



IMPORTANT DRUG WARNING

Aranesp® (darbepoetin alfa) and EPOGEN®/PROCRIIT® (Epoetin alfa) Label Change based on TREAT Results Showing an Increased Risk of Stroke in Chronic Renal Failure Patients Not on Dialysis with Anemia and Type 2 Diabetes Treated to a Hemoglobin of 13 g/dL

December 16, 2009

Dear Health Care Professional:

In collaboration with the FDA, Amgen and Centocor Ortho Biotech Products, L.P. have updated the safety information in the Aranesp® and EPOGEN®/PROCRIIT® product labeling to reflect an increased risk of stroke based on results from a recent clinical study entitled TREAT: Trial to Reduce Cardiovascular Endpoints with Aranesp® Therapy.

TREAT was a randomized, double-blind, placebo-controlled study of 4038 anemic patients with type 2 diabetes and CRF not on dialysis.¹ Patients were randomized in a one-to-one ratio to receive either treatment with Aranesp® to target a hemoglobin level of 13 g/dL or placebo with erythropoiesis-stimulating agent (ESA) rescue therapy only if hemoglobin was less than 9 g/dL. The study failed to meet its primary objectives of demonstrating a reduction in all-cause mortality, cardiovascular morbidity, including heart failure, heart attack, stroke, or hospitalization for myocardial ischemia, or end stage renal disease (ESRD).

Among the components of the primary cardiovascular composite endpoint, the risk of stroke increased by almost two-fold in patients in the Aranesp® arm (101 patients [5.0%] vs. 53 patients [2.6%]; hazard ratio 1.92; 95% confidence interval: 1.38 to 2.68; $p < 0.001$). The risk observed in TREAT is of higher magnitude than seen in previous clinical trials in CRF patients not on dialysis. This safety information is applicable to all ESAs.

Results of this study reinforce the need to follow the approved label guidance to maintain hemoglobin levels within the range of 10 to 12 g/dL.

The **BOXED WARNING, Chronic Renal Failure** section of the Aranesp® and EPOGEN®/PROCRIIT® prescribing information has been updated as shown below:

WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR EVENTS, THROMBOEMBOLIC EVENTS, **STROKE and INCREASED RISK OF TUMOR PROGRESSION OR RECURRENCE**

Chronic Renal Failure:

- **In clinical studies, patients experienced greater risks for death, serious cardiovascular events, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target hemoglobin levels of 13 g/dL and above.**

- Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL.

Cancer:

- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers (see WARNINGS: Table 1).
- To decrease these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusion.
- Use ESAs only for treatment of anemia due to concomitant myelosuppressive chemotherapy.
- ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.
- Discontinue following the completion of a chemotherapy course.

Perisurgery: EPOGEN[®]/PROCRT[®] increased the rate of deep venous thromboses in patients not receiving prophylactic anticoagulation. Consider deep venous thrombosis prophylaxis.

(See WARNINGS: Increased Mortality, Serious Cardiovascular Events, Thromboembolic Events, and Stroke, WARNINGS: Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence, INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION.)

In addition, the **WARNINGS** section has been updated to include the following paragraph:

In a randomized, double-blind, placebo-controlled study of 4038 patients, there was an increased risk of stroke when [Aranesp[®]/darbepoetin alfa] was administered to patients with anemia, type 2 diabetes, and CRF who were not on dialysis. Patients were randomized to [Aranesp[®]/darbepoetin alfa] treatment targeted to a hemoglobin level of 13 g/dL or to placebo. Placebo patients received [Aranesp[®]/darbepoetin alfa] only if their hemoglobin levels were less than 9 g/dL. A total of 101 patients receiving [Aranesp[®]/darbepoetin alfa] experienced stroke compared to 53 patients receiving placebo (5% vs. 2.6%; HR 1.92, 95% CI: 1.38, 2.68; p < 0.001).

Copies of the revised prescribing information, Medication Guide, and Patient Instructions for Use for Aranesp[®] (darbepoetin alfa) and EPOGEN[®]/PROCRT[®] (Epoetin alfa) are enclosed and available on the Amgen Inc. website at www.amgen.com and the Centocor Ortho Biotech Products, L.P. website at www.orthobiotech.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 PROCRT[®], 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 Senior Vice President, Global Development and Chief Medical Officer Amgen	Thomas F. Schaible, PhD. Vice President, Medical Affairs Centocor Ortho Biotech Services, LLC
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¹ Pfeffer MA, Burdmann EA, Chen C-Y, et al. A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease. *N Engl J Med.* 2009;361:2019-32.