



## IMPORTANT DRUG WARNING

**SUBJECT:** Reports of antibody-mediated pure red cell aplasia and transfusion-dependent anemia in patients with Hepatitis C virus (HCV) infection treated with ribavirin and interferon or pegylated interferon and an erythropoiesis-stimulating agent (ESA) concurrently

April 8, 2009

Dear Health Care Professional,

The purpose of this communication is to inform you of an important safety observation of spontaneous reports of antibody-mediated pure red cell aplasia (PRCA) and transfusion-dependent anemia in patients with HCV infection who receive treatment with ribavirin and interferon or pegylated interferon (RBV/IFN) and an erythropoiesis-stimulating agent concurrently. This observation was detected during Amgen and Centocor Ortho Biotech Products, L.P. post-marketing safety surveillance for the ESAs EPOGEN<sup>®</sup> (Epoetin alfa), PROCRI<sup>®</sup> (Epoetin alfa), and Aranesp<sup>®</sup> (darbepoetin alfa). PRCA is an already recognized risk in the approved indications for ESAs and is characterized in the current labeling.

Importantly, ESAs are not approved for the treatment of anemia associated with the use of RBV/IFN in patients with HCV infection. ESAs are approved by the US Food and Drug Administration (FDA) for the treatment of anemia to reduce red blood cell transfusions in certain types of patients<sup>1</sup>. SEE ENDNOTE FOR THE FULL INDICATION STATEMENTS FOR EPOGEN<sup>®</sup>/PROCRI<sup>®</sup> AND ARANESP<sup>®</sup>.

PRCA results in transfusion-dependent anemia. Any patient who develops a sudden loss of response to an ESA accompanied by severe anemia should be evaluated for the etiology of loss of effect, including the presence of binding and neutralizing antibody to erythropoietin. If anti-erythropoietin antibody-mediated anemia is suspected, ESA therapy should be withheld. In patients with antibody-mediated anemia, ESA treatment should be permanently discontinued. Patients should not be switched to other ESAs as antibodies may cross-react.

- For EPOGEN<sup>®</sup> and Aranesp<sup>®</sup>, contact Amgen (1-800-77AMGEN) to perform assays for binding and neutralizing antibodies.
- For PROCRI<sup>®</sup>, contact Centocor Ortho Biotech Products, L.P. (1-888-2ASK OBI).

For more information, please see the US Package Inserts for PROCRI<sup>®</sup>, EPOGEN<sup>®</sup>, and Aranesp<sup>®</sup>, including **WARNINGS, Pure Red Cell Aplasia**. Copies of the Medication Guide, Patient Instructions for Use for EPOGEN<sup>®</sup>, PROCRI<sup>®</sup> and Aranesp<sup>®</sup> and revised prescribing information are enclosed and available on the Amgen Inc. website at [www.amgen.com](http://www.amgen.com) and the Centocor Ortho Biotech Products, L.P. website at [www.orthobiotech.com](http://www.orthobiotech.com).

Prescribing healthcare professionals should review the full prescribing information, including the Medication Guide and Patient Instructions for Use with patients.

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

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

For PROCRIT<sup>®</sup>, please contact Centocor Ortho Biotech Products, L.P.'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,



Sean E. Harper, MD  
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Chief Medical Officer  
Amgen



Thomas F. Schaible, PhD.  
Vice President, Medical Affairs  
Centocor Ortho Biotech Services, LLC

<sup>i</sup> EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup> and Aranesp<sup>®</sup> Indications

EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup>

*Treatment of Anemia of Chronic Renal Failure Patients*

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

Non-dialysis patients with symptomatic anemia considered for therapy should have a hemoglobin less than 10 g/dL.

EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup> is not intended for patients who require immediate correction of severe anemia. EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup> may obviate the need for maintenance transfusions but is not a substitute for emergency transfusion.

Prior to initiation of therapy, the patient's iron stores should be evaluated. Transferrin saturation should be at least 20% and ferritin at least 100 ng/mL. Blood pressure should be adequately controlled prior to initiation of EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup> therapy, and must be closely monitored and controlled during therapy.

*Treatment of Anemia in Zidovudine-treated HIV-infected Patients*

EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup> is indicated for the treatment of anemia related to therapy with zidovudine in HIV-infected patients. EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup> is indicated to elevate or 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 not indicated for the treatment of anemia in HIV-infected patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding, which should be managed appropriately. EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup> use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.

EPOGEN<sup>®</sup>/PROCRIT<sup>®</sup>, at a dose of 100 Units/kg TIW, is effective in decreasing the transfusion requirement and increasing the red blood cell level of anemic, HIV-infected patients treated with zidovudine, when the endogenous

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serum erythropoietin level is  $\leq 500$  mUnits/mL and when patients are receiving a dose of zidovudine  $\leq 4200$  mg/week.

*Treatment of Anemia in Cancer Patients on Chemotherapy*

EPOGEN<sup>®</sup>/PROCRT<sup>®</sup> is indicated for the treatment of anemia due to the effect of concomitantly administered chemotherapy based on studies that have shown a reduction in the need for RBC transfusions in patients with metastatic, non-myeloid malignancies receiving chemotherapy for a minimum of 2 months. Studies to determine whether EPOGEN<sup>®</sup>/PROCRT<sup>®</sup> increases mortality or decreases progression-free/recurrence-free survival are ongoing.

- EPOGEN<sup>®</sup>/PROCRT<sup>®</sup> is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy.
- EPOGEN<sup>®</sup>/PROCRT<sup>®</sup> is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure due to the absence of studies that adequately characterize the impact of EPOGEN<sup>®</sup>/PROCRT<sup>®</sup> on progression-free and overall survival (see WARNINGS: Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence).
- EPOGEN<sup>®</sup>/PROCRT<sup>®</sup> is not indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding (see PRECAUTIONS: Lack or Loss of Response).
- EPOGEN<sup>®</sup>/PROCRT<sup>®</sup> use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.

*Reduction of Allogeneic Blood Transfusion in Surgery Patients*

EPOGEN<sup>®</sup>/PROCRT<sup>®</sup> is indicated for the treatment of anemic patients (hemoglobin  $> 10$  to  $\leq 13$  g/dL) who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions. EPOGEN<sup>®</sup>/PROCRT<sup>®</sup> is not indicated for anemic patients who are willing to donate autologous blood (see BOXED WARNINGS and DOSAGE AND ADMINISTRATION).

Aranesp<sup>®</sup>

*Anemia With Chronic Renal Failure*

Aranesp<sup>®</sup> is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis.

*Anemia With Non-Myeloid Malignancies Due to Chemotherapy*

Aranesp<sup>®</sup> is indicated for the treatment of anemia due to the effect of concomitantly administered chemotherapy based on studies that have shown a reduction in the need for RBC transfusions in patients with metastatic, non-myeloid malignancies. Studies to determine whether Aranesp<sup>®</sup> increases mortality or decreases progression-free/recurrence-free survival are ongoing.

- Aranesp<sup>®</sup> is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy.
- Aranesp<sup>®</sup> is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure due to the absence of studies that adequately characterize the impact of Aranesp<sup>®</sup> on progression-free and overall survival (see WARNINGS: Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence).

Aranesp<sup>®</sup> use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.