Do Erythropoiesis-Stimulating Agents Have a Risk Evaluation and Mitigation Strategy?

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Epoetin alfa and darbepoetin alfa are erythropoiesis-stimulating agents (ESAs), approved for the treatment of anemia (low red blood cells [RBCs]) resulting from chronic kidney disease, chemotherapy, and certain treatments for HIV. These ESAs also are used to reduce the number of blood transfusions during and after certain major surgeries. Erythropoiesis-stimulating agents work like the human protein erythropoietin, which stimulates bone marrow to make RBCs. Epoetin alfa (marketed as Procrit and Epogen) and darbepoetin alfa (marketed as Aranesp) are manufactured by Amgen, Inc. (Thousand Oaks, CA).

In 1989 epoetin alfa was approved for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis, and in 1993 for the treatment of anemia due to the effects of concomitant myelosuppressive chemotherapy. Epoetin alfa also is indicated for anemia due to zidovudine in patients with HIV and reduction of RBC transfusions during certain surgeries.

Darbepoetin alfa was approved in 2001 for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis, and in 2006 for the treatment of anemia due to the effects of concomitant myelosuppressive chemotherapy.

RISK EVALUATION AND MITIGATION STRATEGIES

Both epoetin alfa and darbepoetin alfa increase the risk of death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access and tumor progression or recurrence. Epoetin alfa also can lead to an increase in adverse cardiovascular events, hypertension, seizures, and severe anemia.

In 2008, the FDA determined that Risk Evaluation and Mitigation Strategies (REMS) were necessary for ESAs (darbopoetin alfa and epoetin alfa), to ensure that the benefits for use as treatment for anemia associated with myelosuppressive chemotherapy outweigh the risk of shortened overall survival (OS) and/or the increased risk of tumor progression or recurrence in patients with cancer. The REMS was approved in 2010.

Under the ESA REMS program, referred to as the ESA APPRISE Oncology Program, health care providers (HCPs) that prescribed and/or dispensed darbopoetin alfa to patients with cancer and hospitals that dispensed darbopoetin alfa to patients with cancer were required to enroll and become certified in the ESA REMS. The ESA REMS also required the completion of a Patient and Healthcare Provider Acknowledgement Form for each patient with cancer before the new ESA treatment course to ensure patients were counseled about the benefits and risks of these products.

In April 2017, the FDA determined that the ESA REMS that was limited to the use of epoetin alfa and darbopoetin alfa to treat patients with anemia due to associated myelosuppressive chemotherapy was no longer necessary; the benefits of ESAs outweighed the risks of shortened OS and/or increased risk of tumor progression or recurrence in patients with cancer.[1] The FDA recognized the burden that some REMS can place on HCPs and patients. The agency has authority to modify or remove the REMS to minimize the burden on the health care delivery system of complying with the strategy.

DATA

The FDA discontinued the REMS based on an evaluation of the results of the REMS Assessments submitted by Amgen and additional FDA analyses to understand the impact of the various regulatory and other actions on the use of ESAs. The REMS Assessment showed the following:

- The results from surveyed prescribers demonstrated acceptable knowledge of the product risks of decreased survival and/or the increased risk of tumor progression or recurrence and the need to counsel patients about these risks; and
- The drug utilization data indicated appropriate prescribing of ESAs consistent with the intended use as a treatment alternative to RBC transfusion for anemia associated with myelosuppressive chemotherapy.

The FDA also conducted an evaluation of the impact of multiple actions, including the ESA REMS, on the use of the ESAs using sponsor-submitted data from outpatient oncology practices between 2006 and 2014. During 2004 to 2009, the FDA took multiple regulatory actions, including labeling changes. In 2007, the Center for Medicare and Medicaid Services (CMS) made a National Coverage Determination (NCD) to limit coverage of ESAs for nonrenal disease indications. These actions coincided with the following:

- A decrease in the proportion of patients receiving chemotherapy using ESAs;
- An increase in the proportion of patients receiving chemotherapy who initiate ESAs at a hemoglobin level < 10 g/dL; and
- An increase in the proportion of patients who initiate ESAs at a dosage consistent with product prescribing information.

Full implementation of the ESA REMS in 2011 had minimal impact on trends in these 3 ESA utilization metrics beyond the changes observed after the CMS coverage determination and multiple other FDA regulatory actions.

This information led the FDA to conclude that it was no longer necessary to require the certification of prescribers and hospitals that prescribe and/or dispense ESAs to patients with cancer in order to ensure that the benefits outweigh the risks.

The FDA has released the REMS requirements for the epoetin alfa and darbopoetin alfa ESA products, and the risks can be communicated by the current product prescribing information. The appropriate use of ESAs is supported by the CMS NCD, the American Society of Clinical Oncology, and American Society of Hematology clinical guidelines, which are evidence-based guidelines intended to provide a basis for the standard of care in clinical oncology.

EDUCATION

While the REMS is no longer necessary to ensure the benefits outweigh the risks, the serious risks of shortened OS and/or increased risk of tumor progression or recurrence associated with these drugs remain. The boxed warning language remains as follows: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE. Health care providers are encouraged to discuss the risks and benefits of using ESAs with each patient before initiating use.

REFERENCE

1. U.S. Food & Drug Administration. Information on erythropoiesis-stimulating agents (ESA) epoetin alfa (marketed as Procrit, Epogen), darbepoetin alfa (marketed as Aranesp). https://www.fda.gov/Drugs/DrugSafety/ucm109375.htm. Updated April 13, 2017. Accessed July 13, 2017.