

Evolving Regulatory Landscape with Erythropoiesis-Stimulating Agents and Impact on Managed Care

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Abstract

Erythropoiesis-stimulating agents (ESAs) are a very effective treatment for reducing the need for transfusions in patients affected by anemia and either chronic kidney disease (CKD) or cancer. However, many clinicians remain wary of its use due to safety concerns. It has been shown that higher doses are associated with cardiovascular disease, stroke, or death. These concerns have spurred the US Food and Drug Administration to order Risk Evaluation and Mitigation Strategies (REMS) for clinicians prescribing ESAs to their patients. REMS are a method to ensure safety and provide clinicians and patients with an appropriate gauge of the risks and benefits associated with the administration of ESAs. Whether this restricts its use or lowers costs remains to be determined.

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Introduction

Erythropoiesis-stimulating agents (ESAs) are very effective in reducing the need for transfusions in patients with anemia of either chronic kidney disease (CKD) or cancer. However, a plethora of clinical studies,²⁻⁶ meta-analyses,⁷⁻⁹ and US Food and Drug Administration (FDA) announcements¹⁰⁻¹² have many physicians concerned about the safety of ESAs. Generally, these reports show that higher doses of ESAs and/or targeting higher hemoglobin (Hb) levels are associated with an increased risk of cardiovascular disease, stroke, or death.

Shortly after the publication of safety concerns with ESAs, the FDA made appropriate prescribing information changes to ensure proper dosing schedules and monitoring procedures. At present, if clinicians adhere to the prescribing information for ESAs, the risk to patients is minimal. However, the recent concerns about safety may deter some clinicians from prescribing ESAs to patients who could benefit from them. Of further concern are the changes in Medicare rules and reimbursement policies^{13,14} and the recent FDA requests for Risk Evaluation and Mitigation Strategies (REMS) for ESAs¹⁵ that further dissuade clinicians from prescribing ESAs to patients who may benefit from them.

To address clinicians' concerns in balancing the advantages and risks associated with ESAs, this article offers a brief review of the efficacy, safety, and regulatory aspects of ESAs. This article will also address the recent FDA request that REMS be employed, and what the implementation of REMS means for healthcare professionals treating patients with anemia.

Efficacy and Safety of ESAs

Use of ESAs in Anemia of Chronic Kidney Disease

Numerous randomized controlled trials, beginning with the landmark study by Eschbach et al,¹⁶ have shown that ESAs increase Hb levels in patients with CKD who manifest anemia (**Table 1**).¹⁷

With the initial approval of epoetin alfa in 1989, the primary goal of treatment of anemia in patients with CKD was to increase Hb concentration to greater than 10 g/dL, thus avoiding transfusion. Over the years, clinical practice guidelines may have contributed to use of ESAs in attaining higher Hb targets.^{17,18} Concern over the increased risk of stroke, cardiovascular events, or death in patients given ESAs to achieve higher Hb levels (>13 g/dL) have led to

■ **Table 1.** RCTs With ESAs in Patients With CKD

Author, Year	N	CKD Class	Baseline					Outcome				
			Hb (g/dL)	Oral Iron	IV Iron	ESA Frequency	ESA Route	Initial ESA Dose	Adjustment: Acute		Mean Rise of Hb (g/dL) in 1st 4 Weeks	AEs
									Upward	Downward		
Eschbach, 1989	201 35	HD	7.4 8.1		As needed	TIW	IV	Epoetin 150 300	None	None	1.5 2.5	Seizure in 10 patients in 1st 3 mo, did not distinguish by month, rate of Hb rise or ESA dose
Eschbach, 1989	4 4	4-5 ND	8.9			TIW	SC IV	Epoetin 100 150	None	None	2.6 1.3	None
Nissenson, 1995	78	PD	7.9	86%	As needed	TIW	SC	Epoetin 4000	None	None	1.8	Worsening hypertension in 1st 12 wk, no specific information on 1st 4 wk
Locatelli, 2001	37 129	4-5 ND	9.8 9.2		As needed for low indices	QOW BIW	SC	Darbepoetin 045 µg/kg Epoetin 50 IU/kg	25% of starting dose	25% of starting dose	1.0 1.1	
Toto, 2004	463	3-5 ND	9.8	60%	14%	QOW	SC	Darbepoetin 0.75 µg/kg	Next dose size	Next dose size	0.7	Next dose size
Roth, 1994	43	4-5 ND	7.8	As needed	As needed	TIW	SC	50 IU/kg	75 IU/kg increments	No info	1.6	
Nissenson, 1995	78	PD	7.4	86%	23%	TIW	SC	4000 IU	None	None	1.8	

Footnotes:
 Studies selected included only RCTs; only patients previously naive to ESA; with data available on Hb (or Hct) at 4 (or at both 3 and 5 wk), compared to baseline

Coding of Comparison of Outcomes:
 If Hct reported, Hb was obtained by dividing by 3.3. If 4-wk value was not reported, result was interpolated.

AEs indicates adverse events; BIW, twice per week; CKD, chronic kidney disease; ESAs, erythropoiesis-stimulating agents; Hb, hemoglobin; Hct, hematocrit; IV, intravenous; QOW, every other week; RCTs, randomized controlled trials; SC, subcutaneous; TIW, 3 times a week.
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the current dosing recommendations, which are designed to obtain Hb levels in the range of 10 to 12 g/dL.^{1,19}

Use of ESAs in Anemia and Cancer

It is well established that ESAs reduce the number of transfusions necessary in patients receiving chemotherapy¹ and improve patients’ quality of life.⁹

Studies have reported reduced survival and increased tumor progression and thrombotic events in patients with cancer and anemia given ESAs.¹ These serious safety concerns have been documented over time by the FDA and other organizations (Table 2).^{15,20}

The plethora of data showing increased risk for serious adverse events following ESA use has resulted in 2 major regulatory changes that are applicable to healthcare professionals. First, the Centers for Medicare & Medicaid Services

significantly tightened reimbursement rules on the use of ESAs in patients this year.^{13,14} Second, the FDA recently stated that all ESAs prescribed must be part of a REMS to ensure the safe use of these drugs.¹⁵ Both of these regulatory changes are discussed below.

ESA Safety and Reimbursement Implications

All of these safety concerns have led to many changes in the prescribing information for ESAs as well as significant changes by Medicare regarding reimbursement. As stated in the previous article, Medicare updated its policy with limits on the use of ESAs. In patients with cancer and anemia, ESA treatment should not begin until Hb levels are less than 10 g/dL.¹⁴ In patients with end-stage renal disease, payment will be removed unless the dose is lowered by 25% or 50% once Hb levels exceed 13 g/dL for 3 billing cycles.¹³

■ **Table 2.** A History Lesson in ESAs and Safety

May 2004	The FDA began restricting the use of ESAs after a 2004 ODAC meeting. ODAC discussed safety and recommended more double-blind, placebo-controlled trials with survival as the primary end point
November 2006	FDA issued safety alert, updated in February and March 2007
March 2007	FDA added a “black box” warning to use lowest possible dose of ESAs for anemia
May 2007	ODAC recommended restrictions on ESAs; asked about limiting use in certain tumor types, set new Hb levels for starting therapy, and limiting time used after chemotherapy
July 2007	CMS limited reimbursement of ESAs to treatment initiated at Hb levels <10 g/dL
November 2007	FDA labeling change warned of increased tumor progression, blood clots, and death in patients with advanced head and neck, breast, lymphoid, and non-small-cell lung cancers
March 2008	ODAC recommended that ESAs stay on the market, but that labeling should change to indicate that patients who are receiving curative treatment should not take ESAs; they did not recommend restricting ESA use in certain cancers
June 2008	European Medicines Agency recommended a new warning for ESA use in patients with cancer, stating that blood transfusions are the preferred method of correcting anemia
July 2008	FDA ordered the manufacturer of ESAs (Amgen Inc) to make safety-related labeling changes: ESAs are not indicated for curable cancer patients and should not be used for chemotherapy patients with Hb levels ≥10 g/dL
February 2010	The FDA ordered all ESAs to be prescribed and used under a risk management program to ensure the safe use of these drugs

CMS indicates Centers for Medicare & Medicaid Services; ESAs, erythropoiesis-stimulating agents; FDA, US Food and Drug Administration; Hb, hemoglobin; ODAC, Oncology Drugs Advisory Committee.
Adapted from Brower V. *J Natl Cancer Inst.* 2008;100(19):1344-1351.

Medicare will not cover the use of ESAs for (1) any anemia due to folate deficiency, B₁₂ deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis in patients with cancer; (2) anemia associated with the treatment of acute myelogenous leukemia and chronic myelogenous leukemia, or erythroid cancers; (3) anemia of cancer not related to cancer treatment; (4) any anemia associated only with radiotherapy; (5) prophylactic use to prevent chemotherapy-induced anemia; (6) prophylactic use to reduce tumor hypoxia; (7) patients with erythropoietin-type resistance due to neutralizing antibodies; and (8) anemia due to cancer treatment if patients have uncontrolled hypertension.¹⁴

Risk Evaluation and Mitigation Strategies

The recent request by the FDA that all ESAs be prescribed and used under REMS is appropriate based on the recent safety reports for ESAs. Many medications and biologic products that are deemed to have a “higher than average risk” have been placed into REMS or “active” monitoring systems. REMS inform healthcare professionals and patients about the risks associated with a medication. In many cases, the strategy of REMS is fairly straightforward and simply requires that patients receive a medication guide each time the drug is dispensed (or at the beginning of treatment). For medications with significant safety concerns, REMS involve increased surveillance and/or performance/safety assessment programs. For the latter, a patient registry may be employed, and that is what the FDA is establishing in coordination with Amgen Inc, the manufacturer of ESAs.

In February 2010, the FDA stated that all ESAs must be part of a REMS.¹⁵ More specifically, the FDA stated the program should provide patients with material and guidance to understand the risks associated with ESAs. For patients with cancer, these risks include: (1) ESAs may cause tumors to grow faster; (2) ESA use may be associated with earlier death; and (3) ESAs may cause some patients to develop blood clots and serious heart problems such as a heart attack, heart failure, or stroke. Patients without cancer should know: (1) that the use of ESAs can increase the risk for stroke, heart attack, heart failure, blood clots, and death; and (2) that their healthcare professional has received special training about the use of ESAs in patients with cancer.

All patients receiving ESAs are instructed to read the medication guide to understand the benefits and risks of using an ESA, and to talk with their healthcare professional if they have any questions.¹⁵ Also, patients with cancer will be asked to sign an acknowledgment form that states that they have talked with their healthcare professional about the risks associated with ESAs. This form must be signed before patients begin a course of ESA treatment. Patients without cancer will be asked to get blood tests while using ESAs to help guide the course of therapy and lower the risk of serious adverse events.

Table 3. List of REMS With Additional Requirements Besides Medication Guides

Drug	Generic Name	Indication	Reason for REMS	MG	CP	EASU
Abarelix	Plenaxis	Prostate cancer	Allergic reactions	x	x	x
Alosetron	Lotronex	Irritable bowel syndrome	Ischemic colitis; complications of constipation	x	x	x
Alvimopan	Entereg capsules	Accelerate gastrointestinal recovery following surgery	Myocardial infarction in patients treated with opioids immediately prior to alvimopan use	No	x	x
Ambrisentan	Letairis	Pulmonary arterial hypertension	Liver injury, potential for fetal harm	x		x
Bosentan	Tracleer	Pulmonary arterial hypertension	Birth defects, liver toxicity	x		x
Certolizumab pegol	Cimzia	Crohn's disease	Infection	x	x	
Clozapine	Clozaril, Fazaclo	Schizophrenia	Agranulocytosis	No		x
Dofetilide	Tikosyn	Atrial fibrillation/flutter	Torsades de pointes	No		x
Eculizumab	Soliris	Paroxysmal nocturnal hemoglobinuria to reduce hemolysis	Meningococcal infections	x	x	
Eltrombopag	Promacta	Thrombocytopenia in patients with chronic immune ITP	Hepatotoxicity, bone marrow	x		x
Fentanyl buccal soluble film	Onsolis	Breakthrough pain in adults with cancer	Abuse/diversion	x	x	x
Fentanyl citrate	Actiq	Cancer pain	Pediatric toxicity abuse/diversion	x		x
Fentanyl PCA	Ionsys	Acute postoperative pain	Abuse/diversion	No		x
Golimumab	Simponi injection	Rheumatoid arthritis and ankylosing spondylitis	Histoplasmosis and other invasive fungal infections not consistently recognized	x	x	
Isotretinoin	Accutane, Amnesteem, Claravis, Sotret	Severe nodular cystic acne	Birth defects, depression, psychosis and, rarely, suicidal ideation	x	x	x
Lenalidomide	Revlimid	Myelodysplastic syndrome with deletion 5q cytogenetic abnormality	Blood clots, possibility of birth defects	x	x	x
Mifepristone	Mifeprex	Medical termination of pregnancy	Bleeding and sepsis following medical abortion	x	x	x
Natalizumab	Tysabri	Multiple sclerosis	Multifocal leukoencephalopathy	x	x	x
Prasugrel	Effient	Antithrombotic	Bleeding	x	x	
Romiplostim	Nplate for subcutaneous injection	Thrombocytopenia in patients with chronic immune ITP	Bone marrow reticulin formation and a risk for bone marrow fibrosis	x	x	x
Sacrosidase	Sucraid oral solution	Sucrase replacement	Potential for allergic reaction	No	x	x
Sodium oxybate	Xyrem	Cataplexy associated with narcolepsy	Severe central nervous system events/abuse/diversion	x	x	x
Telbivudine	Tyzeka	Hepatitis B	Peripheral neuropathy	x		
Teriparatide (rDNA origin) injection	Forteo	Osteoporosis	Osteosarcoma	x	x	
Tetrabenazine	Xenazine tablets	Chorea associated with Huntington's disease	Depression and suicidal thoughts and behavior	x	x	

■ **Table 3.** List of REMS With Additional Requirements Besides Medication Guides (*Continued*)

Drug	Generic Name	Indication	Reason for REMS	MG	CP	EASU
Thalidomide Thalomid	Thalidomide Thalomid	Cutaneous manifestations of erythema nodosum leprosum, multiple myeloma	Birth defects	No	x	x
Toxin A injection	Dysport	Cervical dystonia and glabellar lines	Potential for medication error/distant spread of toxin beyond injection site	x	x	

CP indicates communication plan; EASU, Element to Assure Safe Use; ITP, idiopathic thrombocytopenic purpura; MG, Medication Guide; REMS, Risk Evaluation and Mitigation Strategies.

Reprinted with permission from Gilsonan A, et al. Evaluation of Current Risk Evaluation and Mitigation Strategies. Poster presented at: 25th International Conference on Pharmacoepidemiology & Therapeutic Risk Management; August 16-19, 2009. Providence, RI.

The FDA also stated that healthcare professionals who prescribe ESAs for anemia in patients with cancer must: (1) complete a training module that covers the use of ESAs; (2) be enrolled in the ESA APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe Use of ESAs) Oncology program following completion of the training module; (3) sign the patient/healthcare professional acknowledgment form prior to the patient receiving an ESA; and (4) re-enroll in the ESA APPRISE Oncology program every 3 years.¹⁵ Healthcare professionals not enrolled in the ESA APPRISE Oncology program will not be able to prescribe ESAs for use in patients with cancer.

In addition, the FDA requires that hospitals using ESAs for anemia in cancer patients must be enrolled in the ESA APPRISE Oncology program and have a system in place that ensures that all healthcare providers who prescribe ESAs in the hospital are enrolled and comply with the ESA APPRISE Oncology program. Healthcare professionals who prescribe ESAs for anemia in patients without cancer are required to provide a copy of the medication guide to each patient or their representative when an ESA is dispensed; they are not required to enroll in the ESA APPRISE Oncology program.

A preliminary draft of the REMS developed by Amgen Inc²¹ states that the goals of the REMS are as follows: (1) to support informed decisions between patients and their healthcare providers who are considering treatment with ESAs by educating them about the risks associated with their use; and (2) to mitigate the risk of decreased survival and/or poorer tumor outcomes in patients with cancer (through the ESA APPRISE Oncology program). Amgen will also be responsible for conducting real-time monitoring of prescribing and purchases in private-practice settings and clinic

audits, and auditing hospitals to ensure compliance with the ESA APPRISE Oncology program. Failure to comply will result in a suspension of access to ESAs.

The draft of the REMS being developed by Amgen shows that it is going to be a very detailed program requiring many parties to maintain records of ESA use. How this will alter ESA prescriptions remains to be seen. However, REMS are becoming more common. A presentation by Gilsonan et al²² reported that as of July 2009, there were 69 medications with REMS. Of those, 52% (n = 36) required only medication guides, 28% (n = 19) required communication plans, 28% (n = 19) required elements of safe use (13/19 are for drugs deemed to have approved REMS), and 13% (n = 9) required an implementation system similar to the one proposed by Amgen (**Table 3**).

Impact of REMS on Managed Care

Implementation of REMS for ESAs is appropriate based on the safety concerns with these medications. It is very likely that the introduction of REMS to the treatment regimen for anemia will be a time-consuming and cumbersome addition; however, these proactive measures should result in reduced incidence of serious adverse events, emergency department visits, and hospitalizations. The net result will hopefully be reduced overall costs to accompany the reduced incidence of adverse events. Whether or not the increased effort associated with REMS prevents some patients from benefiting from ESAs remains to be seen. Also uncertain at this stage is whether the increased emphasis on laboratory results will prevent patients from receiving individualized care. As ESA manufacturers implement their new REMS programs, payers will have to figure out how to integrate these programs into their utilization management practices.

Conclusions

ESAs are an effective means to treat anemia. However, concern for the safety of patients receiving ESAs has dramatically altered the administration of ESAs in recent years. The FDA's request to require REMS for ESA prescribers is a proactive measure to improve safety outcomes and provide both healthcare professionals and patients with an evidenced-based assessment of the risks and benefits associated with ESA use. Whether the restricted distribution program limits ESA use for some patients or reduces overall costs remains to be determined.

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