 2001-0103 (anemia of cancer; heterogeneous malignancies), 2000-0161 (lymphoid malignancies), DAHANCA (head and neck cancer)] showed increased tumor promotion and/or decreased survival in patients receiving ESAs. This ODAC meeting has been convened to review the results of two additional trials (GOG-191 and PREPARE) and progress made on addressing the risks of ESAs since the 2007 ODAC, in order to provide advice on Amgen's and FDA's proposed risk mitigation strategies.

Eight controlled clinical studies provide evidence of increased mortality and/or tumor promotion when ESAs are given to patients receiving treatment for head and neck cancer, breast cancer, non-small cell lung cancer, or cervical cancer and in anemic cancer patients receiving no active anti-cancer therapy. This information was not available when Procrit and Aranesp were granted marketing authorization for the treatment of anemia in cancer patients receiving chemotherapy. There have been dozens of studies conducted over the past 15 years in which patients were randomized to ESA or no ESA, only one study was designed to detect or exclude whether tumor growth promotion was present (N93-004) and this study was terminated prematurely. The results of eight randomized studies with evidence of tumor promotion or increased mortality, based on a balance of probabilities, suggest a tightly linked association. FDA has placed less weight on the absence of safety signals in other randomized studies, many of which are confounded by small sample sizes, limited data collection, limited duration of follow-up, or ESA use in the control arm at the investigator's discretion. FDA finds that these additional studies

do not negate the evidence of harmful effects demonstrated in the eight randomized studies described in product labeling.

Currently, there is a need to re-assess the risk/benefit ratio for the use of ESAs in patients with cancer and whether continued marketing authorization is indicated. If marketing authorization for this indication continues, additional measures, including labeling restrictions and other strategies for risk management may be necessary to ensure safe use.

FDA requests that the Committee discuss whether the Amgen proposed risk minimization strategy is sufficient or if additional measures should also be implemented as posed in the questions to the committee.

Questions to the Committee

To obtain marketing approval for a new drug or biologic product, an applicant must demonstrate that the product is safe and effective, when administered in accordance with product labeling. Specifically, there must be substantial evidence of clinical benefit (efficacy) demonstrated in adequate and well-controlled clinical trials and FDA must find that the risks of the product do not outweigh the benefits. The key issues we would like you to discuss are whether available data continue to demonstrate that there is a favorable benefit to risk relationship for ESA use for treatment of chemotherapy-induced anemia in patients with cancer and if so, whether the current product labeling is sufficient to ensure safe and effective use.

1. Considering all the available data on the benefit and risks of ESAs in the treatment of anemia due to concomitant cancer chemotherapy, do you recommend that these products continue to be marketed for the indications listed above? *YES or NO*
2. If you recommend that the current indication should be retained, should FDA require that product labeling be modified? Below are four potential approaches to mitigating risks through revised labeling. Please address each of them separately.
 - a. **Note:** To date, only clinical trials in small cell lung cancer have reasonably excluded an increased risk for death among patients receiving ESAs. Trials have demonstrated an increased risk of death and/or tumor promotion in head/neck, non-small cell lung cancer, breast (neoadjuvant and metastatic settings), lymphoid malignancies, and cervical cancers. Tumor types, other than those listed above, have not been adequately studied. ***Should the current indication be modified to restrict use only to patients with small cell lung cancer? YES or NO***
 - b. **Note:** The PREPARE trial demonstrated decreased relapse-free and overall survival in breast cancer patients receiving neoadjuvant chemotherapy. The risk/benefit assessment is different for patients receiving neoadjuvant and

- adjuvant chemotherapies than for patients with metastatic or incurable cancers. ***Should the current indication be modified to include a statement that ESA use is not indicated for patients receiving potentially curative treatments? YES or NO***
- c. **Vote:** Although increased tumor promotion and/or decreased survival have been demonstrated in several tumor types, adverse findings have been duplicated in two malignancies—breast cancer and head and neck cancer. ***Should the current indication be modified to include a statement that ESA use is not indicated for patients with breast and/or head & neck cancers? YES or NO*** (If yes, please specify breast and/or head & neck cancer).
 - d. The only objective evidence of efficacy demonstrated for ESAs has been avoidance of RBC transfusions; however, not all patients with anemia require an RBC transfusion. Product labeling does not specify the hemoglobin level at which ESA treatment should be initiated. ***Assuming a patient is asymptomatic and has no co-morbid conditions, please specify the hemoglobin level at which initiation of an ESA is appropriate.***
3. If the Committee recommends that the indication for treatment of anemia due to concomitant chemotherapy should be retained (as currently approved or with additional labeling changes as above), discuss additional strategies that FDA could require to minimize risk. Below are two options that could be considered. If you have other suggestions, please state them.
- a. **Vote:** An informed consent/patient agreement would explicitly require the oncology patient's authorization or agreement to undergo treatment with an ESA. Both patient and physician (or designate) signatures would be required. In the process, the physician prescribing the ESA treatment would discuss the risks and benefits of ESA therapy and alternative treatments. ***Should the FDA require the implementation of an informed consent/patient agreement for the treatment of chemotherapy induced anemia? YES or NO***
 - b. **Vote:** Examples of restricted distribution programs include STEPS (thalidomide), RevAssist (lenalidomide), and iPLEDGE (isotretinoin). Restricted distribution systems link product access to planned safe and effective use. These programs may require identification and enrollment of healthcare providers who agree to prescribe only in accordance with product labeling and who commit to patient education regarding safe use. Registration of patients may also be required. Certain patient characteristics would be recorded at individual patient registrations (e.g., hemoglobin, chemotherapy type, malignant diagnosis). ***Should FDA mandate a restricted distribution system for oncology patients receiving ESAs? YES or NO***