THE CANCER LETTER

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FDA Urges Lower Target For ESA Use; Market Could Drop By More Than Half

By Paul Goldberg

Citing health risks, FDA last week placed "black box" warnings on erythropoietin products, urging physicians to exercise restraint in prescribing the controversial agents.

"Use the lowest dose of [erythropoiesis stimulating agents] that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid blood transfusions," FDA said in a document released March 9.

"In most cases, physicians would transfuse a patient up to 10 g/dL of hemoglobin, and would not go to a higher level," Richard Pazdur, director of the FDA Division of Oncology Drug Products, said at a press conference announcing the labeling change.

The guidelines from the American Society of Clinical Oncology and the

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CMS Launches National Coverage Analysis, Citing FDA's Black Box Warning On ESAs

By Paul Goldberg

The Centers for Medicare & Medicaid Services March 14 announced that it is "closely reviewing" all Medicare policies related to the administration of erythropoiesis stimulating agents in light of the FDA recent issuances of a black box warning on the agents.

"We pay close attention to FDA black box warnings because the safety of our Medicare beneficiaries is paramount," CMS Acting Administrator Leslie Norwalk said in a statement. "We will carefully examine the effect of these labeling changes on Medicare's policies and we encourage treating physicians to review the warnings and to take them into account when prescribing ESAs for their patients."

Last week, CMS contractors started to deny payment for ESAs in the treatment of anemia of cancer. However, the agency now intends to complement these "local coverage determinations" by launching a "national coverage analysis" on ESA use.

The action is expected to be completed in December, agency document show.

If this analysis results in a coverage decision, local contractors would be prohibited from paying for the agents in some settings.

The agency said its National Coverage Analysis would cover all conditions other than end-stage renal disease.

"We will review the scientific evidence to determine the appropriate use of ESAs for multiple clinical indications," Barry Straube, chief medical

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Cancer QOL Claims For ESAs Inferred From Nephrology

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American Society of Hematology, written years before the negative news about these drugs started to emerge, suggest the hemoglobin target of 12 g/dL.

On May 10, the FDA Oncologic Drugs Advisory Committee will hold an unusual all-day meeting to review the new data on ESAs, which point to safety problems, stimulation of disease progression, and lowered survival.

Estimates based on published data suggests that if oncologists heed Pazdur's words of caution and lower the hemoglobin targets, the U.S. oncology market for ESAs would shrink by well over 50 percent.

The sponsors of ESAs have data that show exactly how these drugs are used, and recently, Amgen Inc., the sponsor of Aranesp, made a selective disclosure based on that information (The Cancer Letter, March 2). The Cancer Letter asked the company to state how many physicians use 10 g/dL as the target for starting treatment with Aranesp, but the company hasn't responded.

However, in a survey published three years ago, 65 percent of physicians said they prescribed the agents to patients whose hemoglobin was at 10 g/dL or above (Adams et al, The American Journal of Medicine, Jan. 1, 2004). If this calculation holds, the lower target suggested by Pazdur could shrink the U.S. oncology market for ESAs from $4.9 billion to $1.7 billion.

The 10 g/dL hemoglobin target isn't arbitrary, Pazdur said at the press conference.

The sponsors of ESAs have demonstrated only that these treatments can reduce the need for blood transfusions, Pazdur said. "We want people to be aware of why these drugs were approved—specifically to reduce blood transfusions," he said. "A blood transfusion will not be given above a level 8 g/dL, and the patients are traditionally transfused to the hemoglobin level of 10."

Amgen argues that the current 12 g/dL target is safe when used in chemotherapy-induced anemia. "These medicines have been studied for more than 15 years in chemotherapy-induced anemia and chronic kidney disease," the company said in a letter distributed to patient advocates after the FDA announcement of the labeling change.

Similarly, in a memo distributed to Amgen staff, company President, CEO and Chairman Kevin Sharer wrote that at the ODAC meeting, the company plans to "discuss what we believe is a very strong track record of well-documented scientific data that demonstrate the safety of our ESAs when used according to the label."

No More QOL Claims in Cancer

Since ESAs are used widely in all settings, from adjuvant to palliative, the questions about their use have emerged as one of the central issues in oncology.

To explore this issue, The Cancer Letter invited physicians, scientists and a patient advocate to submit the questions they would like to have answered by ODAC. *See related story on page 5.*

At this time, the agency's actions are based on the outcomes of recently concluded trials. Data from these trials are yet to be submitted, Pazdur said.

Pazdur said ODAC would examine the relationship between the doses of ESAs and clinical outcomes. "We want ODAC to take a look at the whole issue of dosing of this drug in the oncology patient population," Pazdur said.

Also, the committee will be asked to delineate off-label uses of ESAs as a treatment for anemia of cancer from the approved indication of chemotherapy-induced anemia. The committee would be asked "how different these potential indications are," Pazdur said.

Finally, the oncology advisory committee would serve as a public forum where data on the controversial drugs would be released. "There are many reasons we want to have a greater awareness of the safety issues with these drugs, and I think there are many questions that need to be looked at, including additional clinical trials," Pazdur said. "This is more than just one ODAC

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meeting. We look at this as a process of reevaluating a class of agents."

In addition to urging oncologists to use less Aranesp, FDA has amended the labels of the ESAs, taking out all references to improvement of quality of life in the oncology setting.

"There is no product label regarding quality of life or fatigue reduction for oncology patients," Pazdur said. "There is a quality of life claim for chronic renal failure. Those data will be looked at and reviewed in terms of contemporary patient-reported outcome criteria that the agency has developed. Many of these claims have been in the label for years now, and we are looking at the quality of that data."

The quality of life claims in oncology were extrapolated from data used to support the renal indication. These statements were used to launch direct-to-consumer advertising that, in effect, created "cancer fatigue" as a separate disease and elevated ESAs into the biggest selling product in oncology.

"Many of the claims were put in many years ago," Pazdur said. "We felt that they needed to come out."

The sponsors would be asked to present quality of life data in a manner that would meet today's standard for substantiating such claims.

"We have asked the companies to resubmit the primary data," Pazdur said. "We want to look at that to see if that data will suffice to support marketing claims based on our current standards for patient-reported outcomes."

The negative data have made it essential for the agency to reexamine the ESAs, Pazdur said.

"Physicians should discuss the above information with all patients receiving this class of agents," he said. "Particularly for patients who are on clinical trials, we ask physicians to inform patients and have written informed consent for continued participation. IRBs should also be advised of these findings. Investigators should re-evaluate whether clinical investigation should continue in light of these new safety data. FDA will be issuing letters to all IND sponsors."

FDA regards all ESAs—Aranesp and Johnson & Johnson's Procrit—as a single class of agents. Sometime after the May 10 session of ODAC, the FDA Cardio-Renal Advisory Committee will meet to examine the renal indication.

Pazdur said the Centers for Medicare and Medicaid Services have been informed about the FDA actions.

On March 14, CMS announced that it has launched a "National Coverage Determination" on ESAs in indications that include oncology. *See story, page 1.*

"Additional Challenges Have Surfaced"

Responding to bad news from FDA, Amgen officials are holding a series of briefings with patient advocacy groups.

In a document supplied to patients, the company said that ESAs have a "favorable risk/benefit profile when used according to the prescribing information, based on significant body of evidence.

"Cancer patients receiving chemotherapy have benefited from ESA treatment to reduce blood transfusions for more than a decade," the document sates. "The vast majority of oncologists do not appear to be maintaining Hb levels above 12 g/dL in approved indications. In fact, a review of one of the largest electronic medical records databases in oncology showed 86 percent of patients with CIA receiving ESAs had a Hb under 12 g/dL at ESA administration."

In a communication sent to Amgen employees, company top executive Sharer acknowledged that the company had "anticipated considerable challenges, but since then, additional challenges have surfaced."

The text of Sharer's letter follows:

As you know, attention has been focused on questions about Aranesp safety in recent weeks, especially in light of our communication on the findings of our study in cancer patients with anemia not due to chemotherapy. Additionally, coverage of a Danish investigator-led experimental trial studying Aranesp in an off-label regimen has raised questions. Further, both J&J and Roche have recently communicated disappointing findings from investigational studies with Procrit and peg-EPO beta.

In response to this emerging set of new clinical trial data around the class of erythropoiesis-stimulating agents (ESAs), the FDA has done what it is supposed to do—ask questions about the data and review the overall safety profile of the products.

Accordingly, over the past few weeks we have had discussions with FDA about the safety of ESAs. Last week, we announced our intent to participate in a meeting of the FDA's Oncologic Drug Advisory Committee (ODAC) to be held on May 10, 2007. At that meeting, we plan to discuss what we believe is a very strong track record of well-documented scientific data that demonstrate the safety of our ESAs when used according to the label. Additionally, we are now analyzing the data from our own study involving the use of Aranesp in the treatment of patients suffering from small cell lung cancer. We intend to run our preliminary analysis of that data and provide top-line results at the ODAC meeting.

Today, we announced that the FDA has approved updated safety information, including a boxed warning in the prescribing information, in the U.S. for the ESA class, including Aranesp and Epogen. Please see today's press release for more details. We are currently working with our U.S. field sales force to provide this new information to healthcare professionals.

Outside the U.S., we are in contact with regulatory authorities in Europe, Australia and Canada to provide them with information about these changes. We will continue to promote our products according to the approved label for each country.

So what does this all mean for Amgen, our shareholders and the patients we serve?

First and foremost, patient safety is our top priority. We will always follow the science in the best interest of patients.

We believe the new U.S. ESA class label is good for patients. Our experience with both physicians and payers is that they try their best to do what is right for patients. Over the coming months, physicians and payers will seek direction from us as well as others to understand the new label and to make the most informed treatment decisions.

Much has changed since mid-January, and it is important that we talk openly about the changes, accept our new reality and work carefully to address it appropriately. Nothing is gained by looking away when we run up against tough issues. We've faced them squarely many times before and prevailed. I'm confident that we're up to the task once again.

FDA Letter to Oncologists

On March 9, Pazdur sent out a letter to the members of ASCO, ASH, the Oncology Nursing Society, and Children's Oncology Group.

The text of the document follows:

The FDA previously communicated safety information from clinical trials in cancer patients receiving erythropoiesis-stimulating agents (ESAs).

The FDA has received additional safety information which has been incorporated in product labeling for darbepoetin alfa (Aranesp, Amgen, Inc.) and epoetin alfa (Epogen, Amgen, Inc. and Procrit, Ortho Biotech Products LP). These safety findings have resulted in a boxed warning and additional labeling revisions.

The information contained in the new boxed warning is summarized below:

• Use the lowest dose of ESAs that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid blood transfusions.

• ESAs increased the risk for death and for serious cardiovascular events when administered to target a hemoglobin greater than 12 g/dL.

• A higher incidence of deep venous thrombosis was documented in patients receiving epoetin alfa pre-operatively for reduction of allogeneic blood transfusions. These patients did not receive prophylactic anticoagulation.

• ESAs when administered to cancer patients:

—shortened the time-to-progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a hemoglobin > 12g/dL;

—shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to target a hemoglobin > 12 g/dL; and

—increased mortality in cancer patients not receiving chemotherapy or radiation therapy when administered to target a hemoglobin of 12 g/dL. ESAs are not indicated for this population.

A summary of the studies supporting the above recommendations are provided below:

• A randomized (1:1) trial, "Correction of Hemoglobin and Outcomes in Renal Insufficiency" (CHOIR), evaluated 1432 anemic chronic renal failure patients who were not undergoing dialysis. Patients were assigned to epoetin alfa either targeting a maintenance hemoglobin of 13.5 g/dL or of 11.3 g/dL. A major cardiovascular event (death, MI, stroke or hospitalization for CHF) occurred in 18% in the higher hemoglobin arm compared to 14% in the lower hemoglobin arm (HR 1.3, 95% CI: 1.0 to 1.7, p = 0.03).

• A randomized study, "Maintaining Normal Hemoglobin Levels With Epoetin Alfa in Mainly Nonanemic Patients With Metastatic Breast Cancer Receiving First-Line Chemotherapy: A Survival Study" (BEST), evaluated 939 women with metastatic breast cancer receiving chemotherapy. Patients received either weekly epoetin alfa (to maintain hemoglobin levels of 12-14 g/dL) or placebo for one year. The study was terminated prematurely for higher mortality (8.7% vs. 3.4%) and higher fatal thrombotic event rate (1.1% vs. 0.2%) in the first 4 months in the epoetin alfa arm. At study termination, 12-month survival rates were lower in the epoetin alfa arm (70% vs. 76%; HR 1.37, 95% CI: 1.07, 1.75; p = 0.012).

• A phase 3, randomized, placebo-controlled study evaluated 989 patients with active malignant disease not receiving chemotherapy or radiation therapy.

Patients were randomized to darbepoetin (to achieve a hemoglobin of 12 g/dL) or placebo. No evidence of a statistically significant reduction in RBC transfusions was observed. More deaths occurred in the darbepoetin alfa arm than in placebo (26% vs. 20%) following 16 weeks of treatment. With a median follow-up of 4.3 months, the absolute number of deaths was greater in the darbepoetin alfa group than placebo [49% vs. 46%; HR 1.29; 95% CI: 1.08, 1.55].

• A randomized study (DAHANCA 10) evaluated 522 patients with carcinoma of the head and neck receiving radiation therapy. Patients were randomized to either darbepoetin alfa or placebo. An interim analysis in 484 patients demonstrated a 10% increase in loco-regional failure rate among darbepoetin alfa-treated patients ($p = 0.01$). At the time of study termination, a trend toward worse survival in the darbepoetin alfa-treated arm was observed ($p = 0.08$).

• A trial in advanced non-small-cell-lung cancer patients, randomized to either epoetin alfa (targeting hemoglobin 12-14 g/dL) or placebo. Following an interim analysis in 70 patients, a significant decrease in median survival was observed in the epoetin-treated arm (63 vs. 129 days; HR 1.84; $p = 0.04$).

• A randomized study (SPINE) evaluated 681 patients undergoing spinal surgery who received either epoetin alfa and standard of care (SOC) or SOC alone. These patients did not receive prophylactic anticoagulation. Preliminary analysis showed a higher incidence of deep vein thrombosis in the epoetin alfa group than the SOC (4.7% vs. 2.1%). Twelve patients in the epoetin alfa group and 7 in the SOC had additional thrombotic vascular events. These results have not been published or disseminated previously.

This new information will be discussed at the May 10, 2007 Oncologic Drugs Advisory Committee (ODAC) meeting to re-evaluate the safety and dosing of ESAs in cancer patients.

Additional modifications of the product labeling were made to the "Dosage and Administration" section. These changes emphasize that physicians should prescribe the lowest dose of ESAs that will gradually increase the hemoglobin to the lowest level sufficient to avoid blood transfusions.

FDA reminds physicians that ESAs are approved for the reduction in red blood cell transfusions. These products have not been shown to improve or relieve the symptoms of anemia nor to improve quality of life in patients with cancer.

Physicians should discuss this information with patients in clinical studies and should ask patients to confirm their consent for continued participation. Institutional Review Boards should also be advised of these findings. Investigators should re-evaluate whether clinical investigations should continue in light of these new safety data. FDA will be issuing a letter to IND sponsors with these recommendations.

Please see the FDA Healthcare Professional Sheet regarding evolving safety issues with ESAs, posted at http://www.fda.gov/cder/drug/infopage/RHE/default.htm.

Full prescribing information, including the above changes, is available for Aranesp at http://www.fda.gov/cder/foi/label/2007/103951s5139lbl.pdf and for Epogen/Procrit at http://www.fda.gov/cder/foi/label/2007/103234s5122lbl.pdf. Note that the content of the labels for Epogen and Procrit are the same except for the proprietary name.

Healthcare professionals should report all serious adverse events suspected to be associated with the use of any medicine and device to FDA's MedWatch Reporting Program via an online form at www.fda.gov/medwatch/report.htm, by faxing (1-800-FDA-0178) or mailing the postage-paid Form 3500 available at www.fda.gov/medwatch, or by telephone (1-800-FDA-1088).

Questions For ODAC: Advisors Challenged To Examine Basics As They Review ESAs May 10

The Cancer Letter asked a group of physicians, scientists, payers, and patient advocates to suggest the questions they would like to see addressed by ODAC as it meets May 10 to review data on ESAs.

LEE NEWCOMER, head of oncology services, United Healthcare:

Question 1: Where is the data that the physiology changes between 10 g/dL and 12 g/dL of hemoglobin?

Rationale: We assume that patients "feel" better with levels above 10 g/dL, but how good is that data? The company has sold their product on this premise for years. Now that we know that the drug has potential harmful side effects we should re-examine the "correct" level for a target. I have a New Mexico physician (active in ASCO) insisting that her patients should have higher levels of Hg because they live at higher altitude, but no such requests come from Colorado. Again, I don't think there is any data on this subject.

Question 2: What should the dosing intervals be?

Rationale: Our data shows that the Aranesp product

is often given at weekly levels. Additionally, patient dosing for both products is usually quite erratic. Should we enforce strict intervals as recommended by the manufacturer?

ROBERT ERWIN, president, Marti Nelson Cancer Foundation:

Question 1: Does administration of ESAs cause a loss of efficacy of anti-cancer agents, and if so, is this acceptable under any clinical circumstances?

Rationale: There do not appear to be data from controlled clinical trials addressing the affect of administration of these drugs on overall survival or on time to disease progression in the context of cancer. Recent reports suggest that in some circumstances there are higher deaths in the treatment groups than in the control groups. Are the deaths due to direct side effects of ESA treatment, to inhibition of anticancer drug regimens, or to both?

Question 2: What will be done to reduce ongoing risk to patients currently enrolled in clinical trials, and what changes should be made in the design of future clinical trials to minimize unnecessary risk to cancer patients?

Rationale: Many physicians and patients have assumed that ESAs are beneficial for off-label uses without clinical data to support such uses, and now emerging data suggest unexpected toxicity under a variety of circumstances. The widespread assumption that ESA's are safer than they now appear to be, coupled with aggressive advertising directly to consumers, may have put large numbers of patients at unnecessary risk. We would like to know what plans will be immediately implemented to disclose risks of ESAs to clinical trial participants, to close trials that now appear poorly designed or dangerous in light of new information, to more broadly inform consumers of currently known risks with periodic updates as additional analyses are completed, and to stop inappropriate promotion of these products to cancer patients.

DAVID STEENSMA, oncologist at Mayo Clinic:

Question 1: How the agency is going to define anemia associated with chemotherapy for purposes of the epoetin and darbepoetin label (since the labels will likely affect third-party reimbursement), and for future clinical trials.

Rationale: When epoetin alfa was first approved for the indication of anemia associated with chemotherapy in the early 1990s, almost all of the medical therapies available for treating patients with cancer were so-called traditional cytotoxic drugs. Thankfully, due to the tremendous progress in hematology-oncology research in recent years, the classes of agents available to oncologists and patients have expanded greatly, with a wide range of new antibodies, conjugates, and small molecules. Some of these newer therapies contribute to anemia, and in many cases—also true for patients who are receiving cytotoxics—it is not clear-cut to what extent the anemia is associated with disease alone versus the therapy. For instance, imatinib treatment for chronic-phase CML causes a form of anemia that seems to respond well to erythropoietin treatment (see Cortes J et al *Cancer* 2004), but the anemia caused by imatinib appears quite distinct biologically from the anemia induced by, say, cisplatin therapy for squamous cell carcinoma.

Question 2: How does FDA view the concomitant use of parenteral iron products with ESAs?

Rationale: This is a standard practice among nephrologists and seeing growing use in oncology practices. It is pretty clear now that using IV iron improves both the rate and magnitude of the hemoglobin response to ESAs, and major safety issues other than the usually manageable immediate infusion reactions to the parenteral iron products have not been described. FDA, however, has cautioned against excessive rate of rise of hemoglobin, and I am wondering whether the agency feels this should be a research priority or has any specific concerns along those lines.

CHARLES BENNETT, oncologist at Northwestern University, principal investigator, Research and Adverse Drug events And Reports (RADAR) project:

Question 1: How will the FDA define statistically significant safety risk?

Rationale: Since 2001, there have been several attempts to pool safety results from phase III clinical trials in order to determine the relative risk for venous thromboembolism associated with EPO/Darb treatment. While many of the overall relative risk estimates from these meta-analysis are not considered significant at p=0.05, each estimate favors increased risk for VTE in the treatment arm. Perhaps a broader definition of significant risk (other than p</=0.05) is needed in order to adequately describe safety.

Question 2: Why did the FDA wait until 2007 to convene a safety meeting?

Rationale: Evidence was presented at the 2004 ODAC meeting that raised concern regarding the

safety of Epo/Darb. Why didn't the FDA require annual reporting of safety data rather than wait until additional safety concerns had been published?

Question 3: Will the FDA support a cancer-associated venous thromboembolism safety initiative?

Rationale: Given RADAR's experience with increased rates of VTE in cancer patients receiving thalidomide/lenalidomide, Avastin, and EPO/Darb, all of which have received black box warnings, it is evident that thromboembolic complications are unlikely to be identified from databases. Yet, there have been no phase III trials designed to measure VTE as a primary endpoint.

Question 4: Will the FDA encourage basic science research to explore the role of EPO receptors in tumor progression and survival?

Rationale: There are five ongoing trials examining the role of EPO/Darb on progression-free survival, however, to date there have been no correlative basic science studies to determine whether those patients whose tumors are EPO receptor positive suffer worse survival than those who are EPO receptor negative.

MICHAEL HENKE, oncologist at Klinik fuer Strahlenheilkunde, Freiburg, Germany:

Question 1: How does the agency make sure that ESAs will be safe for cancer patients targeted to hemoglobin levels below 12 g/dL?

Rationale: There is low evidence that ESAs are safe for these patients. In fact, all clinical trials that target to hemoglobin below 12 g/dL were not designed for survival or tumor control. Moreover, the study "anemia of cancer" by Amgen—though not designed for survival and/or cancer control—showed a negative effect of Aranesp on disease progression in pts targeted to hemoglobin below 12 g/dL. Further, Leyland-Jones et al. (2005) and Henke et al. (2003) demonstrate tumor progression to be independent from hemoglobin level. Finally, a "switch at hemoglobin 12 g/dL" separating patients who eventually benefit from ESAs from those who do not, does not seem plausible.

Question 2: How would FDA suggest to better identify cancer patients where ESAs can be administered safely?

Rationale: So far all advice restricts to target hemoglobin level or to ESA-dose. These guidelines seem to rely more on formal reasons and lack largely of a biological rationale. Given the impaired control of ESA treated head & neck cancer pts (Henke et al., RTOG 99-03 and DAHANCA-10) eventually depending from the C20 (EpoR) antigen on cancers cells (Henke et al., 2006), the characterization of cellular features seem to be more adequate.

Question 3: Does the agency suspect that an increased risk of progressing cancer and/or death under ESA might be a feature of most solid cancers?

Rationale: There is strong evidence for decreased cancer control/survival in head & neck cancer (Henke et al., RTOG 99-03 and DAHANCA-10); studies by Leyland-Jones et al. (2005) and Wright et al. (2007) are at least suggestive that ESA might negatively impact most pts with solid cancers.

CMS Statement:

Local Carriers, Private Insurers Reconsider Payment For ESAs

(Continued from page 1)

officer for CMS said in a statement. "It is important to provide the correct coverage of ESAs for each specific clinical indication."

By next year, CMS will be better positioned to monitor the hemoglobin levels at which ESAs are administered to cancer patients. As a result of a Congressional action, standard CMS claim forms will be modified to require oncologists to note their patients' hemoglobin levels at a time treatment is administered.

If used aggressively, this requirement could limit overuse of the agent. Private payers, too, are starting to use similar systems to limit inappropriate use and ensure patients' safety.

ESAs are approved for the treatment of anemia in chronic kidney failure patients, in patients with cancer whose anemia is caused by chemotherapy, in patients with human immunodeficiency virus that are using AZT (zidovudine) and to reduce the number of transfusions in patients scheduled for major surgery.

Also, CMS is reviewing its ESA monitoring policy for patients with ESRD, and who are dialyzed in renal facilities. The Medicare benefit policy is consistent with the National Kidney Foundation and current kidney disease industry guidelines to maintain a target hemoglobin level in the range of 10 g/dL to 12 g/dL (or hematocrit level of 30-36 percent). Under the ESA monitoring policy, CMS initiates a payment reduction if the hemoglobin exceeds 13 g/dL (or hematocrit level of 39 percent) unless the provider provides includes information with the claim that the dosage has already been reduced.

Further information on the national coverage analysis can be found at: http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=203.

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