

# Message to the FDA on ESAs: REMS Is Not Enough, More Studies Are Needed

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Since March 24, 2010, the Food and Drug Administration (FDA) has been requiring a “Risk Evaluation and Mitigation Strategy” (REMS) for all patients who are treated with erythropoiesis-stimulating agents (ESAs) (1). Although regulatory authorities elsewhere in the world have not as yet taken this approach, experience suggests that these agencies often take their cues from the FDA.

Most nephrologists are unaware that the FDA now requires distribution to both dialysis and nondialysis patients of a medication guide that explains the risks and benefits of ESAs. The FDA is also mandating that oncologists—but not nephrologists, at least thus far—register and participate in a program called Assisting Providers and Cancer Patients with Risk Information for the Safe Use of ESAs (APPRISE) (2); however, APPRISE for ESAs in cancer could herald a similar program for ESAs in the anemia of kidney disease. What is REMS? Should nephrologists be required to register in an APPRISE-like program? Should the FDA be doing more to address safety concerns with ESAs?

REMS was announced in February for all patients who receive ESAs, and notices have been sent to ESRD networks asking that medication guides be distributed to patients (3). In addition, for the ESA cancer indication, oncologists need to undergo training on the risks and benefits of ESAs to continue prescribing them. This involves discussion about ESAs with patients who have cancer before beginning a course of treatment. Oncologists have to document that this discussion took place. A health care provider enrollment form that was developed by Amgen and Centocor Ortho Biotech and approved by the FDA must be completed for oncologists to prescribe ESAs (4).

The FDA gained authority to require REMS under the Food and Drug Administration Amendments Act (FDAAA) of 2007 (5). The goal of REMS is to manage a known or potentially serious risk associated with a drug or biologic product. REMS can be a part of a new drug application, abbreviated new drug application, or biologics license application; however, the FDA also has the authority to require REMS from the drug manufacturer if new safety information becomes available. This is clearly the case with both anemia of kidney disease and cancer-induced anemia.

REMS can include a medication guide, patient package insert, a communication plan, elements to ensure safe use, and an implementation system and must include a timetable for assessment. The “elements to ensure safe use” provision entails the setting up of a restricted distribution program for the drug. Currently, the FDA has 97 drugs that are a part of its REMS program. Sixty-nine drugs have only a medication guide requirement; 18 require a medication guide and a communication plan; and 10 require a medication guide, development of a communication plan, elements to ensure safe use, and an implementation system—two of these 10 drugs are epogen and darbepoetin, listed for their cancer-induced anemia indication.

It is quite possible that the FDA will expand REMS to include “elements to ensure safe use” for ESAs in patients with chronic kidney disease (CKD). Some will argue that because all active drugs carry safety risks, the government’s seemingly singular concern with ESAs might be financially motivated. This seems very unlikely because, in the United States at least, the regulatory and reimbursement functions are separated, the latter being the domain of the Centers for Medicare and Medicaid Services. In fact, despite the publication of studies demonstrating higher risk for death and/or cardiovascular complications in patients who have a higher hemoglobin (Hb) target (6–9), as well as warnings by the FDA in the ESA label (10,11), extensive off-label use of ESAs continues. The percentage of dialysis patients with a Hb level of >12 g/dl remains at approximately 40% (12)—above what is recommended in the ESA label and by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (13) (Figure 1). Indeed, since the approval of Epogen in the United States in 1989, there has been a steep increase in the mean Hb concentration and average ESA dosage used in dialysis patients (12) (Figure 2). ESA use in the United States is more than twofold greater than in other Western countries (Figure 3) (14). Some have speculated that this is because of Medicare reimbursement policies (15); others have presented data that there are economic incentives for overuse of ESAs (16), especially among for-profit dialysis chains. Biologic mechanisms have also been invoked, such as Hb variability (17). Recently, the publication of the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) (9) has precipitated another round of safety review for ESAs in patients with kidney disease. Although TREAT was neutral for its primary end points of mortality and cardiovascular complications or mortality and the incidence of ESRD, it

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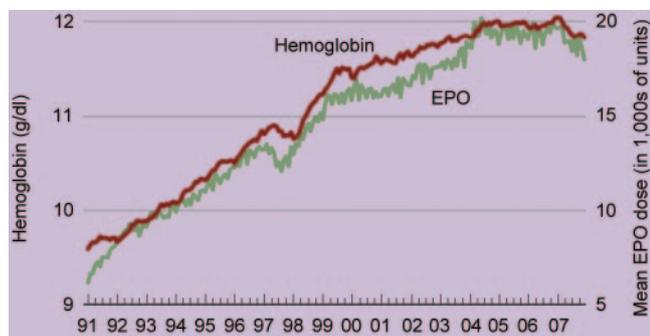


Figure 1. The mean monthly hemoglobin and mean weekly epoetin (EPO) dosage from 1991 to 2007. The figure is reproduced from the US Renal Data System Annual Data Report 2009. The figure shows the progressive increase in both the hemoglobin and EPO dose over time.

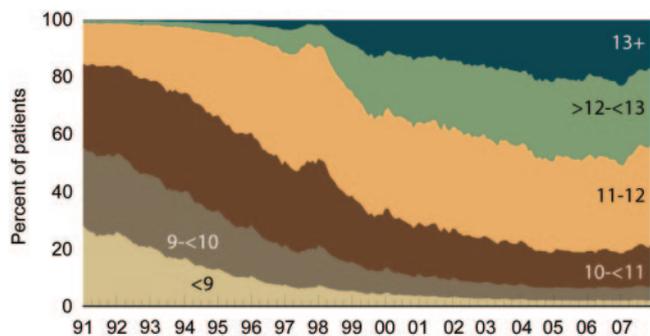


Figure 2. The distribution of mean monthly hemoglobin concentration from 1991 to 2007. The figure is reproduced from the US Renal Data System Annual Data Report 2009. The figure shows the progressive increase in the percentage of patients with a hemoglobin level >12 g/dl over time.

showed a twofold higher risk for stroke with darbepoetin therapy, a higher risk for thromboembolism, and a higher rate of cancer deaths in darbepoetin-treated patients. Cancer rates are higher in patients who are on dialysis compared with the healthy population (18), further raising concerns about the potential effect of incautious use of ESAs in these patients.

The FDA plans to convene another advisory committee later in 2010 (19) to evaluate the safety of ESAs. If the FDA decides that an expanded REMS program for patients with CKD is necessary, then it would be on a larger scale than for patients with cancer; it would resemble the opiate REMS program, which covers 21 drugs and 3.7 million patients. Treatment for cancer-induced anemia is limited to a smaller number of patients and a smaller number of providers, whereas treatment of anemia in patients with kidney disease entails millions of patients and many thousands of providers. The care of patients with kidney disease and its complications is overseen by many different specialties and occurs in a variety of settings: Multi-specialty group settings, outpatient dialysis units, hospitals, and free-standing clinics. The impact and the cost could be quite substantial across the health system.

Conversely, the “elements to ensure safe use” provision con-

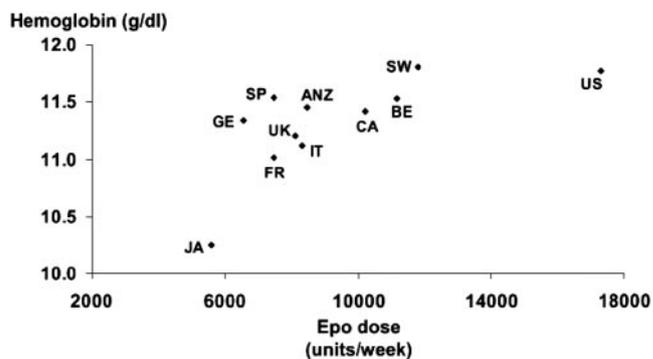


Figure 3. Unadjusted EPO dosage and mean Hb level by country, Dialysis Outcomes and Practice Patterns Study II (DOPPS II) data 12 countries 2002 to 2003 among prevalent dialysis patients. ANZ, Australia/New Zealand; BE, Belgium; CA, Canada; FR, France; GE, Germany; IT, Italy; JA, Japan; SW, Sweden; SP, Spain; US, United States; UK, United Kingdom. Adapted from reference 14, with permission.

tained within REMS provides the FDA with a unique opportunity to create an ESA safety culture in the treatment of anemia. REMS could be a powerful driver for individualization of anemia care. For example, the FDA could require that ESA treatment be initiated only after documentation of safe use conditions and discussion. Discussion with the patient about the pros and cons of ESA treatment. The program could require nephrologists to ensure that other sources of anemia, such as occult blood loss or iron deficiency, be ruled out. Ongoing treatment could require completing a regular checklist that includes investigating potential causes of ESA resistance and cross-checking Hb and iron stores. The FDA could exercise its statutory powers and require that all patients with CKD be entered into a registry. This would be redundant for dialysis patients because the US Renal Data System is already in place; however, it could be important for nondialysis patients in gathering information about risk. The FDA could also require that patients who are administered ESAs be more closely monitored to prevent a rapid rise in Hb, an issue that the FDA recently emphasized in a perspective article in the *New England Journal of Medicine* (19) and that I discussed in a previous editorial (20). Besides these actions, the FDA could require targeted continuing medical education to improve the knowledge of physicians in treating anemia in patients.

An APPRISE-like program would be onerous for both dialysis providers and nephrologists. The FDA is already requiring patient counseling and distribution of educational materials to all patients with CKD; this seems sufficient at the present time. Engaging in more formalized counseling and requiring the signing of an informed consent might confuse patients or even generate alarm and anxiety. Asking nephrologists to register in an FDA-mandated program to prescribe ESAs is surely an excessive response for a specialty that has been using ESAs for more than two decades, even if some of this use has been off-label. An APPRISE-like program might limit flexibility in treating patients, something that most nephrologists believe is essential in treating anemia.

The elements to ensure a safe-use provision of REMS would be superimposed on bundling of ESAs into a single payment for dialysis that is due to begin on January 1, 2011. Already, it is thought that bundling will create a powerful incentive to administer lower dosages of ESAs because dialysis providers will be paid a flat fee for dialysis for each patient regardless of the ESA dosage used in treating the patient's anemia. The superimposition of REMS might tempt some providers to modify their use of ESAs because of the additional burden of APPRISE training and documentation or because of the financial benefits of doing so. The FDAAA has specific language that prohibits this from occurring. In addition, REMS has in place built-in mechanisms to review the effects of the program on practice and to impose corrective action on providers.

If the FDA were simply to expand the REMS program for the ESA kidney indication to include APPRISE, then I believe that the FDA will have missed an opportunity to enhance further the safety of ESAs in patients with CKD. The four large randomized, controlled trials—Normal Hematocrit (6), Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin  $\beta$  (CREATE) (7), Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) (8), and TREAT (9)—have demonstrated, through an aggregate experience of 7000 patients, with respect either to the primary composite or to a prespecified secondary end point, that there is risk associated with targeting a higher Hb level with higher dosages of ESA. A recent meta-analysis (21) of 27 trials that comprised 10,452 patients reinforces the conclusions from the aforementioned randomized controlled trials. A higher Hb target was associated with an increased risk for stroke (relative risk [RR] 1.51; 95% confidence interval [CI] 1.03 to 2.21), hypertension (RR 1.67; 95% CI 1.31 to 2.12), and vascular access thrombosis (RR 1.33 95% CI 1.16 to 1.53) compared with a lower Hb target. There was increased risk for mortality (RR 1.09; 95% CI 0.99 to 1.20) and serious cardiovascular events (RR 1.15; 95% CI 0.98 to 1.33), although these did not reach statistical significance. There may be multiple potential explanations (22–25) for these observations, but almost everyone accepts that additional studies are needed; however, there is no incentive for industry to conduct such studies because, as an influential Institute of Medicine report (26) states, there is a “possibility that unfavorable results would negatively influence market share.” This is especially true if one were to invoke exposure to high dosages of ESA as a potential explanation and a clinical trial to test this hypothesis is deemed necessary.

Although I support the FDA's REMS initiative, rather than going down the road of an APPRISE-like program, the FDA should instead consider exercising its statutory authority under Title IX “Enhanced Authorities Regarding Postmarket Safety of Drugs” to require additional studies to be conducted by the manufacturers of ESAs. The FDA's authority accrues from an amendment to section 505 of the Federal Food, Drug, and Cosmetic Act (21 USC 355) contained within the FDAAA legislation (5). The FDA would be well within its rights to ask for these studies. This is because the amendment was incorporated into the FDAAA precisely for instances when safety becomes an issue after approval of a drug. Under the new law, the FDA

can mandate a clinical trial or trials of a drug to assess risk. And, certainly the billions of dollars in profit made by industry in ESA sales should easily accommodate a program to rigorously test the long-term safety of ESAs. The FDA should also provide guidance to the ESA manufacturers on design and timing of the trial(s).

Quoting from the Institute of Medicine's report “The Future of Drug Safety: Promoting and Protecting the Health of the Public” (26), “As a country we have chosen to place a significant degree of decision-making about the availability and potential use of medicines in the hands of a science-based regulatory body. The FDA is the first gatekeeper regarding access to drugs in exercising approval authority.” Although REMS for ESAs is a first step, it is not enough. The FDA ought to go further but not down the path of an onerous registration program like APPRISE. Instead, the FDA should insist on additional science to evaluate formally the safety of ESAs in treating CKD anemia. The time to do that is now.

## Disclosures

A.K.S. was principal investigator of the CHOIR study and a member of the Executive Committee for the TREAT study. He presented on ESAs and anemia to the FDA Cardiovascular Disease and Renal Advisory Committee (CDRAC) September 2007 and to the US Congress House of Representatives, Ways and Means Committee in December 2006 and June 2007. He is a member of Medicare Evidence Development & Coverage Advisory Committee and was an expert presenter on behalf of the Centers for Medicare and Medicaid Services Meeting to Discuss ESA Coverage for CKD Patients in March 2010. A.K.S. has received consulting income from Amgen, Johnson and Johnson, Fibrogen, and Watson and has received grant support from Amgen, AMAG, Johnson and Johnson, and Watson.

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