



IMPORTANT DRUG WARNING

SUBJECT: Additional Trials Showing Increased Mortality and/or Tumor Progression with EPOGEN®/PROCRIT® and Aranesp®

March 7, 2008

Dear Health Care Professional:

On November 8, 2007, the Aranesp® and EPOGEN®/PROCRIT® labeling were revised to describe the results of six studies showing increased mortality and more rapid tumor progression in patients with cancer receiving ESAs. This letter is to alert you that information from two additional trials have been included in the product labels as described below.

Based on the results of these studies, the **Boxed Warnings** section of the EPOGEN®/PROCRIT® and Aranesp® prescribing information has been revised as follows:

Cancer:

- ESAs shortened overall survival and/or time to tumor progression in clinical studies in patients with advanced-breast, non-small cell lung, head and neck, lymphoid, and cervical cancers when dosed to target a hemoglobin of ≥ 12 g/dL.

Additional modification made to the product labels are summarized as follows:

WARNINGS: Increased Mortality and/or Tumor Progression section

- Updated table

| Study / Tumor / (n) | Hemoglobin Target | Achieved Hemoglobin (Median Q1,Q3) | Primary Endpoint | Adverse Outcome for ESA-containing Arm |
|--|----------------------------------|------------------------------------|--|--|
| Chemotherapy | | | | |
| Cancer Study 1 Metastatic breast cancer (n=939) | 12-14 g/dL | 12.9 g/dL 12.2, 13.3 g/dL | 12-month overall survival | Decreased 12-month survival |
| Cancer Study 2 Lymphoid malignancy (n=344) | 13-15 g/dL (M) 13-14 g/dL (F) | 11.0 g/dL 9.8, 12.1 g/dL | Proportion of patients achieving a hemoglobin response | Decreased overall survival |
| Cancer Study 3 Early breast cancer (n=733) | 12.5-13 g/dL | 13.1 g/dL 12.5, 13.7 g/dL | Relapse-free and overall survival | Decreased 3 yr. relapse-free and overall survival |
| Cancer Study 4 Cervical Cancer (n=114) | 12-14 g/dL | 12.7 g/dL 12.1, 13.3 g/dL | Progression-free and overall survival and locoregional control | Decreased 3 yr. progression-free and overall survival and locoregional control |
| Radiotherapy Alone | | | | |

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|---|------------------------------|-----------------------------|--|---|
| Cancer Study 5 Head and neck cancer (n=351) | ≥15 g/dL (M) ≥14 g/dL (F) | Not available | Locoregional progression-free survival | Decreased 5-year locoregional progression-free survival Decreased overall survival |
| Cancer Study 6 Head and neck cancer (n=522) | 14-15.5 g/dL | Not available | Locoregional disease control | Decreased locoregional disease control |
| No Chemotherapy or Radiotherapy | | | | |
| Cancer Study 7 Non-small cell lung cancer (n=70) | 12-14 g/dL | Not available | Quality of life | Decreased overall survival |
| Cancer Study 8 Non-myeloid malignancy (n=989) | 12-13 g/dL | 10.6 g/dL 9.4, 11.8 g/dL | RBC transfusions | Decreased overall survival |

The label has been updated based on an interim analysis for Cancer Study 3 (the 'PREPARE' study). The study is ongoing and data collection and follow-up continue. The following new text describing this study has been added to the **WARNINGS: Increased Mortality and/or Tumor Progression** section of the labels:

Cancer Study 3 (the 'PREPARE' study) was a randomized controlled study in which Aranesp[®] was administered to prevent anemia conducted in 733 women receiving neo-adjuvant breast cancer treatment. An interim analysis was performed after a median follow-up of approximately 3 years at which time the survival rate was lower (86% vs. 90%, HR 1.42, 95% CI: 0.93, 2.18) and relapse-free survival rate was lower (72% vs. 78%, HR 1.33, 95% CI: 0.99, 1.79) in the Aranesp[®]-treated arm compared to the control arm.

The label has been updated based on additional follow-up of Cancer Study 4 (protocol GOG 191)¹ which was terminated prematurely in late 2003 following an unplanned review of safety data undertaken by the Gynecologic Oncology Group (GOG) at the request of Johnson & Johnson Pharmaceutical Research & Development (J&JPRD). The following new text describing this study has been added to the **WARNINGS: Increased Mortality and/or Tumor Progression** section of the labels:

Cancer Study 4 (protocol GOG 191) was a randomized controlled study that enrolled 114 of a planned 460 cervical cancer patients receiving chemotherapy and radiotherapy. Patients were randomized to receive Epoetin alfa to maintain hemoglobin between 12 and 14 g/dL or to transfusion support as needed. The study was terminated prematurely due to an increase in thromboembolic events in Epoetin alfa-treated patients compared to control (19% vs. 9%). Both local recurrence (21% vs. 20%) and distant recurrence (12% vs. 7%) were more frequent in Epoetin alfa-treated patients compared to control. Progression-free survival at 3 years was lower in the Epoetin alfa-treated group compared to control (59% vs. 62%, HR 1.06, 95% CI: 0.58, 1.91). Overall survival at 3 years was lower in the Epoetin alfa-treated group compared to control (61% vs. 71%, HR 1.28, 95% CI: 0.68, 2.42).

Amgen and Ortho Biotech are disseminating this important new prescribing information to inform prescribing healthcare professionals about the safety of Aranesp® and EPOGEN®/PROCRIT®. Over the coming weeks, our field forces will be calling on healthcare professionals and will communicate this important new safety information. Prescribing healthcare professionals are encouraged to review the full prescribing information, including the patient package insert, with patients in order to make appropriate treatment decisions based on the benefit-risk profile of these products. Copies of the revised prescribing information and patient package insert for Aranesp® and EPOGEN®/PROCRIT® are enclosed and available on Amgen's website at www.amgen.com and Ortho Biotech's website at www.procrit.com.

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

For Aranesp® and EPOGEN®, please contact Amgen's Medical Information Connection™ at 1-800-77-AMGEN.

For PROCRIT®, please contact Ortho Biotech's Medical Information at 1-888-227-5624.

Alternatively, adverse events may be reported to FDA's MedWatch reporting system

- by phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178),
- online (<https://www.accessdata.fda.gov/scripts/medwatch/>) or
- mailed, using the MedWatch for FDA 3500 postage paid form, to the FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787

Sincerely,



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| Sean E. Harper, MD Senior Vice President, Global Development and Chief Medical Officer Amgen | Craig Tendler, MD Vice President, Medical Affairs Ortho Biotech |
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References:

1. Thomas G, Ali S, Hoebbers F, et al. Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 120 g/dL with erythropoietin vs above 100 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. *Gynecol Oncol* 2007.

