



## IMPORTANT DRUG WARNING and NEW PRESCRIBING INFORMATION

March 12, 2007

Dear Health Care Professional:

In collaboration with the FDA, Amgen\* and Ortho Biotech\*\* have updated the safety information in the Aranesp<sup>®</sup> (darbepoetin alfa) and EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup> (Epoetin alfa) product labeling to reflect recent safety data arising from clinical studies of erythropoiesis-stimulating agents (ESAs). This information is applicable to all ESAs. Amgen and Ortho Biotech wish to advise you of important changes to the safety information for these products that include the addition of boxed warnings (see below).

### **WARNINGS: Erythropoiesis-Stimulating Agents**

**Use the lowest dose of [Aranesp<sup>®</sup>/EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup>] that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion (see **DOSAGE AND ADMINISTRATION**).**

**[Aranesp<sup>®</sup>/EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup>] and other erythropoiesis-stimulating agents (ESAs) increased the risk for death and for serious cardiovascular events when administered to target a hemoglobin of greater than 12 g/dL (see **WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events**).**

#### **Cancer Patients: Use of ESAs**

- **shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a hemoglobin of greater than 12 g/dL;**
- **shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to target a hemoglobin of greater than 12 g/dL;**
- **increased the risk of death when administered to target a hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for this population.**

**(See **WARNINGS: Increased Mortality and/or Tumor Progression**)**

**Patients receiving ESAs pre-operatively for reduction of allogeneic red blood cell transfusions: A higher incidence of deep venous thrombosis was documented in patients receiving Epoetin alfa who were not receiving prophylactic anticoagulation. Antithrombotic prophylaxis should be strongly considered when EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup> is used to reduce allogeneic red blood cell transfusions. Aranesp<sup>®</sup> is not approved for this indication (see **WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events**).**

Updated safety information as reflected in the boxed warning is applicable to all patients treated with ESAs, including Aranesp<sup>®</sup> and EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup>. The **WARNINGS** and **DOSAGE AND ADMINISTRATION** sections of the product labeling have also been updated to reflect this new safety information.

The boxed warning information reflects the following studies in the revised labels:

A recently published randomized prospective trial entitled "Correction of Hemoglobin and Outcomes in Renal Insufficiency" (CHOIR) evaluated 1432 anemic chronic renal failure patients who were not undergoing dialysis. Patients were assigned to Epoetin alfa treatment targeting a maintenance hemoglobin concentration

of 13.5 g/dL or 11.3 g/dL. A major cardiovascular event (death, myocardial infarction, stroke or hospitalization for congestive heart failure) occurred among 125 (18%) of the 715 patients in the higher hemoglobin group compared to 97 (14%) among the 717 patients in the lower hemoglobin group (HR 1.3, 95% CI: 1.0, 1.7,  $p = 0.03$ ).<sup>1</sup>

A randomized controlled clinical study, previously summarized in the label and published in 2005, entitled, "Maintaining Normal Hemoglobin Levels With Epoetin Alfa in Mainly Nonanemic Patients With Metastatic Breast Cancer Receiving First-Line Chemotherapy: A Survival Study" (BEST) evaluated 939 women with metastatic breast cancer receiving chemotherapy. Patients received either weekly Epoetin alfa or placebo for up to a year. This study was designed to show that survival was superior when Epoetin alfa was administered to prevent anemia (maintain hemoglobin levels between 12 and 14 g/dL or hematocrit between 36% and 42%). The study was terminated prematurely when interim results demonstrated that a higher mortality at 4 months (8.7% vs. 3.4%) and a higher rate of fatal thrombotic events (1.1% Epoetin alfa vs. 0.2% placebo) in the first 4 months of the study were observed among patients treated with Epoetin alfa. Based on Kaplan-Meier estimates, at the time of study termination, the 12-month survival was lower in the Epoetin alfa group than in the placebo group (70% vs. 76%; HR 1.37, 95% CI: 1.07, 1.75;  $p = 0.012$ ).<sup>2</sup> This study was previously communicated to oncologists in an Ortho Biotech Dear Health Care Professional letter dated August 13, 2004 and an Amgen Dear Health Care Professional letter dated October 25, 2004.

A recently completed phase 3, double-blind, randomized, placebo-controlled 16-week clinical study evaluated 989 patients with active malignant disease not receiving chemotherapy or radiation therapy. There was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions. In addition, there were more deaths in the darbepoetin alfa treatment group [26% (136/515)] than the placebo group [20% (94/470)] at 16 weeks (completion of treatment phase). With a median survival follow up of 4.3 months, the absolute number of deaths was greater in the darbepoetin alfa treatment group [49% (250/515)] compared with the placebo group [46% (216/470); HR 1.29, 95% CI: 1.08, 1.55].<sup>3</sup> This information was previously communicated to oncologists in an Amgen Dear Health Care Professional letter dated January 26, 2007.

The results of the following studies have not been previously communicated to physicians in an Amgen or Ortho Biotech Dear Health Care Professional letter:

A preliminary report from a clinical study (DAHANCA) evaluated 522 patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy. Patients were randomized to darbepoetin alfa or placebo. An interim analysis in 484 patients demonstrated a 10% increase in locoregional failure rate among darbepoetin alfa-treated patients ( $p = 0.01$ ). At the time of study termination, there was a trend toward worse survival in the darbepoetin alfa-treated arm ( $p = 0.08$ ).<sup>4</sup>

A multicenter, randomized, double-blind, placebo-controlled trial in which patients with advanced non-small-cell lung cancer unsuitable for curative therapy were treated with Epoetin alfa targeting hemoglobin levels between 12 and 14 g/dL or placebo. Following an interim analysis of 70 of 300 patients planned, a significant difference in median survival in favor of patients in the placebo group was observed (63 vs. 129 days; HR 1.84;  $p = 0.04$ ).<sup>5</sup>

A randomized controlled study (referred to as the 'SPINE' study), in which 681 adult patients not receiving prophylactic anticoagulation and undergoing spinal surgery received either 4 doses of 600 U/kg Epoetin alfa (7, 14, and 21 days before surgery, and the day of surgery) and standard of care (SOC) treatment, or SOC treatment alone. Preliminary analysis showed a higher incidence of deep vein thrombosis (DVT), determined by either Color Flow Duplex Imaging or by clinical symptoms, in the Epoetin alfa group [16 patients (4.7%)] compared to the SOC group [7 patients (2.1%)]. In addition, 12 patients in the Epoetin alfa group and 7 patients in the SOC group had other thrombotic vascular events.

Physicians are encouraged to review the full prescribing information. A copy of the revised prescribing information for Aranesp<sup>®</sup> and EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup> is enclosed.

The FDA is assembling an Oncologic Drugs Advisory Committee (ODAC) meeting on May 10, 2007. Amgen and Ortho Biotech are fully committed to participating in this expert review and update of the safety and efficacy of ESAs, including Aranesp<sup>®</sup> and EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup>.

Amgen and Ortho Biotech are committed to broadly disseminating this important new prescribing information so that prescribers are informed about the safety of Aranesp<sup>®</sup> and EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup>. Over the coming weeks, our field forces will be calling on healthcare professionals and will communicate this important new safety information.

Amgen and Ortho Biotech recommend that physicians and other healthcare professionals follow the FDA-approved dosing instructions in the Aranesp<sup>®</sup> and EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup> prescribing information. The **DOSAGE AND ADMINISTRATION** section of the product labeling has been updated to reflect the safety information discussed above.

Aranesp<sup>®</sup> is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis and the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.

EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup> is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis (ESRD) and patients not on dialysis. EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup> is indicated to elevate and maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients.

EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup> is also indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.

EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup> is also indicated for the treatment of anemia related to therapy with zidovudine in HIV-infected patients and for the treatment of anemic patients (hemoglobin > 10 to ≤ 13 g/dL) scheduled to undergo elective, noncardiac, nonvascular surgery who are at high risk for perioperative blood loss to reduce the need for allogeneic blood transfusion. EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup> is not indicated for patients who are willing to donate autologous blood.

Aranesp<sup>®</sup> and EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup> are not approved for patients with active malignant disease receiving neither chemotherapy nor radiation therapy.

Amgen and Ortho Biotech have and will continue to expeditiously notify clinical study investigators of important safety information and to advise them to appropriately inform patients and IRBs. Investigators are reminded to update informed consent documents to reflect this new information.

Should you have any questions, require further information on product safety, or wish to report adverse patient experiences:

- For Aranesp<sup>®</sup> and EPOGEN<sup>®</sup>, please contact Amgen's Medical Information Connection™ at 1-800-77-AMGEN.
- For PROCRIT<sup>®</sup>, please contact Ortho Biotech's Medical Information at 1-888-227-5624.
- Alternatively, adverse events may be reported to FDA's MedWatch system via an online form at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm), by faxing (1-800-FDA-0178), or mailing the postage-paid Form 3500 available at [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or by telephone (1-800-FDA-1088).

Sincerely,



Sean E. Harper, MD Corporate Chief Medical Officer Amgen	Marc Kamin, MD Chief Scientific Officer Ortho Biotech Clinical Affairs, LLC
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## References

1. Singh AK, Szczech L, Tang KL, et al. Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease. *N Engl J Med*. 2006; 355: 2085-98.
2. Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining Normal Hemoglobin Levels With Epoetin Alfa in Mainly Nonanemic Patients With Metastatic Breast Cancer Receiving First-Line Chemotherapy: A Survival Study. *JCO*. 2005; 23(25): 1-13.
3. [http://www.clinicalstudyresults.org/documents/company-study\\_2157\\_0.pdf](http://www.clinicalstudyresults.org/documents/company-study_2157_0.pdf)
4. [http://frejacms.au.dk/dahanca/get\\_media\\_file](http://frejacms.au.dk/dahanca/get_media_file)
5. Wright JR, Ung YC, Julian JA, et al. Randomized, Double-Blind, Placebo-Controlled Trial of Erythropoietin in Non-Small-Cell Lung Cancer with Disease-Related Anemia. *JCO*. 2007; 25(9): 1-6.

\*Aranesp<sup>®</sup> and EPOGEN<sup>®</sup> are marketed by Amgen Inc.

\*\*PROCRI<sup>®</sup> is marketed by Ortho Biotech Products, L.P.