Safety Labeling for ESAs Gets Strengthened

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The Food and Drug Administration has revised the boxed warning for erythropoiesis-stimulating agents in response to concern about the potential for complications associated with high doses of such agents.

The development comes on the heels of six recently completed studies that suggested an increased risk of death, blood clots, strokes, and heart attacks in patients with chronic kidney failure who took erythropoiesis-stimulating agents (ESAs) in higher than recommended doses. In studies of head and neck cancer patients who took ESAs, those on higher than recommended doses experienced more rapid tumor growth.

In light of the revised warnings, at press time the Centers for Medicare and Medicaid Services (CMS) had announced that it would review all Medicare coverage policies related to the administration of ESAs. CMS also announced that it opened a national coverage analysis to evaluate ESA use in non–renal disease applications.

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"These [labeling changes] emphasize that physicians should prescribe the lowest dose of ESA that will gradually increase the hemoglobin to the lowest level sufficient to avoid blood transfusion," Dr. Richard Pazdur, director of the FDA Office of Oncology Drug Products in the Center for Drug Evaluation and Research, said during a teleconference announcing the changes.

The drugs affected by the action include darbepoetin alfa (Aranesp) and epoetin alfa (Epogen and Procrit), all of which are manufactured by Amgen Inc.

The new information contained in the boxed warning consists of three key points, Dr. Pazdur said. They include:

► Administer the lowest dose of an ESA in order to gradually increase the hemoglobin concentration to the lowest level necessary to avoid blood transfusions.

► Know that using ESAs increases the risk for death and for serious cardiovascular events when administered to target a hemoglobin level of greater than 12 g/dL.

► Understand that a higher incidence of deep vein thrombosis has been documented in patients receiving epoetin alfa preoperatively for reduction of allogeneic blood transfusion. These patients did not receive prophylactic anticoagulation.

The revised boxed warning also includes new information for cancer patients receiving ESAs to target a hemoglobin level of greater than 12 g/dL. In these patients, ESAs shortened the time to progression in those with advanced head and neck cancer. They also shortened overall survival and increased death attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy.

In addition, the boxed warning now notes that cancer patients not receiving chemotherapy or radiation therapy demonstrated increased mortality when given ESAs to target a hemoglobin level of 12 g/dL; ESAs are not indicated for this population.

Dr. Pazdur emphasized that he and his associates have seen only the "top-line" data from the six ESA studies. More specific data are "being submitted to the agency by the investigators and various sponsors" and will be discussed at the Oncologic Drugs Advisory Committee meeting on May 10, where the labeling may be revised further.

ESAs are approved to treat anemia in patients with chronic kidney failure and in patients with cancer whose anemia is caused by chemotherapy.

"For oncology patients, these products have not been shown to improve or relieve symptoms of anemia or to improve the quality of life in patients with cancer," Dr. Pazdur noted. "The FDA is currently reviewing all quality of life claims in the product label."

He advised physicians to discuss the new safety information "with all patients receiving this class of agents. Particularly for patients that are in clinical trials, we ask physicians to inform patients and have written informed consent for continued participation in clinical trials." ■