

Amgen's Ongoing Commitment to the Safety of its ESA Products

At Amgen, our mission is to serve patients. It defines everything we do. The safety of erythropoiesis-stimulating agents (ESAs) in the approved indication of anemia caused by chemotherapy has been demonstrated in carefully monitored, well-controlled clinical trials, and no evidence of an increased risk of tumor promotion or shortened survival has been observed within the labeled treatment setting. Evidence from comprehensive analyses of controlled clinical trials continues to support a favorable risk/benefit of darbepoetin alfa and Epoetin alfa when administered per the label to the indicated patient population – patients with non-myeloid cancers where anemia is due to their chemotherapy.

Recent discussions related to the safety of ESAs were stimulated by the results of clinical trials that sought to document the utility of these agents when used in settings different from those outlined in the FDA approved label, e.g. targeting high hemoglobin levels in chemotherapy patients, anemia in patients not receiving chemotherapy, or radiotherapy in the absence of chemotherapy.

These experimental studies have led Amgen and Johnson & Johnson Pharmaceutical Research & Development (J&JPRD) to develop a comprehensive clinical study program designed to address outstanding questions about ESA safety. The specific tumor types evaluated in studies raising safety concerns included breast cancer, non-small cell lung cancer (NSCLC), lymphoproliferative malignancy, and head and neck cancer. To assess the safety of ESAs when used to treat chemotherapy-induced anemia in these settings, Amgen and J&JPRD have bolstered ongoing pharmacovigilance programs, which were agreed to with the FDA after the 2004 Oncologics Drugs Advisory Committee (ODAC) meeting, with a suite of new, proposed clinical trials.

The original pharmacovigilance program included both investigator-sponsored and company-sponsored studies. Six of these studies (3 in breast cancer and 1 each in small-cell lung cancer [SCLC], non-Hodgkin's lymphoma [NHL], and head and neck cancer [HNC]) became formal post-marketing commitments with FDA in 2006, and all studies that Amgen has responsibility for have either been completed or are on track for completion by the commitment date. The next available data set, the PREPARE trial in metastatic breast cancer patients, is expected later this year.

Table 1. Current ESA Postmarketing Commitment Pharmacovigilance Studies

Study Designation(s) (Sponsor/Institute)	Tumor Type
DE-2001-0033 PREPARE (AGO)	Neoadjuvant breast
DE-2002-0015 ARA 03 ARA PLUS (WSG)	Adjuvant breast
EPO-ANE-3010 (J&JPRD)	Metastatic breast
20010145 (Amgen)	Small-cell lung
FR-2003-3005 LNH 03-6B (GELA)	Non-Hodgkin's lymphoma
SE-2002-9001 DAHANCA 10 (DAHANCA)	Head and neck



Proposed New ESA Pharmacovigilance Studies

Six additional pharmacovigilance studies to address these potential safety concerns in subjects with NSCLC (2 studies) and lymphoproliferative malignancy (4 studies) are planned. Based on the safety signals observed with higher hemoglobin levels, a study to evaluate the effect of hemoglobin target on the risk/benefit profile of ESAs is also planned. These studies have been discussed in concept with FDA, and general agreement has been reached regarding the scope of the pharmacovigilance programs.

Overall, the ongoing and planned pharmacovigilance studies will result in a robust body of well-controlled data to address concerns regarding survival and tumor progression in these patient populations, including 3 studies in breast cancer, 3 studies in lung cancer (1 SCLC and 2 NSCLC), 5 studies in lymphoproliferative malignancy, 1 study in head and neck cancer, and 1 study to evaluate the effect of target hemoglobin levels.

Amgen, along with other manufacturers of ESAs, is also collaborating with the Cochrane Group to facilitate an independent, third-party, patient-level analysis using all available data from randomized controlled clinical studies of ESAs.

Amgen continues to analyze and communicate data from clinical trials, from combined study-level analyses and combined patient-level data as they become available.

In addition, Amgen has implemented a robust risk management plan to ensure that providers and patients are made aware of important new data related to ESA safety. This plan includes ongoing market-based pharmacovigilance, the formal pharmacovigilance study program, timely interactions with regulatory agencies, updates to the FDA approved label, press releases, communication with physicians via Dear Health Care Provider letters, and direct communications to patients via upcoming Medication Guides.

Based on a comprehensive analysis of the evidence in numerous preclinical and clinical studies, Amgen believes there is no definitive evidence of erythropoietin (EPO) receptor involvement in tumor progression. Amgen continues to work internally and to support the work of professional societies and other academic groups to develop workshops and symposia to address the EPO receptor topic.

Amgen will continue to work with federal regulators and the world's top experts in this area to address outstanding questions, and to assure that practicing physicians and patients have access to the latest information on the safety of ESAs so they can make informed decisions about the best use of these products.