

Erythropoiesis-stimulating agents – REMS removal

- On April 13, 2017, the [FDA announced](#) that the risk evaluation and mitigation strategy (REMS) requirement for the erythropoiesis-stimulating agents (ESAs), epoetin alfa ([Procrit[®]](#), [Epogen[®]](#)) and darbepoetin alfa ([Aranesp[®]](#)), regarding their use in patients with anemia due to chemotherapy, is no longer necessary.
- Epoetin alfa and Aranesp are approved for the treatment of anemia resulting from chronic kidney disease, chemotherapy, certain treatments for human immunodeficiency virus, and also to reduce the number of blood transfusions during and after certain major surgeries.
- The FDA has concluded that the ESA REMS is no longer required based on a REMS assessment, data submitted from the manufacturer, and analyses of the impact of regulations and other actions on ESA utilization.
- The purpose of the ESA REMS was to ensure that the benefits of these products outweigh their risks of shortened overall survival (OS) and/or increased risk of tumor progression or recurrence in patients with cancer.
- While the ESA REMS is no longer necessary, the serious risks of shortened OS and/or increased risk of tumor progression or recurrence associated with these products remain.
 - The ESA drug labels will maintain their *Boxed Warnings* and other safety sections noting an increased risk of tumor progression or recurrence, as well as death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access.
- Healthcare providers are encouraged to discuss the risks and benefits of using ESAs with each patient before initiating use.
- The FDA REMS assessment showed that:
 - Surveyed prescribers demonstrated acceptable knowledge of the ESA risks of decreased survival and/or the increased risk of tumor progression or recurrence and the need to counsel patients about these risks.
 - Drug utilization data indicates the appropriate prescribing of ESAs consistent with the intended use as a treatment alternative to red blood cell transfusion for anemia associated with myelosuppressive chemotherapy.
- The FDA conducted an evaluation of the impact of multiple actions, including the ESA REMS, on the utilization of the ESAs using sponsor-submitted data from outpatient oncology practices between 2006 and 2014.
- During 2004-2009, 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 non-renal disease indications. These actions coincided with:
 - 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
 - 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 three 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 it is 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 the benefits outweigh the risks. 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 evidence-based clinical guidelines, which are intended to provide a basis for the standard of care in clinical oncology.



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