



# THE AMERICAN SOCIETY OF HEMATOLOGY

1900 M Street, NW, Suite 200, Washington, DC 20036 ph 202.776.0544 fax 202.776.0545 e-mail ASH@hematology.org

## 2007

### President

Andrew I. Schafer, M.D.  
University of Pennsylvania  
School of Medicine  
3400 Spruce Street, 100 Centrex  
Philadelphia, PA 19104-4261  
ph 215.662.5402 x1  
fax 215.349.8734  
andrew.schafer@uphs.upenn.edu

### President-Elect

Kenneth Kaushansky, M.D.  
Department of Medicine  
University of California, San Diego  
402 Dickinson Street, Suite 380  
San Diego, CA 92103-8911  
ph 619.543.2259  
fax 619.543.3931  
kkaushansky@ucsd.edu

### Vice President

Nancy Bellmer, M.D.  
Chief, Hematology Division  
Brigham & Women's Hospital  
75 Francis Street  
Boston, MA 02115-6110  
ph 617.732.8840  
fax 617.732.8706  
nbellmer@partners.org

### Secretary

Armand Keating, M.D.  
Princess Margaret Hospital  
610 University Avenue, Suite 5 211  
Toronto, Ontario M5G 2M9  
CANADA  
ph 416.946.4505  
fax 416.946.4530  
armand.keating@uhn.on.ca

### Treasurer

Linda J. Burns, M.D.  
Division of Hematology,  
Oncology, and Transplantation  
University of Minnesota  
420 Delaware Street, SE  
Mayo Mail Code 286  
Minneapolis, MN 55455-0341  
ph 612.624.8144  
fax 612.625.9393  
burns112@umn.edu

### Councillors

Nancy C. Andrews, M.D., Ph.D.  
Erin J. Druker, M.D.  
D. Gary Gilliland, M.D., Ph.D.  
David Ginsburg, M.D.  
Katherine A. High, M.D.  
Richard A. Larson, M.D.  
Semuel M. Silver, M.D., Ph.D.  
Robert F. Todd, III, M.D., Ph.D.

### Editors-in-Chief

Sanford J. Shattil, M.D., Blood  
Peter D. Emanuel, M.D., The Hematologist

### Executive Director

Martha L. Liggett, Esq.  
The American Society of Hematology  
1900 M Street, NW, Suite 200  
Washington, DC 20036  
ph 202.776.0544  
fax 202.776.0545  
mliggett@hematology.org

June 13, 2007

Steve E. Phurrough, MD, MPA  
Director, Coverage and Analysis Group  
Centers for Medicare & Medicaid Services  
Mail Stop C1-09-06  
7500 Security Boulevard  
Baltimore, MD 21244

RE: National Coverage Analysis for Erythropoiesis Stimulating Agents (ESAs) for Non-Renal Disease Indications (CAG-00383N)

Dear Dr. Phurrough:

The American Society of Hematology (ASH) represents over 11,000 hematologists in the United States who are committed to the treatment of blood and blood-related diseases. ASH members include hematologists and hematologist/oncologists who regularly render services to Medicare beneficiaries. The Society appreciates this opportunity to comment on the Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N).

Of paramount importance to ASH is to ensure that all coverage decisions are guided by the best available scientific evidence to ensure the highest degree of patient safety and to protect against not only the overuse of ESAs, but their underuse and misuse as well. Consequently, the Society is deeply concerned that CMS's proposed decision memo inappropriately restricts use of ESAs because a number of its proposals are not supported by scientific data, rely on poor quality data, or are in conflict with expert scientific analysis.

In addition, ASH is concerned that CMS's proposed decision memo does not take into consideration the discussion during FDA's May 10, 2007 Oncology Drug Advisory Committee meeting, particularly a conclusion that the anemia of myelodysplasia (MDS) should not be included in decisions for restricted use. As FDA is the agency responsible for evaluating drugs for safety and efficacy, ASH believes CMS should not issue its proposal prior to the FDA's scientific review and final decisions on this issue.

Further, ASH notes that the proposed CMS restriction on MDS conflicts with a CMS-approved quality measure for the Physician Quality Reporting Initiative (PQRI). The quality measure involves the use of ESAs in MDS patients (see <http://www.cms.hhs.gov/PQRI/Downloads/PQRIMeasuresList.pdf>).

**68. Myelodysplastic Syndrome(MDS): Documentation of Iron Stores in Patients Receiving Erythropoietin Therapy:** Percentage of patients aged 18 years and older with a diagnosis of MDS who are receiving erythropoietin therapy with documentation of iron stores prior to initiating erythropoietin therapy.

ASH developed this evidence-based quality measure with consultation by CMS because of the recognized value of using ESAs to treat these patients. The measure was vetted through the Society and the AMA Physician Consortium for Performance Improvement, endorsed by the AQA, and then approved by CMS as part of the PQRI program. The proposal to restrict coverage in patients with MDS is contrary to the PQRI where CMS recognizes MDS as a condition for which ESA treatment can be considered a standard of practice. Consequently, CMS's proposed restriction for MDS contradicts the national consensus about appropriate quality care and demonstrates a lack of internal consistency within the agency.

ASH's comments on the proposed NCD follow. We note that because all ESAs have the same mechanism of action, ASH believes that the NCD should apply to all ESAs (marketed as Procrit, Epogen, and Aranesp). While some local carriers have separate coverage policies for darbepoetin alfa (Aranesp) and epoetin alfa (Epogen and Procrit), ASH believes there should be a single national coverage policy because the products are basically interchangeable and use of one is essentially equal to the use of the other.

#### ***Coverage of ESAs for Patients with Conditions Other than End-Stage Renal Disease***

##### ***Anemia of Myelodysplasia -***

In its proposed decision memo, CMS proposes broad coverage restrictions to the FDA-approved indication for ESAs in chemotherapy-induced anemia and broad restrictions for off-label uses. ASH strongly disagrees with CMS's conclusion that there is sufficient evidence to restrict coverage of ESAs for treatment of the anemia of myelodysplasia (MDS). To the contrary, there is evidence to support the use of ESAs in patients with anemia associated with MDS with less than five percent blasts.

**Definition of Myelodysplasia:** Myelodysplastic syndromes (MDS) are a heterogeneous group of hematological malignancies characterized by dysplastic and ineffective hematopoiesis and a variable risk of transformation to acute leukemia. MDS with less than five percent blasts can include the following (World Health Organization classification) forms of MDS:

- Refractory anemia (RA) (238.72)
- Refractory anemia with ringed sideroblasts (RARS) (238.72)
- Refractory cytopenia with multilineage dysplasia (RCMD) (238.72)
- Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS) (238.72)
- Myelodysplastic syndrome, unclassified (MDS-U) (238.75)
- MDS associated with isolated del(5q) (238.74)

Refractory anemia can be defined as a red cell production deficiency that cannot be assigned to a specific vitamin or mineral deficiency.

ASH recommends that Medicare cover treatment with ESAs in patients with MDS who meet the following criteria:

1. Hemoglobin (Hgb) of 10 g/dl or Hematocrit (Hct) of 30% or less
2. Patients who have a reasonable expectancy of longer survival
3. Patients who need or are anticipated to need frequent transfusions
4. Treatment with ESAs will end or reduce the need for transfusions

Scientific Rationale for Coverage: Since the FDA approved epoetin as a pharmaceutical in 1989 for anemia of chronic renal failure, numerous studies have examined its potential use as an alternative to transfusions in the management of anemia in patients with cancer and specifically in patients with MDS. CMS should consider this evidence.

Published data on the safe and effective use of ESAs in MDS patients spanning more than a decade are available. Examples include: A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes (Italian Cooperative Group, 1998) and Treatment of anemia in myelodysplastic syndromes with granulocyte colony-stimulating factor plus erythropoietin: results from a randomized phase II study and long-term follow-up of 71 patients. (Hellstrom-Lindberg et al, 1998). Studies with long-term follow-up have shown no negative impact on survival or evolution to leukemia (Jadersten M et al, 2005). In fact, these studies have shown that ESAs with or without G-CSF (granulocyte colony stimulating factor) can induce long-lasting responses and transfusion independency in defined subsets of MDS patients. A recent pooled analysis of nearly 2600 individuals with low-risk MDS indicated that those receiving ESAs with or without G-CSF demonstrated greater overall and progression-free survival than those patients who did not receive growth factors, after controlling for baseline patient characteristics. (Golshayan AR et al, 2007).

Even more recent studies, some in abstract form but with manuscripts in preparation, continue to buttress the role of ESAs for patients with MDS without evidence that ESAs increase the rate of transformation to acute leukemia. Miller, et al., reported on 105 MDS patients treated with either supportive care or erythropoietin (EPO). (Miller KB, et al 2004, manuscript in preparation). In this study, the response rate, defined as at least a decrease in transfusion requirement, was 35% in the EPO (erythropoietin) arm and 9% in the supportive care arm (p=.002). Transformation to AML (acute myeloid leukemia) occurred in 3.6% of patients on supportive care and 0.0% of patients receiving EPO. Toxicities were comparable across all patients. Neither EPO nor the addition of G-CSF was associated with an increased rate of transformation to acute leukemia. In another trial the effect of growth factor treatment was evaluated in 363 patients with MDS with different probability of response. All patients were transfusion dependent (n=176) or anemic with hemoglobin level below 10 g/dL (n=187). The erythroid response (transfusion independence) was seen in 41% of treated patients with median duration of 23 months (range: 3-116+). There was no significant impact on risk of leukemic transformation in patients with low (p=0.75) or high (p=0.21) transfusion need. (Jadersten M, et al 2006.).

This is a sampling of studies addressing the long term use of erythropoietin with or without G-CSF in MDS patients compared to either randomized controls or historical controls. These studies have shown no negative impact on survival or leukemic evolution and, thus, these data conflict with and do not substantiate CMS's statement that the evidence is sufficient to conclude that ESA treatment is not reasonable and necessary for these Medicare beneficiaries because of a possible deleterious effect of the ESA on their underlying disease. Indeed, they provide strong evidence that treatment of anemia in MDS patients with erythropoietin with or without G-CSF can induce positive effects, including long-lasting transfusion independence without risk of leukemic transformation.

To ensure that CMS's final decision memo for ESAs reflects the state of the science and is based on principles of evidence-based medicine, CMS needs to consider these data on the safe and effective use of ESAs in MDS patients. (See also Hellstrom-Lindberg, 2005, Hellstrom-Lindberg, Eva, et al., 2003; Terpos, Evangelos, et al., 2002; Hellstrom-Lindberg, Eva, et al., 1998; Hellstrom-Lindberg, Eva, et al., 1997; Stein, Richard S., et al, 1991).

It is also important to note, that the studies showing significant and life-threatening events in certain patients who were treated with ESAs for non-renal diseases do not appear to have included patients with MDS, but only patients who had end-stage solid cancers and/or renal disease. In addition, in those studies, the patients' hemoglobin levels typically were kept above 12 g/dl while patients with MDS and other bone marrow failure syndromes rarely reach a hemoglobin level that high. Thus, findings from these studies should not be applied to patients with MDS.

ASH understands that CMS is concerned about potential risks that can be associated with use of ESAs (cardiovascular, thrombotic events, hypertension) documented in physician references, such as Micromedex. While ASH supports use of these types of references and guidelines to help physician decision making, the Society also recognizes that specialists who treat complex hematologic diseases must also consider each patient's individual circumstance and the standard of practice in the community to determine appropriate care. Removing coverage for ESAs for patients with MDS will be an arbitrary policy that is not justified by sufficient scientific evidence, does not reflect the standard of practice of experts in the field, and that will harm some Medicare beneficiaries.

#### Other Proposed Restricted Conditions -

ASH proposes clarification on the following conditions for which CMS is seeking public comment that "ESA treatment is not reasonable and necessary for beneficiaries either because of a deleterious effect of the ESA on their underlying condition or because the underlying disease increases their risk of adverse effects related to ESA use":

- The anemia of myeloid cancers: As discussed above, MDS should be excluded from this restriction.

- The anemia of cancer not related to cancer treatment: Erythroid hypoplasia leading to anemia may occur weeks to months following cessation of chemotherapy or radiation therapy. This may be the first sign of MDS, however MDS may never develop. The use of ESAs may decrease transfusion requirements in these patients. Even though the causal relationship between the anemia and previous treatment may be difficult to document, it would be reasonable not to exclude these patients from receiving ESAs.
- Any anemia associated with radiotherapy: Many patients receive chemotherapy concomitant with radiotherapy, or in series with radiotherapy. The restrictive language should be specific for anemia during primary treatment with radiotherapy.
- Patients with thrombotic episodes related to malignancy: There is no clinical evidence that these patients are at higher risk for complications related to treatment with ESAs. There is, of course, much published evidence demonstrating that an increase incidence of thrombotic episodes are related to certain malignancies and with certain therapies in the treatment of malignancies. Appropriate anticoagulation may be required. Given the concern of a general increase in VTE when ESAs are used to increase the hemoglobin above 12 g/dl, physicians need to carefully monitor the hemoglobin in these patients, as they would for any patient receiving ESAs.

#### ***CMS Proposed NCD Treatment Limitations***

1. *The hemoglobin/hematocrit levels immediately prior to initiation of dosing for the month should be <9 g/dl/27% in patients without known cardiovascular disease and <10 g/dl/30% in patients with documented symptomatic ischemic disease that cannot be treated with blood transfusion-*

ASH opposes CMS's proposed policy of initiating therapy at 9 g/dl in each month because it is not supported by scientific evidence. CMS has not provided any clinical or scientific rationale for setting a hemoglobin upper limit at 9 g/dl when the recently revised FDA label is not to exceed 12 g/dl. ESAs should be started in appropriate clinical settings at a hemoglobin level at or below 10 g/dl/ 30%. It should be understood that the hemoglobin level of 10 g/dl is not a trigger, but guidepost for the assessment of the patient's physiologic needs. ASH notes, however, that there may be extenuating circumstances when treating patients with co-morbidities, such as cardiac or pulmonary disease, (which should be documented) that could justify use of ESAs before the hemoglobin has decreased to 10 g/dl/30%.

The therapeutic goal should be a hemoglobin level of no higher than 12 g/dl and recommends that the dose of ESA be modified in accordance with the recent FDA black box warning when the hemoglobin approaches 12 g/dl. ASH believes it is important to encourage doctors to be vigilant in monitoring patient blood counts when treating with ESAs and iron levels in non-responders.

2. *Maximum Covered Treatment Duration*

ASH believes that the treatment recommendation should be based upon the disease and CMS's proposed limitation of 12 weeks is without support in the clinical evidence and should be re-evaluated. Chemotherapy regimens are frequently prolonged and may last beyond 12 weeks. In

addition, patients experience a variable number of courses of chemotherapy in a year depending on tumor type, extent of disease, and response to therapy. As such, CMS's proposal is arbitrary and could hurt Medicare beneficiaries who are prescribed chemotherapy regimens in excess of 12 weeks or who require multiple courses in a year.

Further, ASH notes that a patient may continue to suffer from anemia for some time following completion of chemotherapy treatment and consequently recommends that coverage of ESAs be continued for treatment of anemia for 90 days post chemotherapy. If the anemia persists beyond 90 days after completion of chemotherapy, it would be reasonable to re-evaluate the anemia to determine if this continues to be a result of the chemotherapy, thereby justifying continuation of ESA treatment, or if another process is in place. ASH believes most patients should recover within this time period, but notes evidence from randomized clinical trials concerning this issue is not available and recommends prospective studies concerning this topic.

### 3. Maximum Covered Treatment Dose

CMS's proposed restriction is inconsistent with the FDA-approved dosing regimen for ESAs. The dose of ESAs is to be titrated drugs used to achieve specific hemoglobin levels. The starting doses and dose adjustment guidelines are clearly delineated in the product label and clinical practice guidelines. Moreover, the FDA-approved labeling for darbepoetin alfa states that one of the product's dosing regimens allows for administration at a dose of 500 mcg every three weeks (*i.e.*, up to 1,000 mcg per six weeks unless there are dose reductions). Limiting the total dose of darbepoetin alfa to 630 mcg per 4 weeks will limit the ability for physicians to effectively manage anemia in patients who may require a higher than average dose to respond and disadvantage patients who are prescribed every-three-week dosing given with their chemotherapy regimens. Similarly, the labeled dose of epoetin alfa is 40,000 U per week and the product label recommends an increase to 60,000 U per week (*i.e.*, 360,000 U per six weeks), for patients who do not have satisfactory response after 4 weeks of therapy. (Rizzo DJ, Lichtin AE, Woolf SH, et al, 2002)

### 4. Discontinue Use of ESA in Non-Responders After 4 Weeks

ASH believes CMS's proposal is not based on scientific evidence. ESAs should not be continued after six to eight weeks in the absence of response, assuming the appropriate dose increase (titration) has been attempted in low-responders.

### 5. Discontinue Use of ESA if Increase in Fluid Retention

ASH believes this proposal is not founded in scientific evidence. Because this recommendation is not based on clinical evidence, it should be removed from the final decision memo.

### 6. Discontinue Use of ESA if Rapid Rise in Hemoglobin/Hematocrit

While ASH agrees that patients should not experience too rapid a rise in their hemoglobin/hematocrit level, the proper response, as with other medical interventions, should be for the physician to make a dosage adjustment not to discontinue use. ASH believes this proposal should be removed from the final decision memo.

***CMS Proposal to Allow ESA Therapy for Beneficiaries with Cancer Only Within Clinical Research Studies***

ASH opposes CMS's proposal that ESAs be available to Medicare beneficiaries only in the context of clinical studies. This proposed restriction for an FDA-approved indication would be inappropriate and unprecedented for any Medicare covered drug or biological. Further the proposal is not justified based on the multitude of published evidence supporting ESA use. Therefore, this proposal should not be finalized.

***Additional Concerns with CMS Proposed NCD***

***Impact of Transfusions as Alternative Treatment -***

The alternative to ESA therapy would be transfusion. In patients with MDS, where chronic transfusions would substitute for the use of ESAs, the risks would be substantial and would include alloimmunization, TRALI (transfusion-related lung injury), and iron overload. The treatment of iron overload in and of itself carries substantial risk to the patient. Furthermore, the inconvenience to the patient and the impact on the quality of life associated with transfusions should be taken into account in these chronically ill patients.

ASH also notes that ESAs help to reduce the need for transfusions and thereby alleviate strain on the nation's blood supply. Therefore, the impact on the blood supply also should be taken into account when determining changes in the use of these products.

***Additional Research Needed -***

ASH acknowledges that we need to learn more about the optimal uses and potential side-effects of ESAs. The use of ESAs in the area of hematologic malignancies requires further clinical study. ASH encourages the development of larger Phase III studies, perhaps under the CMS CED program to help answer these questions.

***Conclusion***

In conclusion, ASH has deep concerns about the proposed NCD. Based on scientific evidence and expert consensus of clinicians, the Society opposes the proposed restriction for anemia of MDS and the proposed limitations on ESA treatment dose and duration. While emerging safety concerns raised in recent studies indicate the need for CMS to review its policies concerning ESAs, ASH believes the proposed NCD inappropriately restricts use of ESAs because a number of the proposals are not supported by the preponderance of scientific data or are in conflict with expert scientific analysis.

ASH would like to work with CMS as the agency evaluates the evidence for its proposed coverage policy and the consequences of the proposal on patients with MDS and other

hematologic malignancies. ASH is currently finalizing revisions to its evidence-based clinical practice guidelines on ESAs with the American Society of Clinical Oncology. The updated guidelines are expected to be published in September and we will share them with CMS upon their completion. In the meantime, please do not hesitate to contact the Society at [mbecker@hematology.org](mailto:mbecker@hematology.org) if we can answer any question or provide assistance.

Sincerely,



Andrew I. Schafer, MD  
President



Samuel Silver, MD, PhD  
Chair, ASH Reimbursement Subcommittee  
Councilor, ASH Executive Committee

Italian Cooperative Study Group: A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes. *British Journal of Haematology*. 103: 1070-1074, 1998

Jadersten M, Montgomery SM, Dybedal I, et al: Long-term outcome of treatment of anemia in MDS with erythropoietin and G-CSF. *Blood*. 106(3): 803-11, 2005

Jadersten M, Luca Malcovati, Ingunn Dybedal, et al: Treatment with Epo and GCSF improves survival in MDS patients with low transfusion need. Proc Am Soc Hematology meeting, 12/06. *Blood* 108(11): 158a, 2006

Leyland-Jones B, Semiglazov V, Pawlicki M, et al: Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: A survival study. *J Clin Oncol* 23: 5960-5972, 2005

Leyland-Jones B, BEST Investigators and Study Group: Breast cancer trial with erythropoietin terminated unexpectedly. *Lancet Oncol* 4: 459-460, 2003

Littlewood TJ, Bajotla E, Nortier JW, et al: Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving non-platinum chemotherapy: Results of a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 19:2865-2874, 2001

Miller KB, Kim HT, Greenberg P, et al: Phase III prospective randomized trial of EPO with or without G-CSF versus supportive therapy alone in the treatment of myelodysplastic syndromes (MDS): Results of the ECOG- CLSG Trial (E1996). Proc Am Soc Hematology meeting, 12/04. *Blood*. 104(11): 24a, 2004. (manuscript in preparation)

Park S, Grabar S, Kelaidi C, et al, for the Groupe Francophone des Myélodysplasies (GFM): Has treatment with EPO +/- G-CSF an impact on progression to AML and survival in low/int-1-risk MDS? A comparison between French-EPO patients and the IMRAW database. Proc International MDS Symposium, Florence, May 2007. *Leukemia Res*: 31 (Suppl 1): S113, 2007

Rizzo DJ, Lichtin AE, Woolf SH, et al: Use of epoetin in patients with cancer: Evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *J Clin Oncol* 20:4083-4107, 2002

Stein, Richard S., et al: Pharmacologic doses of recombinant human erythropoietin in the treatment of myelodysplastic syndromes. *Blood*. 78: 1658-1663, 1991

Terpos, Evangelos, et al: Prolonged administration of erythropoietin increases erythroid response rate in myelodysplastic syndromes: a phase II trial in 281 patients. *British Journal of Haematology*. 118: 174-180, 2002

Witzig TE, Silberstein PT, Loprinzi CL, et al: A phase III randomized double-blind study of epoetin alfa versus placebo in anemic patients with cancer undergoing chemotherapy. *J Clin Oncol* 23: 2606-2617, 2005



**SWEDISH CANCER INSTITUTE**

June 4, 2007

Steve Phurrough, M.D., MPA  
Coverage and Analysis Group  
Centers for Medicare and Medicaid Services  
Department of Health & Human Services  
Mailstop: C1-13-18  
7500 Security BLVD  
Baltimore, MD 21244

**RE: Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N)**

EXECUTIVE DIRECTOR  
Albert B. Einstein, Jr., MD

Dear Dr. Phurrough:

1221 Madison St.  
Arnold Pavilion  
Suite 1110  
Seattle, WA 98104  
Phone (206) 215-3536  
Fax (206) 215-3537  
www.swedish.org

The Swedish Cancer Institute at the Swedish Medical Center in Seattle, Washington appreciates this opportunity to comment on the Centers for Medicare and Medicaid Services' (CMS) proposed decision regarding the Medicare National Coverage Determination (NCD) for Erythropoiesis Stimulating Agents (ESAs).<sup>1</sup> The Swedish Cancer Institute has grown into the Northwest's largest cancer-care program, offering patients the most extensive range of services and expertise in the region. The Swedish Cancer Institute includes leading cancer specialists, a broad range of treatment options, state-of-the-art facilities and equipment, and cancer care that is as personal as it is progressive and comprehensive.

As a result of the proposal by CMS, more patients with Myelodysplastic syndrome (MDS) and chemotherapy induced anemia may require blood transfusions, which are most often given in the hospital setting. This may put a serious strain on the nation's blood supply, thus affecting not only cancer and MDS patients, but many other types of patients as well. It may also add an additional strain on hospital resources, with hospitals having to utilize more space and personnel to administer the transfusions.

Swedish is concerned that the increased number of transfusion patients may create an extra administrative burden, as well as a burden on resources that, until now, were being used for other purposes. When conducting a blood transfusion, services such as blood typing, transfusion monitoring, and usage of bed space and hospital personnel must all be taken into account.

---

<sup>1</sup> <http://www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?id=203>

171

Currently, MDS and chemotherapy induced anemia patients are able to get similar results from ESAs as they would be getting from blood transfusions. However, it is a much less time consuming process. Some blood transfusions can last many hours, causing a strain not only on the patient, but also on the hospital.

The Swedish Cancer Institute feels that the best course of action for CMS to take would be to cover for all indications already on the FDA labels and to also use the guidelines for ESA usage that are already in place from the American Society of Hematology (ASH). CMS should also deny coverage for an over-usage or usage of the treatment beyond what is allowed by the FDA and the compendia.

Swedish greatly appreciates this opportunity to comment on the proposed NCD. We support the proper usage of these drugs and the effects they can have on a patient's quality of life, and in no way condone its purported over-usage.

We would be pleased to answer any questions regarding these comments. Please contact me if Swedish can be of any assistance as CMS continues to evaluate and develop its approach to coverage of ESAs.

Sincerely,

A handwritten signature in black ink, appearing to read 'Albert B. Einstein, Jr.', with a stylized, cursive script.

Albert B. Einstein, Jr., MD, FACP  
Executive Director  
Swedish Cancer Institute  
Swedish Medical Center

Joshua J. Ofman, MD, MSHS  
Vice President  
Global Coverage and  
Reimbursement  
Global Health Economics



Amgen Inc.  
One Amgen Center Drive  
Thousand Oaks, CA 91320  
805.447.0787  
Fax 805.480.1254  
Email [jofman@amgen.com](mailto:jofman@amgen.com)  
[www.amgen.com](http://www.amgen.com)

June 1, 2007

Steve Phurrough, MD, MPA, CPE  
Director, Coverage and Analysis Group  
Office of Clinical Standards and Quality  
Centers for Medicare and Medicaid Services  
Department of Health and Human Services  
Mail Stop: C1-09-06  
7500 Security Boulevard  
Baltimore, Maryland 21244

Re: Proposed Decision Memorandum for Erythropoiesis Stimulating Agents for Non-Renal Disease Indications (CAG-00383N)

Dear Dr. Phurrough:

Amgen Inc. (Amgen) is a science-based company, committed to developing innovative products that treat grievous illnesses. The highest levels of patient safety are an important part of this commitment throughout the lifecycle of our products. We communicate proactively and regularly with the U.S. Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services (CMS) regarding the safety of our products, and Amgen is committed to working with CMS to provide objective, rigorous, and evidence-based information in response to the agency's Proposed Decision Memorandum (PDM) for Erythropoiesis Stimulating Agents (ESAs) for Non-Renal Disease Indications (CAG-00383N) released on May 14, 2007.<sup>1</sup> Amgen scientists developed the breakthrough molecules known as ESAs and have perhaps the world's most significant knowledge base and experience with this class of biologicals.<sup>2</sup>

As we have shared with CMS previously, Amgen takes seriously the recent safety concerns. We are also attentive to the concerns of CMS regarding the appropriate use of this class of products. Based on our understanding of the important benefits associated with ESA use in oncology, we have prepared a detailed response to the proposed National Coverage Determination (NCD) and offer specific scientific and clinical recommendations for the agency's consideration in preparing a finalized NCD on ESAs. These recommendations are intended to help CMS balance understandable safety concerns with the need to provide appropriate access to ESAs, which serve an important and well-recognized supportive care role in many types of cancer.<sup>3</sup>

311

## I. EXECUTIVE SUMMARY

---

Anemia—defined as a below-normal level of red blood cells, hemoglobin, or both—is a debilitating complication that is common in cancer patients receiving chemotherapy, patients with cancer not receiving chemotherapy, and patients with myelodysplastic syndrome. Individuals with cancer-related anemia may present with a range of symptoms—most frequently fatigue, but also potentially including dizziness, shortness of breath, palpitations, lack of endurance, and angina, among others.

ESA therapy revolutionized anemia management. For nearly 15 years, ESAs have been employed by physicians to reduce the burden of red blood cell transfusions in patients receiving myelosuppressive chemotherapy. Clinical studies make plain that, compared with placebo, ESA treatment reduces by half the number of transfusions in such patients and extends the time to first transfusion. In addition, ESA treatment helps alleviate the signs and symptoms of anemia, which provoke physicians to transfuse red blood cells, and clinical trials report improvements in patient-reported outcomes for chemotherapy patients.

While CMS has a legitimate role to play in determining coverage policy for ESAs under the authority granted to it by Congress (*i.e.*, to determine the uses that are “reasonable and necessary”), in finalizing a NCD for these products, we urge CMS to guide its decisions by several important principles, including:

- That the coverage policy should be based strictly on the principles of evidence-based medicine, avoiding a physiologic rationale as a basis for coverage restriction and also avoiding coverage parameters that have never been studied in clinical trials or utilized in clinical practice;
- That CMS should acknowledge the role of the FDA in its judicious evaluation of the safety profile of the ESAs, and avoid using coverage policy to play the role of the FDA by issuing prescribing instructions;
- That the agency’s decisions should reflect the paramount importance of the physician’s role in delivering optimal cancer treatment for his or her patients;
- That the agency’s actions should be made in full compliance with relevant laws, regulations, and past CMS statements on the development of coverage policies; and
- That the agency should ensure that the coverage process is open and transparent to all stakeholders.

Importantly, CMS has proposed broad coverage restrictions to the FDA-approved indication for ESAs in chemotherapy-induced anemia (CIA),<sup>4</sup> as well as broad restrictions to off-label uses. However, there is an absence of compelling clinical evidence in CIA patients on which to base these restrictions. The underlying logic of the PDM, which restricts coverage for ESAs in CIA in addition to off-label uses, appears to be based on the following three suppositions:

1. That safety signals observed in isolated off-label, experimental, or investigational uses should be extrapolated to ESA therapy in CIA and that these isolated studies are apparently judged to be of greater weight than the entire body of relevant data in CIA patients.

2. That the hypothesis that erythropoietin (EPO) receptors (EPO-R) may be expressed on tumors is valid, that these receptors—interacting with ESAs—could perhaps promote tumor growth, and that this unproven phenomenon would prove deleterious to cancer patients.
3. That a hemoglobin initiation level not to exceed 9.0 g/dL will minimize any risks while maintaining patient benefit.

***In response to the first supposition, Amgen encourages CMS not to extrapolate the safety signals in off-label and experimental conditions to CIA based on individual studies, but rather to rely on a robust analysis of all available evidence to guide coverage policy.***

The reasons that the approach adopted in the PDM is scientifically and clinically unjustified are summarized as follows:

- CMS can be confident that Amgen has been diligent in our pharmacovigilance, has supplied all available data to the FDA in a timely manner, and has proactively shared these data with health care professionals. The entire body of relevant data is included in the analyses contained herein.
- Robust analyses of CIA studies, including both study-level and patient-level meta-analyses, support a neutral impact of ESAs on survival.
- Although subgroup analyses point to decreased overall survival in ESA-treated patients with head and neck cancer undergoing radiotherapy, and in patients with anemia of cancer (AOC) who have active cancer not receiving or planning to receive chemotherapy or radiation therapy, these findings should not be extrapolated to the broad population of CIA patients.
- Several ongoing studies will continue to inform CMS, health care providers, and patients about the safety of ESAs.
- Several prominent medical societies and experts have also questioned the evidence base underlying the PDM.

***In response to the second supposition, Amgen urges CMS to complete a careful, critical assessment of the clinical literature and evidence-base regarding EPO-R.***

Such an assessment leads to a conclusion that there is no definitive evidence of EPO receptor involvement in tumor progression for the following reasons:

- While published papers provide data seemingly consistent with the hypothesis of EPO-R involvement in tumor progression, examination of the evidence shows it to be either flawed or circumstantial. This view has been confirmed by independent reviews of the literature, and is shared by several experts in the fields of oncology and immunohistochemistry.
- Several additional facts, which help support this view, are as follows:
  - EPO-R is not expressed at significant levels in human cancer cells, and EPO itself does not stimulate tumor growth.
  - The EPO-R gene does not behave as an oncogene.
  - There exist no satisfactory antibody reagents for detecting EPO-R, and the most commonly used EPO-R polyclonal antibody (*i.e.*, Santa Cruz C-20) was shown to detect heat shock protein HSP70, not EPO-R, in tumor samples.

- Experiments designed to detect cell surface EPO-R on tumor cell lines by measuring binding of radio-labeled EPO showed no evidence of EPO binding, and therefore no evidence that EPO-R is present on these cells.

***In response to the third supposition, Amgen notes that the agency's proposed policy of initiating therapy at 9.0 g/dL in each month is not supported by scientific evidence.***

Importantly, CMS has not provided any clinical or scientific rationale for setting an implicit hemoglobin upper limit at 9.0 g/dL (*i.e.*, initiation at 9.0 g/dL in each month) when the recently revised FDA label is not to exceed 12.0 g/dL.

#### Key Points on Initiation Level

- Almost all randomized clinical trials (RCTs) have initiated ESA therapy when the hemoglobin level is less than 11.0 g/dL. As a result, evidence-based clinical practice guidelines have recommended the initiation of ESA therapy in cancer patients when the hemoglobin level is less than 11.0 g/dL.
- In placebo-controlled trials, when ESA-treated patients initiate therapy at hemoglobin < 9.0 g/dL, 68 percent receive at least one transfusion; however, if the hemoglobin is between 10.0 and 11.0 g/dL, only 26 percent receive at least one transfusion. Thus, the agency's proposed policy would increase the percentage of patients who receive at least one transfusion.
- A meta-analysis of studies with an average hemoglobin level between 10.0 to 12.0 g/dL at baseline showed neutral outcomes with respect to overall survival (odds ratio, 0.86; 95 percent CI 0.69 – 1.08).
- Comparison of strategies for early intervention (generally, initiation of therapy at approximately 12 g/dL) and later intervention (generally, initiation of therapy when hemoglobin level drops below 10 g/dL) have been evaluated in a number of RCTs. A meta-analysis of these studies has demonstrated an approximate 50 percent reduction in the risk of transfusion favoring the early intervention approach (relative risk, 0.55, 95 percent CI 0.42 – 0.73).

#### Key Points on Hemoglobin Target Level

- Most of the RCTs that define the efficacy and safety of the ESAs targeted hemoglobin levels of 11.0 to 13.0 g/dL, with dose withholding at a minimum of 13.0 g/dL. These data represent the highest level of evidence upon which CMS typically bases coverage policies.
- Current evidence-based clinical practice guidelines (*i.e.*, American Society of Hematology [ASH]/ American Society of Clinical Oncology [ASCO], National Comprehensive Cancer Networks (NCCN), European Organisation for Research and Treatment of Cancer [EORTC]) recommend targeting hemoglobin levels in the range of 11.0 to 13.0 g/dL.
- The recent FDA label change, in response to safety findings, includes a change from a target hemoglobin of 10.0 to 12.0 g/dL to a hemoglobin limit of 12.0 g/dL. **The recent FDA Oncology Drugs Advisory Committee (ODAC) panel voted, based on an analysis of existing data, that this level not be changed.**

- When survival outcomes are evaluated through meta-analysis in CIA, the hemoglobin threshold of 12.0 g/dL to 13.0 g/dL is not associated with an increase in mortality, with an odds ratio for overall survival of 0.87 (95 percent CI, 0.54, 1.38).
- Finally, in a recent Agency for Healthcare Research and Quality (AHRQ) meta-analysis of ESA safety, the relative risk of venous thromboembolism (VTE) does not vary when hemoglobin thresholds range from > 13.0 g/dL to 16.0 (Seidenfeld et al., 2006).
- While Amgen does not recommend that physicians target a hemoglobin level > 12.0 g/dL in anemic cancer patients, clinicians must practically manage hemoglobin targets and variability. To manage patients effectively, physicians need discretion to determine, for the individual patient, whether to reduce the dose or withhold the dose when the hemoglobin level temporarily exceeds 12.0 g/dL.

***CMS has proposed a limit of 12 weeks per year for ESA treatment. This timeframe is without support in the clinical evidence and should be re-evaluated carefully in light of the best available data.***

Chemotherapy regimens in cancer patients are frequently prolonged, and may last beyond 12 weeks. Moreover, patients experience a variable number of courses of chemotherapy in a year depending on tumor type, extent of disease and response to therapy. As such, the agency's proposal could inadvertently discriminate against Medicare beneficiaries who are prescribed chemotherapy regimens in excess of 12 weeks or who require multiple courses in a year. There is insufficient evidence to support this recommendation.

Moreover—as Amgen has commented previously and ASH has recommended—the duration of ESA therapy might need to be up to 90 days after completion of chemotherapy with longer durations depending on individual patient circumstances due to the myelosuppressive effects of chemotherapy.

### **Overview of Amgen's Recommendations**

While there is little scientific basis to support many of the coverage restrictions proposed by CMS, there are aspects of the policy that are clinically and scientifically reasonable, and where Amgen and CMS share common views. Amgen agrees with several of the agency's non-coverage recommendations provided that specific clarifications (noted below in italics) are made, as detailed in Table 1.

**Table 1: Overview of Amgen's Recommendations on Eight Areas of Agreement with the PDM**

Proposal to Restrict Coverage in Eight Areas	Amgen Recommendation
<ol style="list-style-type: none"> <li>1. Anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis</li> <li>2. Anemia of myeloid cancers, <i>specifically acute myeloid leukemia (AML) and chronic myeloid leukemia (CML)</i></li> <li>3. Anemia associated with the treatment of myeloid cancers or erythroid cancers</li> <li>4. Anemia associated with <i>primary treatment with radiotherapy</i></li> <li>5. Prophylactic use to prevent chemotherapy-induced anemia <i>in patients who have never suffered from CIA</i></li> <li>6. Prophylactic use to reduce tumor hypoxia <i>in non-anemic patients</i></li> <li>7. Patients with erythropoietin-type resistance due to neutralizing antibodies</li> <li>8. Anemia due to cancer treatment if patients have uncontrolled hypertension</li> </ol>	<p>Consider Finalizing These 8 Proposed Coverage Limitations</p>

Note: The italicized text represents specific clarifications that would make the proposed policy clearer.

In light of the clinical evidence, Amgen recommends that CMS reconsider a series of proposed coverage restrictions, as noted in Table 2.

**Table 2: Overview of Amgen's Recommendations on 10 Restrictions for CMS to Reconsider Based on Clinical Evidence**

Proposal to Restrict Coverage in 10 Areas	Review of Clinical Evidence	Coverage Recommendation
<ol style="list-style-type: none"> <li>1. Use with anti-angiogenic and anti-epidermal growth factor receptor (EGFR) monoclonal antibody therapies</li> </ol>	<ul style="list-style-type: none"> <li>• ESAs do not stimulate angiogenesis based on a comprehensive review of the literature and Amgen's experimental results</li> <li>• The PDM appears to have blended the results from two separate and unrelated studies: (1) the PACCE study of Vectibix™ (panitumumab) in colon cancer patients and (2) the study of darbepoetin alfa in patients with AOC (Amgen Study 20010103)</li> </ul>	<ul style="list-style-type: none"> <li>• Because this recommendation is not based on any clinical evidence, it should not be finalized</li> </ul>

Proposal to Restrict Coverage in 10 Areas	Review of Clinical Evidence	Coverage Recommendation
2. Anemia of cancer (AOC)	<ul style="list-style-type: none"> <li>• Anemia of cancer represents a heterogeneous group of patients with solid and hematologic tumors in various stages of disease</li> <li>• There is published evidence of benefit from controlled clinical trials, without evidence of detrimental survival outcomes, in certain subgroups of patients receiving ESAs for AOC</li> <li>• We urge caution in extrapolating the safety finding in a specific subgroup of patients with active cancer not receiving or planning to receive chemotherapy or radiation therapy, to all AOC patients</li> </ul>	<ul style="list-style-type: none"> <li>• CMS should not provide coverage in AOC patients with active cancer not receiving or planning to receive chemotherapy or radiation therapy</li> <li>• CMS should provide coverage for other patients with AOC</li> </ul>
3. Patients with thrombotic episodes related to malignancy	<ul style="list-style-type: none"> <li>• There is insufficient evidence of increased relative risk in patients with prior thrombosis</li> <li>• ESA use in patients with thrombotic episodes is not a contraindication or a warning in the prescribing information</li> </ul>	<ul style="list-style-type: none"> <li>• Because this recommendation is not based on clinical evidence, it should not be finalized</li> </ul>
4. Myelodysplastic syndrome (MDS)	<ul style="list-style-type: none"> <li>• A systematic review of 59 studies (2,106 patients) with epoetin alfa and single arm studies of darbepoetin alfa support the safety and efficacy of ESAs in treatment of anemia associated with MDS (Ross et al., 2007)</li> <li>• Without ESA therapy, many MDS patients must undergo chronic red blood cell transfusions, carrying substantial risks, such as iron overload</li> </ul>	<ul style="list-style-type: none"> <li>• The restriction is unwarranted based on the available scientific evidence, and should not be finalized</li> </ul>

Proposal to Restrict Coverage in 10 Areas	Review of Clinical Evidence	Coverage Recommendation
5. Limits on hemoglobin level for ESA initiation and hemoglobin target	<ul style="list-style-type: none"> <li>• The PDM blends initiation threshold and target hemoglobin level, and ESAs have never been studied with an initiation level of hemoglobin &lt; 9.0 g/dL</li> <li>• Scientific evidence suggests that the greatest avoidance of transfusion occurs when ESAs are initiated at hemoglobin &lt; 11.0 g/dL</li> <li>• There is practical evidence of a target hemoglobin level, allowing physician flexibility in managing individual patients who require a dose reduction rather than a dose withholding at hemoglobin &gt; 12.0 g/dL</li> </ul>	<ul style="list-style-type: none"> <li>• CMS should implement an initiation level of hemoglobin &lt; 11.0 g/dL, which is evidence-based</li> <li>• CMS should consider the need for physician discretion to dose reduce rather than withhold when hemoglobin exceeds 12.0 g/dL during chemotherapy</li> </ul>
6. Limits on duration of ESA therapy	<ul style="list-style-type: none"> <li>• Chemotherapy regimens in cancer patients are frequently prolonged and last beyond 12 weeks, and the number of courses of chemotherapy in a year is highly variable</li> </ul>	<ul style="list-style-type: none"> <li>• Duration of therapy should be individualized for the particular patient</li> <li>• Because this recommendation is not based on clinical evidence, it should not be finalized</li> </ul>
7. Limits on ESA dosing	<ul style="list-style-type: none"> <li>• ESAs are dosed to achieve hemoglobin targets, and there is no known association between ESA dose and suboptimal outcomes</li> <li>• FDA label specifies to use lowest dose necessary to achieve hemoglobin objectives, and the dose and hemoglobin levels cannot be managed independently</li> </ul>	<ul style="list-style-type: none"> <li>• Because this recommendation is not based on clinical evidence, it should not be finalized</li> </ul>
8. Limits on dose adjustments	<ul style="list-style-type: none"> <li>• The criteria in the PDM are not predictive of response based on published literature</li> </ul>	<ul style="list-style-type: none"> <li>• Because this recommendation is not based on clinical evidence, it should not be finalized</li> <li>• CMS should allow for dose titration and continued product use based on the prescribing information</li> </ul>

<b>Proposal to Restrict Coverage in 10 Areas</b>	<b>Review of Clinical Evidence</b>	<b>Coverage Recommendation</b>
9. Limits on patients with weight gain and fluid retention	<ul style="list-style-type: none"> <li>• This proposal is not founded in scientific evidence</li> </ul>	<ul style="list-style-type: none"> <li>• Because this recommendation is not based on clinical evidence, it should not be finalized</li> </ul>
10. Limits on ESA use within clinical research programs	<ul style="list-style-type: none"> <li>• In CIA, the evidence supports a positive benefit-to-risk profile when used according to the prescribing information and a neutral risk on survival and tumor progression</li> <li>• Well-described risks and patient-monitoring recommendations are included in the FDA-approved product labeling</li> </ul>	<ul style="list-style-type: none"> <li>• Such a restriction for an FDA-approved indication would be inappropriate and unprecedented for any Medicare covered drug or biological</li> <li>• It is not justified given the multitude of published evidence supporting ESA use</li> <li>• Therefore, this consideration should not be finalized</li> </ul>

To support our recommendations, Amgen offers comments addressing the following areas:

- II. Analysis of the Clinical and Scientific Basis of the PDM (see page 10);
- III. Benefits of ESA Treatment (see page 37);
- IV. Analysis of the Policy Implications of the Proposed Non-Covered and Covered Clinical Indications (see page 40);
- V. Proposed Coverage Limitations (see page 45); and
- VI. Discussion of Limitation of Coverage to Only Beneficiaries Enrolled in Clinical Research Programs (see page 51).

## **II. ANALYSIS OF THE CLINICAL AND SCIENTIFIC BASIS OF THE PDM**

---

***CMS has proposed broad coverage restrictions to the FDA-approved indication for ESAs in CIA. However, there are no compelling clinical data in CIA patients on which to base these restrictions.***

The underlying logic of the PDM, which proposes dramatic coverage restrictions in the FDA-approved indication of CIA,<sup>6</sup> appears to rest on three suppositions. These suppositions are as follows:

1. That safety signals observed in isolated off-label, experimental, or investigational uses should be extrapolated to ESA therapy in CIA and that these isolated studies are apparently judged to be of greater weight than the entire body of relevant data in CIA patients.
2. That the hypothesis that EPO receptors (EPO-R) may be expressed on tumors is valid, that these receptors—interacting with ESAs—could perhaps promote tumor growth, and that this unproven phenomenon would prove deleterious to cancer patients.
3. That a hemoglobin initiation level not to exceed 9.0 g/dL will minimize any risks while maintaining patient benefit.

Below, we discuss these suppositions in turn.

**Response to  
Supposition 1:**                    **CMS should not extrapolate the safety signals in off-label and experimental uses and patient populations to CIA based on individual studies, but should rather rely on a robust analysis of all available evidence to guide coverage policy.**

**The reasons that the approach adopted in the PDM is scientifically and clinically unjustified are summarized below:**

- A. CMS can be confident that the entire body of relevant data is included in these analyses and that Amgen has been completely transparent with the FDA and CMS. There are 14 studies listed by CMS as “terminated, suspended, or otherwise not completed”, the implication being that data are not available for analysis or have been omitted from analyses. In fact, summary data are available for 11 of these studies and all of the available studies have been included in the study level meta-analyses. These analyses, therefore, provide a comprehensive assessment of the safety of ESAs in cancer patients and patients treated for CIA, in particular.
- B. These robust and comprehensive analyses of RCTs in CIA, including both study-level and patient-level meta-analyses, support a neutral impact of ESAs on overall survival and progression-free survival. These analyses strongly support Medicare coverage of ESAs in CIA.
- C. The 14 studies identified by the FDA as having “adequate follow-up” reflect a heterogeneous mixture of studies on-label, off-label and experimental uses. However, meta-analyses of these trials support the conclusions from Amgen’s robust, comprehensive meta-analyses and provide no evidence of adverse survival outcomes in patients receiving ESAs in CIA.

- D. Combined analyses of all relevant data, including data from studies in off-label uses, have identified subgroups of patients for whom the totality of data does and does not indicate a potential survival risk. These analyses point to an ESA-associated mortality risk in patients with head and neck cancer undergoing radiotherapy, and in patients with AOC who have active cancer not receiving or planning to receive chemotherapy or radiation therapy. Within CIA, some individual studies have raised safety signals, but others have not, and the weight of evidence across all CIA studies does not indicate that mortality is affected overall, in solid tumors (including breast cancer and lung cancer), or lymphoproliferative diseases.
- E. While ongoing studies will continue to inform CMS and other stakeholders about the safety of ESAs, the currently available body of evidence strongly supports coverage in CIA.
- F. Amgen is not alone in questioning the supposition that CMS should extrapolate the safety signals from a subset of individual, experimental studies to all patients with the proposed coverage restrictions in CIA.

For each of the points summarized above, we provide a detailed discussion below.

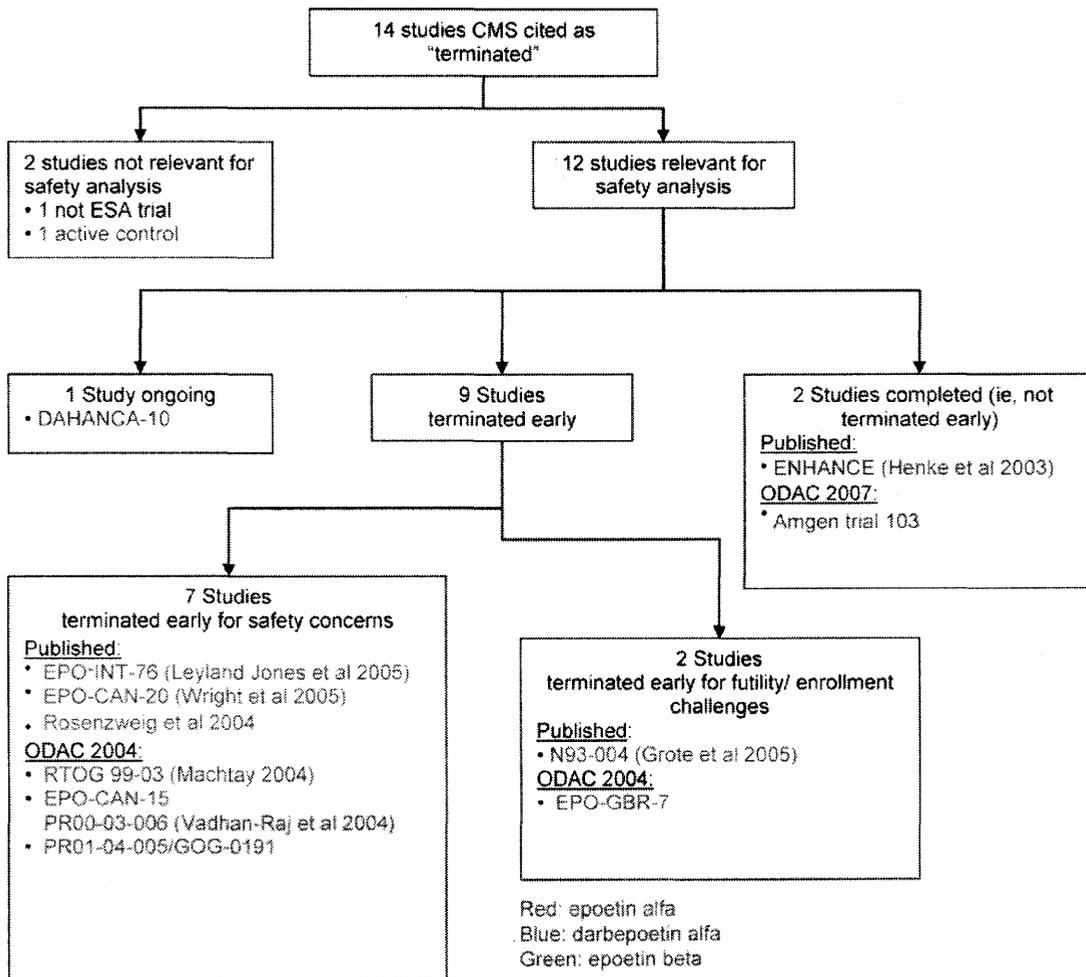
- A. *CMS can be confident that Amgen has been fully transparent and that all the relevant individual studies are included in this analysis.*

Based on the results of the individual studies that have raised safety concerns, Amgen has taken appropriate steps to safeguard patient safety by updating product labeling and broadly communicating the results of these studies as they have become available. Amgen has been fully compliant and transparent with regard to its participation in ODAC meetings and provided the FDA with full electronic datasets of its studies to permit FDA analysis of the data. With respect to Amgen's pharmacovigilance program that arose out of the 2004 ODAC meeting, Amgen has completed the Amgen-sponsored '20010145' study (which provided data earlier than was expected) and provided these data to the FDA (available at [ClinicalStudyResults.org](http://ClinicalStudyResults.org)). Amgen has actively engaged with and supported the 4 investigator initiated studies and been diligent in the provision of study updates and data in a timely manner to the FDA.<sup>7</sup>

There are 14 studies listed by CMS as "terminated, suspended, or otherwise not completed" (Chart 1 and Table 3). Data from 11 of the 14 studies were, in fact, included in the study level meta-analyses provided to FDA, ODAC, and CMS. Of the three remaining studies, one (DAHANCA-10) is still ongoing, one used an active comparator study (the Roche epoetin beta study: Hirsch et al., 2007), and one study was apparently cited in error. It should be noted that ten of the studies that were listed as missing by CMS were in fact disclosed and analyzed at the 2004 ODAC and again at the 2007 ODAC. These same ten studies are also included in the most recently published meta-analysis by the independent Cochrane study group (Bohlius et al., 2006b).

We summarize below the key points of each of the studies that CMS cited.

**Chart 1: Studies Referenced by CMS in the PDM  
 as “Terminated, Suspended, or Otherwise Not Completed”**



In summary, Amgen has taken the results of all individual studies that have raised concerns seriously, has acted in a timely manner to ensure patient safety, has included the results of all of these studies in its analyses, and has been diligent in the generation and provision of data to agencies to further understand the safety concerns that have been raised.

B. *Robust and comprehensive analyses of RCTs in CIA, including both study-level and patient-level meta-analyses, support a neutral impact of ESAs on overall survival and progression-free survival. These analyses strongly support Medicare coverage of ESAs in CIA.*

As previously indicated, thorough analysis of safety signals requires that a three-level approach to available data be taken, as follows:

- assessment of individual study data,
- meta-analysis of patient level data from multiple studies, and
- meta-analysis of study level data.

Amgen has engaged in analysis at all three of these levels in its assessment of safety of ESAs in oncology patients. Amgen conducted meta-analyses using both the odds ratio (for study-level analyses) and the hazard ratio (for patient-level analyses). Amgen presents the results of these meta-analyses using a random-effects model as this approach incorporates an assessment of variability between trials.<sup>8</sup> For the odds and hazard ratios, when the 95 percent confidence intervals include unity, no statistical significant differences between groups can be concluded.

The FDA recognizes patient-level integrated analyses as key data in regulatory filings to support safety (21 CFR 314, ICH E9). Such evidence is considered the highest level on the hierarchy of evidence (Seidenfeld et al., 2006; Harris et al., 2001). For time-dependent endpoints such as time to death, these analyses provide the most complete and rigorous description of the data. For these reasons, analyses of randomized controlled trial data conducted at the level of individual patients should rank the highest in evaluation of the safety of ESAs, and any coverage policy that CMS adopts in CIA should be based primarily on this evidence. Study-level meta-analyses also play an important role in evaluating the evidence base. While not as rigorous as patient-level analyses, appropriately conducted and analyzed study-level analyses contribute greatly to the overall safety assessment, as has recently been described with regard to the safety assessment of rosiglitazone-associated cardiac events (Nissen and Wolski, 2007). However, critical to the validity of any meta-analyses are the criteria for study selection with the exclusion of any randomized trials carefully justified. Any analyses that are performed where controlled randomized trials are not included (e.g., due to time period, design or other reasons) need to be carefully justified and performed as a sensitivity analyses to a more comprehensive analysis of all the evidence.

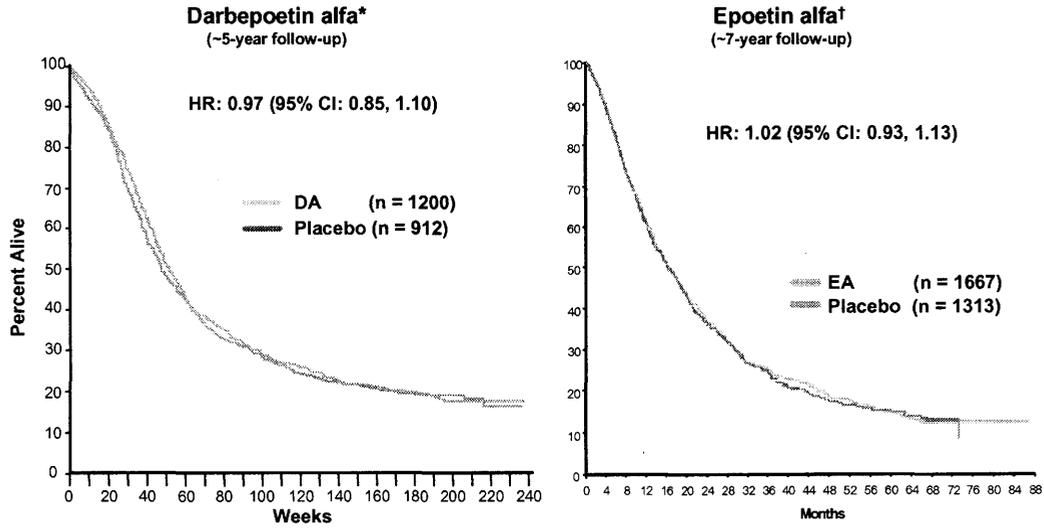
**Table 3: Biostatistical Perspective on the Importance of Meta-analyses**

Susan Ellenberg, Former FDA Biostatistician and Current Professor of Biostatistics and Associate Dean for Clinical Research at the University of Pennsylvania

“Some argue that you get the most reliable answers from meta-analysis, because you are putting together all of the information from randomized studies... but you never quite know how people selected the studies that went into meta-analyses.” (Cancer Letter, June 1, 2007)

A robust analysis of studies using individual patient-level data, including all placebo-controlled studies, demonstrates that ESA treatment poses no increased risk on overall survival or progression-free survival in patients with CIA. Kaplan-Meier plots for darbepoetin alfa and epoetin alfa studies are shown in Charts 2 and 3, respectively.

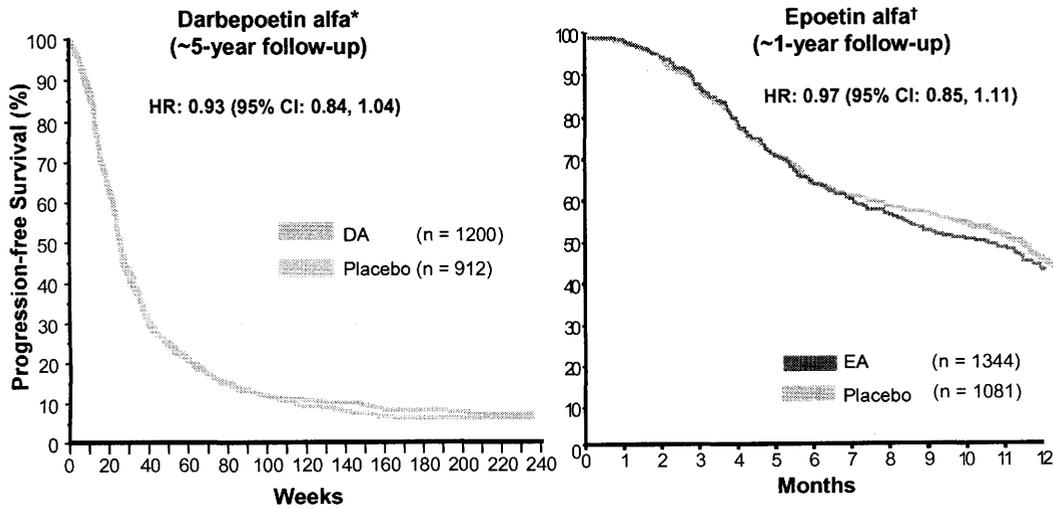
**Chart 2: No Impact on Overall Survival in Placebo-controlled CIA Studies**



\* 6 Randomized, placebo-controlled darbepoetin alfa CIA studies  
 † 11 Randomized, placebo-controlled Epoetin alfa in CIA studies (including BEST)

Presented at ODAC 2007

**Chart 3: No Impact on Investigator-determined Progression-free Survival In Placebo-controlled CIA Studies**



The median time (95% CI) to progression-free survival including long term follow up in weeks was 26 (25, 28) for darbepoetin alfa and 26 (24, 27) for placebo.

\* 6 Randomized Placebo-controlled Darbepoetin alfa CIA Studies

† 11 Randomized Placebo-controlled Epoetin alfa CIA Studies

In fact, no study in CIA has demonstrated an adverse effect of ESAs on tumor progression, as demonstrated in Table 4.

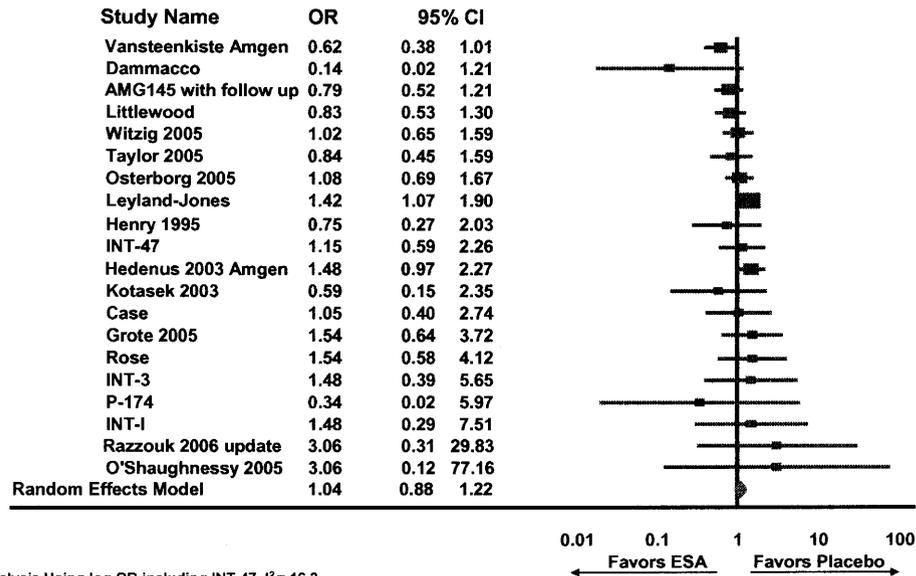
**Table 4: No Study in CIA Patients Reported Adverse Progression Outcomes**

Study	Total (N)s	Tumor	Response	HR, RR, or %ESA & % Control
Aapro et al., 2006 (BRAVE)	463	Metastatic breast	PFS	HR: 1.07 (0.89-1.3)
Blohmer et al., 2004	257	Cervical	RFS	15% & 24%
Grote et al., 2005	224	SCLC	PD (after 3 cycles)	7% & 8%
Leyland-Jones et al., 2005 (BEST; EPO-INT-76)	939	Breast	PD (final)	42% & 46%
			PFS	RR: 1.0 (p=0.98)
Möbus et al., 2007	658	Breast	5-year DFS (p=0.89)	72% & 71%
Strauss et al., 2005	74	Cervical	PD	RR: 1.08 (0.62-1.87)
Wilkinson et al., 2006	173	Ovarian	PD	11% & 2%
Amgen Study 20010145	597	SCLC	PFS	HR: 1.02 (0.86 – 1.21)

PD = disease progression; PFS = progression-free survival; DFS = disease-free survival;  
 RFS = relapse-free survival

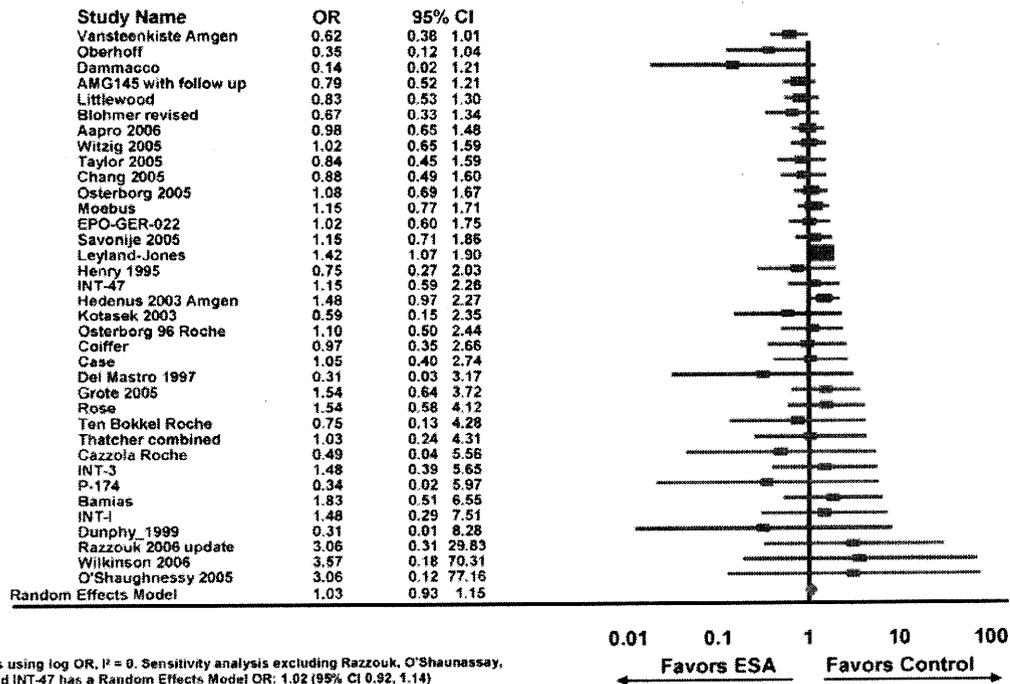
Finally, when an appropriate study-level meta-analysis is conducted of all CIA ESA studies (both published and unpublished), the findings of the patient-level meta-analysis are confirmed. As summarized on the following pages, this analysis is robust, as the same finding of a neutral impact on survival is shown when only placebo-controlled studies are included (Chart 4); when all studies with non-ESA controls are included (Chart 5); and when solid, lymphoproliferative, or mixed tumor populations are analyzed (Table 5).

**Chart 4: Combined Study-level Analysis of Overall Survival in Placebo-Controlled CIA Studies**



Meta Analysis Using log OR including INT-47,  $I^2 = 16.2$ .  
 Sensitivity analysis excluding O'Shaughnessy and Razzouk has a Random Effects Model OR of 1.03 (95% CI: 0.92, 1.20)  
 3 studies did not report any deaths.

**Chart 5: Meta-analysis of Death for All CIA Studies**



Meta Analysis using log OR,  $I^2 = 0$ . Sensitivity analysis excluding Razzouk, O'Shaughnessy, Wilkinson, and INT-47 has a Random Effects Model OR: 1.02 (95% CI 0.92, 1.14)  
 Three studies did not report any deaths (Hedenus, Cascinu, and Kurz) but were randomized CIA studies.

**Table 5: Combined Study Level Analysis of Overall Survival in CIA Studies by Tumor Type**

<b>Tumor Type</b>	<b>Random Effects OR (95% CI)s</b>	<b>I<sup>2</sup></b>
Solid (21 Studies)	1.00 (0.86, 1.16)	7.4%
Mixed (8 Studies)	0.96 (0.75, 1.24)	0%
Hematologic (7 Studies)	1.18 (0.87, 1.60)	8.7%

C. *The 14 studies identified by the FDA as having “adequate follow-up” reflect a heterogeneous mixture of studies on-label, off-label and experimental uses. However, meta-analyses of these trials support the conclusions from Amgen’s robust, comprehensive meta-analyses and provide no evidence of adverse survival outcomes in patients receiving ESAs in CIA.*

There have been six individual studies in which significant safety signals with ESAs in cancer patients have been observed (listed in Table 6) and results from these studies led to the ODAC meetings in 2004 and 2007. Amgen takes the safety signals generated by individual studies very seriously. The recent safety concerns have arisen primarily in the off-label and experimental population of patients with active cancer not receiving chemotherapy or radiotherapy and many have limitations regarding their conduct, interpretation or generalizability. While there are limitations in the individual trials and no consistent evidence of a detrimental effect in independent studies despite similar trials in the same population (e.g., Leyland-Jones et al., 2005 and Aapro et al., 2006 in newly diagnosed metastatic breast cancer patients), these concerns require a scientifically rigorous and objective review of all the relevant evidence across current licensed and unlicensed indications. It is critical that the results of these studies are appropriately integrated into the total body of evidence that exists for ESA use in oncology before conclusions can be drawn.

**Table 6: Review of Studies that Have Raised Safety Concerns for ESA Use**

Study	Population	Primary Objective	Hemoglobin Target (g/dL)	Overall Survival	Comments/Limitations
<b>Trials of ESAs in combination with chemotherapy</b>					
Total # of controlled trials in setting: 39					
Total number of controlled trials with possible negative signals regarding overall survival: 2					
BEST (Leyland Jones et al., 2005)	Metastatic breast	12-month overall survival	12-14	HR=1.37 (95% CI: 1.07, 1.74) p=0.012	<ul style="list-style-type: none"> <li>Conducted above current recommended use of ESAs</li> <li>No impact on PFS observed (HR=1.00 [95% CI: 0.85, 1.18] p=0.98)</li> </ul>
Amgen Study 20000161 (Hedenus et al., 2003)	Lympho-proliferative disease	Hemoglobin response	≤ 13-14 (women) ≤ 13-15 (men)	HR=1.36 (95% CI: 1.02, 1.82)	<ul style="list-style-type: none"> <li>No robust evidence of significant survival difference (alternate methods [e.g., odds ratio or relative risk], alternate study populations [ITT vs as treated] and unadjusted analyses are all neutral)</li> <li>Heterogeneous population enrolled with significant imbalances favoring placebo within key stratum</li> <li>No impact on PFS observed (RR=1.01 [95% CI: 0.79, 1.29])</li> </ul>
<b>Trials of ESAs without either radiotherapy or chemotherapy</b>					
Total # of controlled trials in setting: 9					
Total number of controlled trials with possible negative signals regarding overall survival: 2					
Amgen Study 20010103 (Glaspy et al., 2007)	Mixed tumors	Reduction of occurrences of transfusion	12-13	HR=1.22 (95% CI: 1.03, 1.45) p=0.022	<ul style="list-style-type: none"> <li>Heterogeneous population enrolled with significant imbalances within strata</li> <li>No robust evidence of significant survival difference (analyses adjusted for imbalances in known prognostic factors are neutral)</li> </ul>
Wright et al., 2007	NSCLC	QOL	12-14	HR=1.84 (95% CI: 1.01, 3.35) p=0.04	<ul style="list-style-type: none"> <li>Terminated early because of safety issues (70 of 300 patients enrolled)</li> <li>Data on 62 patients presented at ODAC 2004</li> </ul>
<b>Trials of ESAs in combination with radiotherapy</b>					
Total # of controlled trials in setting: 7					
Total number of controlled trials with possible negative signals regarding overall survival: 2					
ENHANCE (Henke et al., 2003)	Head and neck cancer	Effect of high hemoglobin on locoregional progression-free survival	> 14 (women) > 15 (men)	RR=1.39 (95% CI: 1.05, 1.84), p=0.02	<ul style="list-style-type: none"> <li>Significant number of protocol violations</li> <li>Inconsistent findings across study populations and strata (per protocol analysis indicated no difference in survival)</li> </ul>
DAHANCA-10 (provisional interim data)	Head and neck cancer	Loco-regional control	14-15.5	No significant difference in overall survival (p=0.08)	<ul style="list-style-type: none"> <li>Only very limited summary data from interim analysis available on website</li> <li>~ 10% difference in 3 year loco-regional control in favor of control group (p=0.01)</li> </ul>

Two studies (one study in breast cancer patients receiving chemotherapy [BEST, EPO-INT-76; Leyland-Jones et al., 2005] and one in head and neck cancer patients treated with radiotherapy [ENHANCE, MF4449; Henke et al., 2003]) first raised safety concerns that resulted in the 2004 ODAC meeting on ESAs in cancer. Two other studies in the six

studies listed above were also discussed at that meeting (Amgen Study 20000161 and Wright et al., 2007). Amgen Study 20000161 was an anemia treatment study in patients with a range of lymphoproliferative diseases. The interim results from the long-term follow-up was reported at the 2004 ODAC with a hazard ratio (HR) for overall survival (OS) of 1.33 (95 percent CI: 0.95, 1.86) (Amgen Inc., ODAC Briefing Book 2004). The final long-term follow-up data, adjusting for stratification factors, now report an HR for OS of 1.36 (95 percent CI: 1.02, 1.82) (Amgen Inc., ODAC Briefing Book 2007). Analyses unadjusted for baseline factors or utilizing the intention to treat (ITT) dataset are non-significant for survival, but with similar HRs to the adjusted analysis. Important baseline imbalances in factors known to be prognostic for disease outcomes were observed within individual strata. Progression-free survival (PFS) data from this study have remained neutral over the same time period (final long-term PFS HR=1.01 [95 percent CI: 0.79, 1.29]).

Two studies that have raised additional safety concerns with ESAs have become available since the 2004 ODAC. One study in head and neck cancer patients receiving radiotherapy is still ongoing and no data have been published or presented (DAHANCA-10). The other study, Amgen Study 20010103, was a placebo-controlled study in patients with active cancer not receiving or planned to receive chemo- or radiotherapy (Glaspy et al., 2007). The study enrolled a heterogeneous patient population and had a number of baseline imbalances in known prognostic factors for survival; for these reasons, it is difficult to draw definitive conclusions from the study. The results of this study have been fully disclosed to regulatory agencies, investigators and the broader clinical and scientific community.

Importantly, other data pertaining to the question of the impact of ESAs on survival have also become available in this timeframe including the BRAVE study (Aapro et al., 2006) (in 463 metastatic breast cancer patients receiving chemotherapy) and the Amgen Study 20010145 (available at [ClinicalStudyResults.org](http://ClinicalStudyResults.org)) (in 597 patients with small cell lung cancer [SCLC] receiving chemotherapy). Both of these studies suggest a neutral impact of ESAs on survival in CIA. All of these data (and updated survival data for several other studies) have been included in the analyses Amgen has presented to FDA and CMS (Amgen Inc., ODAC Briefing Book, 2007).

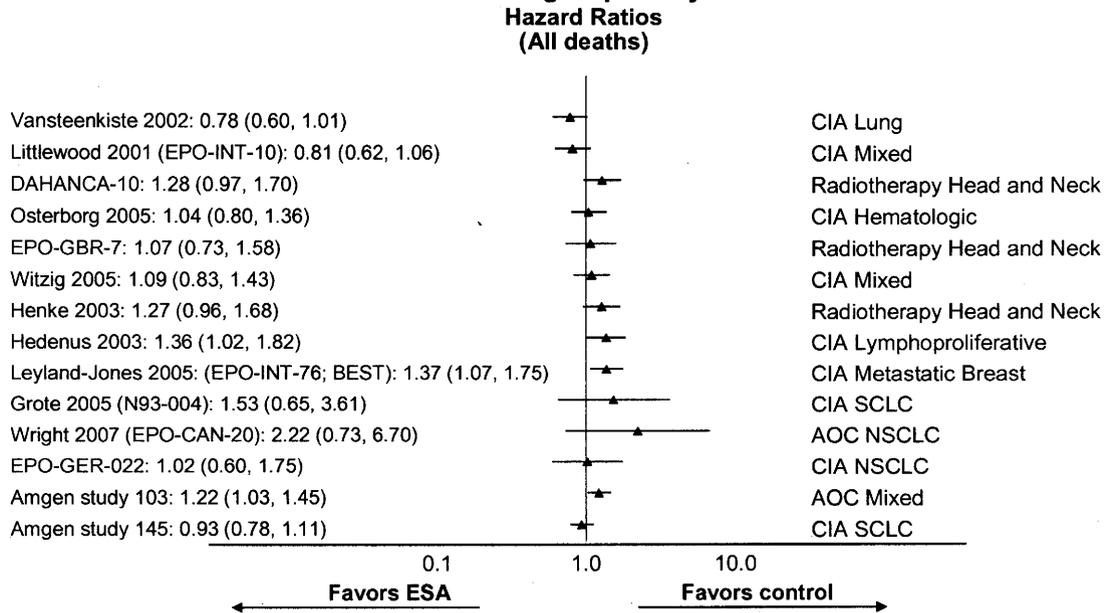
At the 2007 ODAC, the FDA presented an overview of data from individual studies they deemed of adequate design to inform the question of safety and overall survival. The FDA presentation summarized 14 trials, 9 trials evaluating the combination of ESAs with chemotherapy, 3 trials of ESAs in combination with radiotherapy and 2 trials evaluating ESAs in patients not receiving either chemotherapy or radiotherapy. The extrapolation of this dataset to CIA and the summary discussed by the FDA at ODAC is based on several assumptions that need to be thoughtfully considered as it relates to the need for CMS to limit coverage in CIA.

The criteria for the FDA summary were phase 3 studies with adequate follow-up (undefined further). However, the justification for these criteria is unclear and the application of their criteria inconsistent, with important limitations in the justification and presentation of these study data:

- Studies of ESA use in different patient populations (e.g., CIA, AOC, radiotherapy) and indications for treatment (e.g., anemia treatment, anemia prevention, and targeting high hemoglobin levels to hyper-oxygenate tumors) were mixed together without appropriate assessment of heterogeneity and exploration of sources of heterogeneity.
- The FDA included all studies they considered to have adequate long-term follow-up, yet 3 important studies were not included. These 3 studies (Möbus et al., 2007; Aapro et al., 2006 [BRAVE], and Chang et al., 2005 [EPO-CAN-17]) all demonstrated neutral survival outcomes in over 1000 breast cancer patients followed for two to five years.
- The FDA analysis included only studies with long-term follow-up (Chart 6). It is unclear, however, what criteria the FDA adopted in identifying the 14 studies included in their analysis presented at ODAC, except that they are “phase 3 studies” with “adequate follow-up”. However, it is apparent that adverse survival outcomes were observed in the BEST (Leyland-Jones et al., 2005) and Amgen Study 20010103 (Glaspy et al., 2007) studies within a 4 month period. While longer-term follow-up is desirable, controlled studies with shorter duration of follow-up should at least be identified and included in the analysis to understand if such studies confirm or refute the finding of early mortality in cancer patients treated with ESAs. Moreover, in assessing mortality it is critical to count every death equally, whether it occurs early in a study or during follow-up after the study-specific treatment period has completed, since patient survival is a completely objective assessment from the first day of study throughout follow-up to the last patient contact. Omitting studies from the analysis that did not meet an arbitrary period of follow-up risks unnecessarily limits the available evidence base with which to inform the risk assessment.

In order to provide an objective, comprehensive assessment of ESA safety in cancer patients, Amgen has engaged in analysis of individual study data, meta-analysis of patient-level data from multiple studies, and meta-analysis of study level data in its assessment of safety of ESAs in oncology patients. Additionally, Amgen has performed an additional meta-analysis using the studies selected as “appropriate” by FDA to evaluate the consistency of our findings.

**Chart 6: FDA Summary Presented at ODAC was Not Comprehensive: Survival Summary Is Limited to Studies with Longer Follow-up and Combines Populations Without Sub-group Analysis**



**Amgen's Analysis: Overall HR: Random Effect 1.10 (0.97, 1.25)**

FDA did not perform a formal meta-analysis of these 14 trials. When a meta-analysis is performed on these trials, evidence of significant heterogeneity is observed overall with an apparent difference in conclusions drawn between studies of ESAs in patients receiving chemotherapy and those studies evaluating ESAs outside of the chemotherapy setting. In the meta-analysis of the studies receiving ESAs and chemotherapy, there was no evidence of any detrimental outcome on survival observed (HR, 1.04, 95 percent CI 0.87 – 1.24;  $I^2 = 56.5$  percent). This finding is consistent with the meta-analysis of all chemotherapy trials (n=39) regardless of length of follow-up (Table 7).

Some evidence of a detrimental outcome is observed in the group of studies evaluating ESAs outside of the chemotherapy setting, however, these data are difficult to interpret due to the small number of trials (n=5) and the weighting of the ENHANCE study (approximately 20 percent; Henke et al., 2003) and Amgen Study 20010103 (approximately 50 percent) in the meta-analytic estimate for this study group. Again, this finding is consistent with the use of meta-analysis of all non-chemotherapy trials (n=17) regardless of length of follow-up.

**Table 7: Meta-analysis of 14 Studies Deemed as Having  
 “Adequate Follow-up” by the FDA**

	Odds Ratio (95% CI)	Hazard ratio (95% CI)
All Chemotherapy studies (n = 9)	1.04 (0.85, 1.28) Heterogeneity, p=0.06, I <sup>2</sup> =46%	1.04 (0.87, 1.24) Heterogeneity, p=0.02, I <sup>2</sup> =56.5%
Non-CIA studies with “adequate follow-up” (n = 5)	Cannot be calculated; no information on DAHANCA- 10*	1.23 (1.09, 1.39) Heterogeneity, p=0.79, I <sup>2</sup> =0%
All studies with “adequate follow-up” (n=14)	Cannot be calculated; no information on DAHANCA- 10*	1.10 (0.97, 1.25) Heterogeneity, p=0.02, I <sup>2</sup> =50%

\* For the DAHANCA-10 study, odds ratio calculation requires knowledge of the number of deaths in each treatment group, which was not reported on the DAHANCA website. For the calculation of hazard ratios for DAHANCA-10, an approximation (Parmar et al., 1998) was based on the reported total number of deaths and the p-value on treatment difference. Judging from the explanation given at ODAC by the FDA regarding its derivation of the hazard ratio for DAHANCA-10, it appeared that FDA adopted a similar approach for the approximation. Random effects model estimates presented.

As described, three important studies that appear to meet the FDA inclusion criteria for analysis, all in breast cancer patients receiving chemotherapy, were not included by FDA in their summary of phase 3 trials with “adequate long-term follow-up.” All of these trials demonstrate neutral survival outcomes for ESAs, supporting the conclusions drawn from the meta-analyses of CIA studies (Table 8).

**Table 8: Three Additional Studies Deemed to  
 Have “Adequate Follow-up” per FDA Criteria**

Overall Survival	Tumor Type	Treatment (n)	HR or OR for OS	95% CI	Follow-up
Aapro et al., 2006 (BRAVE)	Metastatic breast cancer	Chemotherapy (non-anemic patients) (n = 463)	1.07 HR	0.87–1.33	Study duration: 24 weeks + 18 month follow-up
Möbus et al., 2007	High risk adjuvant breast cancer	Chemotherapy (n=658)	1.15 OR	0.77-1.71	Median follow-up: 62 months
Chang et al., 2005 (EPO-CAN-17)	Adjuvant (80%) and metastatic (20%) breast cancer	Chemotherapy (n=354)	0.94 HR	0.55 - 1.60	Survival data collection: 2 years

Therefore, if CMS chooses to extrapolate the recent safety findings from individual studies to CIA, performing a comprehensive analysis would conclude that the risk is neutral. When considered in the context of the available evidence base relevant to an assessment of risk, these individual study conclusions should not provide greater weight

to CMS than the rigorous combined analysis of the entire relevant evidence base – particularly within CIA, the licensed indication.

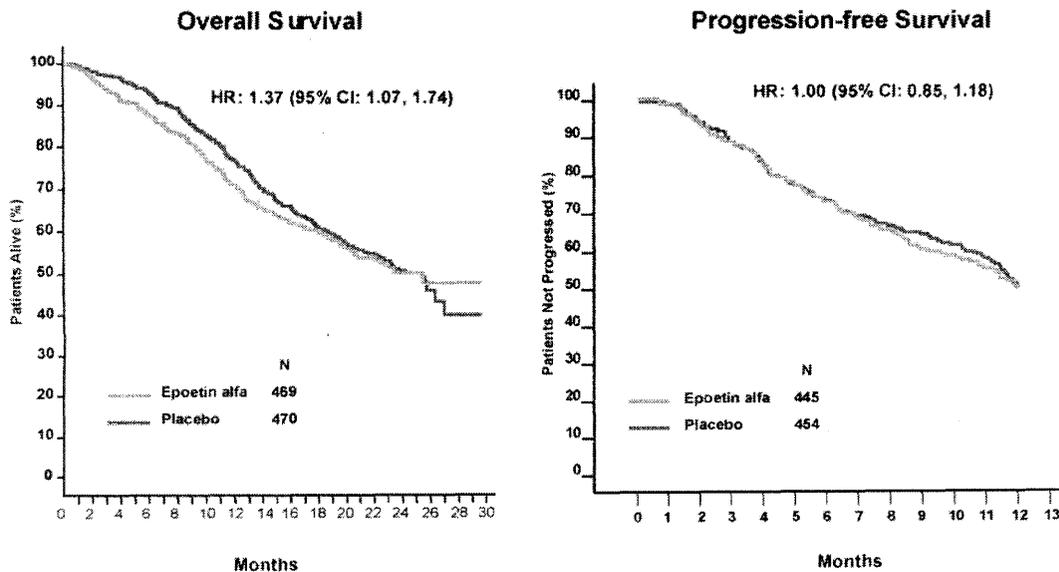
D. *Combined meta-analyses of all relevant data have identified subgroups of patients where the totality of data does and does not indicate a potential survival risk. Within CIA, some individual studies have raised safety signals, but others have not and the weight of evidence across all CIA studies does not indicate that mortality is affected overall, in solid tumors (including breast cancer and lung cancer), or in lymphoproliferative diseases. The study-level meta-analyses point to an ESA-associated mortality risk in patients with AOC who have active cancer not receiving or planning to receive chemotherapy or radiation therapy and in patients with head and neck cancer undergoing radiotherapy treated to a hemoglobin level  $\geq 12.0$  g/dL.*

Amgen has performed study-level meta-analyses of randomized placebo- or non-ESA-controlled clinical trials. In the analysis of all 55 placebo- or non-ESA controlled studies (12,678 patients), there was an overall neutral survival risk; (OR 1.08; 95 percent CI 0.98 – 1.18). There was also an overall neutral effect on survival among the 39 studies in which chemotherapy was administered (OR 1.03, 95 percent CI 0.93 – 1.15).

#### Breast Cancer

Within the CIA studies, data from the BEST study has raised concerns about tumor progression and survival (Leyland-Jones et al., 2005). The overall survival and progression-free survival results from the final report of this study are shown in Chart 7.

**Chart 7: BEST Study Overall Survival and Time to Disease Progression**



CMS is appropriately concerned about the adverse survival signal in this trial, and Amgen shares this concern. The approach to ESA therapy in BEST was to institute early and aggressive intervention with ESAs. Of 939 patients enrolled, 64 percent had

hemoglobin  $\geq$  12.0 g/dL and 80 percent had hemoglobin  $\geq$  11.0 g/dL when epoetin alfa was initiated (Ortho Biotech ODAC Briefing Book 2004). While the interim results indicated an increase risk of death and disease progression, the final study report for BEST showed that there was no statistically significant difference in either tumor response or disease progression whereas the negative signal with respect to death remained.

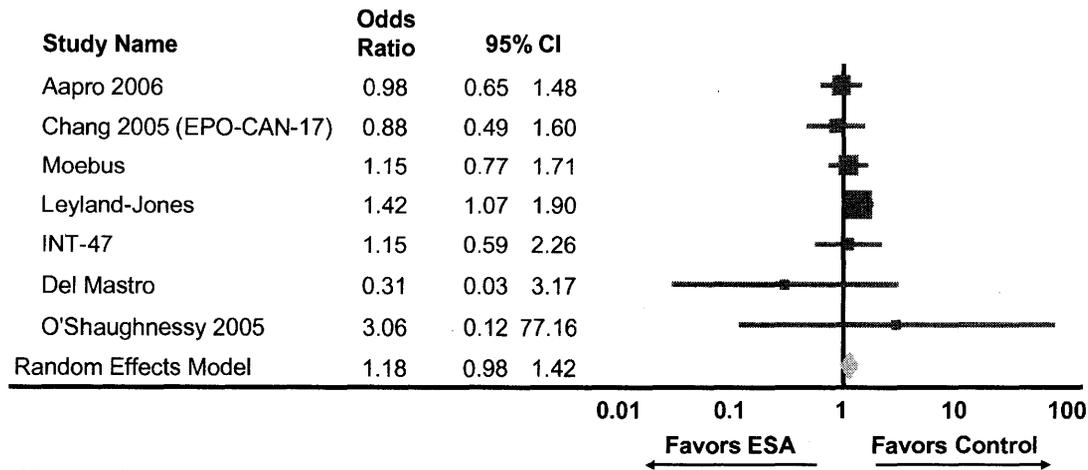
It is important to recognize that BEST is the only breast cancer study of 7 randomized studies of ESAs in breast cancer that has shown a negative survival signal. It is therefore important to compare the results of BEST to other trials in breast cancer patients that have similar study design characteristics. Three other non-ESA-controlled breast cancer studies (representing 1,475 patients) also collected long-term follow-up information (Aapro et al., 2006, Möbus et al., 2007, Chang et al., 2005). Three additional non-ESA-controlled studies (including 376 patients) did not collect follow-up information but did report deaths. These six studies, as well as the BEST study, are summarized in Table 9. In all studies other than BEST, the ESA groups had neutral survival risks relative to the control group. This clinical finding is consistent with the lack of preclinical evidence that pharmacologic concentrations of EPO act as a growth factor for breast cancer cells. Aapro, et al., 2006 is closed to enrollment and has presented its 18-month follow-up data. Möbus, et al., 2007 is an on-going adjuvant chemotherapy study and has presented data through a median of 62 months of follow-up. In addition, there are three other on-going studies (PREPARE, ARA-Plus, and EPO-ANE-3010) that have not released data related to survival to date. Data from these five on-going studies will provide additional important data to assess risk in this patient population when they are completed.

**Table 9: Summary of Studies of Breast Cancer Studies Evaluating Tumor Progression**

	<b>Tumor Type</b>	<b>Treatment (n)</b>	<b>HR or OR for OS</b>	<b>95% CI</b>	<b>Follow-up</b>
<b>Studies with negative signal</b>					
Leyland Jones et al., 2005 (INT-76; BEST)	Metastatic	Chemotherapy (non-anemic patients) (n=939)	HR: 1.37 (12 month survival)	1.07 – 1.74	Median follow-up: 52 weeks
<b>Studies with neutral signal</b>					
Aapro et al., 2006 (BRAVE)	Metastatic	Chemotherapy (non-anemic patients) (n=463)	HR: 1.07	0.87 – 1.33	Study duration 24 weeks + 18 month follow-up
Möbus et al., 2007	High-risk adjuvant	Chemotherapy (n=658)	OR: 1.15	0.77 – 1.71	Median follow-up: 62 months
Chang, et al., 2005 (EPO-CAN-17)	Adjuvant (80%) and metastatic (20%)	Chemotherapy (n=354)	HR: 0.94	0.55 – 1.60	Survival data collection: 2 years
Pronzato, et al., 2002 (EPO-INT-47)	All stages	Chemotherapy (n=220)	OR: 1.15	0.59 – 2.26	N/A
Del Mastro, et al., 1997	Stage II	Accelerated adjuvant chemotherapy (n=62)	OR: 0.31	0.03 – 3.17	N/A
O'Shaughnessy, et al., 2005	Stages I – III	Adjuvant or neoadjuvant chemotherapy (n=94)	OR: 3.06	0.12 – 77.16	N/A

When the study-level data from these seven breast cancer studies are meta-analyzed (see Chart 8), there was an overall neutral risk despite the large contribution (weighted at about 40 percent of the overall result) of the BEST study results (OR 1.18 [95 percent CI: 0.98, 1.42; I<sup>2</sup> = 0 percent]).

**Chart 8: Survival is Risk-neutral in Breast Cancer Studies**



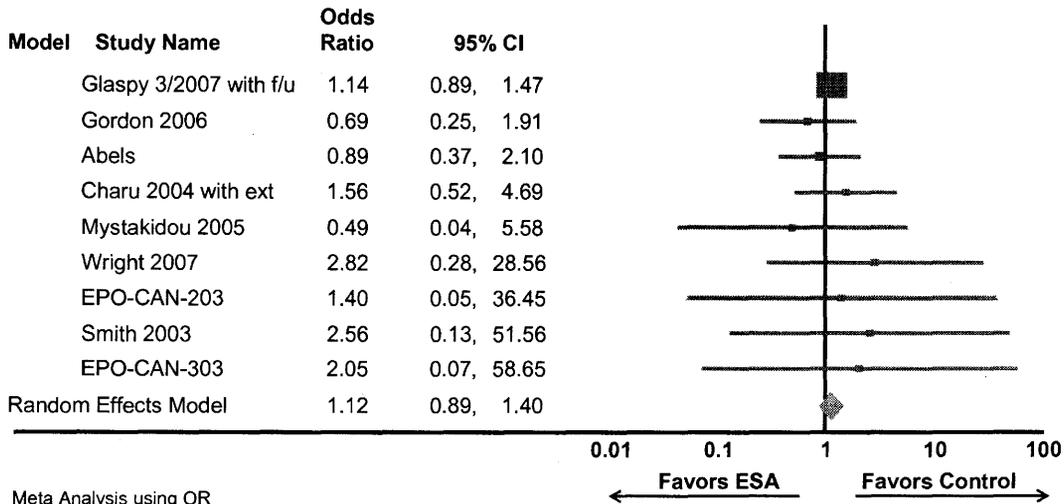
Meta Analysis using OR  
 $I^2 = 0$

Note: Cochrane report + Amgen data on-file; INT-47 refers to Pronzanto et al., 2002

Anemia of Cancer

In the area of AOC, the studies of concern for adverse safety signals for ESAs are the Amgen 20010103 study (Glaspy et al., 2007) and the EPO-CAN-20 study (Wright et al., 2005). Both of these studies indicate increased risk of mortality in ESA-treated patients with active cancer who have exhausted all options and are not receiving or planning to receive chemotherapy or radiation therapy. It is worthwhile to note that while the HR for OS in the Amgen 20010103 study of 1.22 (95 percent CI of 1.03 to 1.45) favored the placebo group, the HR was reduced when post-hoc analyses were adjusted for baseline imbalances in known prognostic factors (HR: 1.15, with a 95 percent CI of 0.96 to 1.37). While the meta-analysis across all anemia of cancer studies indicates that the mortality risk may be neutral (HR:1.12; 95 percent CI: 0.89, 1.40), the setting represents a very heterogeneous patient group, and the increased risk in patients with active cancer not receiving nor planning to receive chemotherapy should be considered in coverage policy determination (Chart 9).

**Chart 9: Combined Analysis of Overall Survival in AOC Studies is Risk-neutral, However, There is a Potential Increased Risk in Patients with Active Cancer Neither Receiving nor Planning to Receive Further Chemotherapy\***



Meta Analysis using OR  
 $I^2 = 0\%$

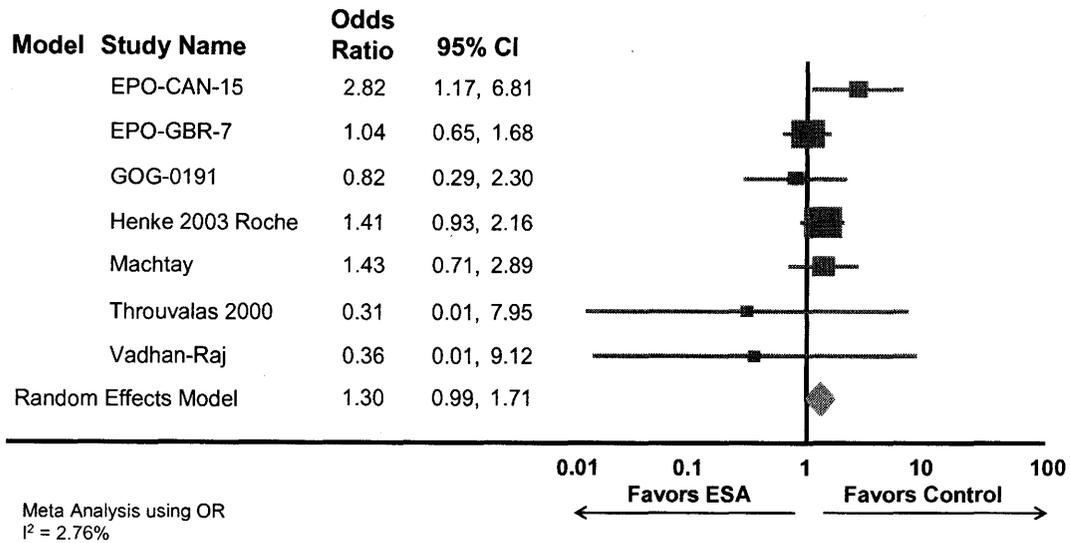
\* Glaspy et al, AACR 2007 presentation of an earlier interim analysis

Cochrane Report + Data on file, Amgen

Radiotherapy Studies Treating to a Hemoglobin  $\geq 12.0$  g/dL

In radiotherapy studies, particularly for head and neck cancer studies where higher hemoglobin levels (*e.g.*,  $\geq 12.0$  g/dL) were targeted in an attempt to potentiate radiation effects on tumors through hyper-oxygenation, there may be an increased risk of mortality, as shown in Chart 10 (OR 1.30 ; 95 percent CI 0.99 –1.71).

**Chart 10: Radiotherapy Studies Treating to Hemoglobin Levels Greater than 12.0 g/dL Show Increased Risk**



Cochrane Report + Data on file, Amgen

E. *While ongoing studies will continue to inform CMS and other stakeholders about the safety of ESAs, the currently available body of evidence strongly supports coverage in CIA.*

A study-level meta-analysis of 39 CIA placebo- or non-ESA-controlled ESA studies (including 9652 patients) demonstrated a neutral impact on survival (1.03 95 percent CI 0.93 –1.15). The available data strongly support coverage in CIA.

The ongoing studies include the use of darbepoetin alfa in breast cancer patients undergoing neoadjuvant chemotherapy (PREPARE; Möbus et al., 2007; DE-2001-0033) or the use of darbepoetin alfa in breast cancer patients undergoing adjuvant chemotherapy (ARA-Plus; Warm et al., 2007; DE-2002-0015), in patients with non-Hodgkin’s lymphoma treated with chemotherapy (Delarue et al., 2006), the use of epoetin alfa in metastatic breast cancer treated with chemotherapy (EPO-ANE-3010; Ortho Biotech ODAC Briefing Book 2004), and the previously described Möbus and Apro studies (Möbus et al., 2007; Apro et al., 2006). Together, these studies will generate safety data in more than 4800 patients.

In those settings outside CIA where data exist to demonstrate risk of adverse outcomes, coverage can appropriately be restricted based on the data. These data from experimental populations should not be broadly extrapolated to CIA patients in an evidence-based and scientifically rigorous coverage decision.

- F. *Amgen is not alone in questioning the supposition that CMS should extrapolate the safety signals from individual studies to all patients with the proposed coverage restrictions.*

Many aspects of the PDM are not supported by the clinical evidence and are in conflict with well-established clinical practice guidelines; therefore, the CMS proposal would be inconsistent with standard of care if finalized as proposed.

CMS determines whether an item or service is reasonable and necessary for the diagnosis or treatment of an illness or injury by relying on clinical evidence and evidence-based medicine (EBM).<sup>9</sup> Further, the agency has drafted guidelines to establish a framework for the evaluation process. In this guidance, CMS states that National Coverage Assessments (NCA) "decisions call for the best scientific and clinical evidence available concerning the effectiveness of various medical diagnostic procedures and therapies, and the highest attainable level of expertise to evaluate such evidence" (Table 10).<sup>10</sup>

**Table 10: Definition of EBM Cited Publicly by CMS**

EBM: Definition

*"Evidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research."<sup>11</sup>*

Amgen supports the use of this approach by CMS as it provides an appropriate scientific framework for the review of data to inform decision-making. However, in this PDM, the agency appears to have deviated from its own standards, as the PDM recommends an approach that is inconsistent with how the products were studied in well-designed randomized controlled trials, and relies upon a pathophysiologic rationale to support its proposed coverage restrictions in CIA.

As noted earlier, CMS has selectively relied upon evidence in the PDM but has highlighted certain evidence and cited details of particular medical specialty guidelines that support its position. However, in some instances, CMS does not mention these same societies' overall conclusions and recommendations for ESAs. The selective inclusion of data is inappropriate for a scientifically rigorous, evidence-based analysis that serves as a basis for a product coverage decision, and Amgen encourages CMS to conduct a more thorough review of the complete evidence base for these products before finalizing its policy.

The conclusions that CMS reaches in its review of the evidence outlined in the PDM diverge from the opinions of experienced clinical oncologists. For this reason, many experts in the field of oncology have already shared concerns with CMS. Examples of their comments are provided in Table 11.

**Table 11: Reactions from Clinical Oncology Experts to the Proposed NCD**

<p><u>American Society of Clinical Oncology (ASCO)</u></p> <p><i>The ESA coverage proposals “have no scientific basis and are in direct conflict with both published scientific evidence and expert opinion...” (ASCO Statement to CMS)</i></p> <p><u>American Society of Hematology (ASH)</u></p> <p><i>“The Society is deeply concerned that CMS’s proposed coverage decision inappropriately restricts use of ESAs because a number of the proposals are not supported by scientific data, rely on poor quality data, or are in conflict with expert scientific analysis...” (ASH Statement to CMS)</i></p> <p><u>Dr. S. Gail Eckhardt, Chair, FDA’s ODAC</u></p> <p><i>“I was shocked to see how the CMS restrictions go way beyond the scientific evidence that indicates what’s actually proven beneficial or non-beneficial...” (Eckhardt, Cancer Letter, May 18, 2007)</i></p>
--

ASCO and ASH are leading science-based organizations focused on cancer care in the U.S., and their guidance should be carefully considered in determining the scientific and clinical evidence that CMS should weigh most critically before issuing its final decision.

**Response to  
Supposition 2:**                    **In the PDM, CMS appears to rely largely on a hypothesis about the putative role of EPO-R in tumor growth; however, the principal evidence cited by CMS on EPO-R does not stand up to even casual scrutiny and, thus, cannot serve as a reliable basis for an evidence-based coverage policy.**

EPO stimulates the formation of red blood cells by binding to and activating EPO-R, which is found on the surface of red blood cell progenitors. ESAs share this same mechanism of action to stimulate red blood cell formation. Some of the agency’s suppositions about EPO-R that were included in the PDM appear to be largely based on two unsubstantiated hypotheses: (1) that ESAs promote tumor growth, and (2) that they do so through interaction with an EPO receptor present on tumor cells.

These hypotheses have been extensively studied by investigators around the world since concerns about ESAs and tumor promotion were discussed at the May 2004 meeting of the ODAC to review ESAs (Amgen Inc., ODAC Briefing Book 2004). Based on a comprehensive analysis of the evidence in numerous preclinical and clinical studies (Sinclair et al., 2007; Osterborg et al., 2007) Amgen believes there is no definitive evidence of EPO-R involvement in tumor progression, and no reliable evidence that the EPO-R is present on cancer cells.

The weight of the evidence shows that the EPO-R is not encoded by an oncogene (*i.e.*, a gene that causes transformation of normal cells into cancerous cells). There are multiple lines of evidence supporting this conclusion. For example, the EPO-R, even when expressed as an activated mutant protein, does not stimulate cancer cell growth.

An additional line of evidence comes from an analysis of levels of EPO-R mRNA, the direct precursor of the EPO-R protein. When the levels of EPO-R mRNA are directly compared in normal versus cancer cells, there is no difference between them. This evidence clearly refutes the notion that the EPO-R provides an important advantage to cancer cells.

Several published studies have purported to show that the EPO-R plays a role in tumor cell signaling, proliferation, migration or survival. However, these studies lacked critical controls, and often employed concentrations of ESA up to 1,000 times greater than the maximum concentrations achieved in patients. A very important element of the evidence that has seemed to support this unsubstantiated hypothesis is the purported detection of EPO-R on cancer cells, which relies upon antibodies against the EPO-R. However, most antibodies employed in these studies are non-specific, and bind to multiple proteins of different sizes rather than the EPO-R. In fact, the most widely used polyclonal antibody marketed to detect EPO-R actually detects heat shock protein 70 (HSP70) instead. Unlike EPO-R, HSP70 has long been known to be an important factor in predicting prognosis in cancer patients. Thus, the reports suggesting that EPO-R is expressed on tumor cells have actually been examining HSP70 (in addition to other proteins). There is no compelling evidence that the EPO-R itself is expressed on the surfaces of tumor cells, as detailed in Appendix A.

In summary, Amgen believes that there is no definitive evidence demonstrating any of the following:

- a link between EPO-R and involvement in tumor progression,
- the presence of EPO-R on cancer cells, and
- cancer cells responding to EPO signals.

Eminent scientific experts in the field have drawn the same conclusions (Brown et al., 2007; Osterborg et al., 2007; Constantinescu, 2007). Finally, we note in Table 12 the agency's own position on the importance of relying on high quality evidence for Medicare coverage decisions.

**Table 12: CMS Perspective on the Importance of Basing Coverage on EBM Methods**

Why CMS Bases Coverage on EBM

*CMS notes that a rigorous EBM-driven framework helps guide researchers and payers because "lower quality studies are more likely to be wrong" and "deductions from basic biology and pathophysiology may be unreliable." (CMS, 2005)*

**Response to  
Supposition 3:           The agency's proposed policy of initiating therapy at a  
hemoglobin level of 9.0 g/dL in each month is not supported  
by scientific evidence and does not recognize current  
standards of clinical care.**

The proposed policy appears to blend two critical clinical concepts necessary for the effective care of anemic cancer patients: (1) when to start therapy and (2) when to withhold therapy based on the hemoglobin level (*i.e.*, the threshold hemoglobin level). Clinical care requires that clinicians initiate therapy to prevent transfusion, a decision made based on signs and symptoms of anemia and the myelosuppressive effects of chemotherapy administration. Once therapy is initiated, a target hemoglobin level is chosen, as clinicians cannot precisely control ESA response. Dose adjustment rules are clearly articulated in the revised FDA label to guide clinicians about how to titrate the ESA to achieve the desired hemoglobin levels, which should not exceed a threshold level of 12.0 g/dL.

The proposed policy of initiating ESA therapy at hemoglobin < 9.0 g/dL and then waiting for the hemoglobin level to drop below 9.0 g/dL in each month essentially sets the hemoglobin target range at 9.0 g/dL. There is simply no evidence to support this practice, and more importantly, there is no clinical experience of this practice in the clinical trials that have established the safety and efficacy of the ESA class.

***Scientific evidence suggests that most transfusions are prevented when ESAs are initiated at a hemoglobin level between 10.0 and 11.0 g/dL.***

In the United States, the lower limits of normal hemoglobin values are 12.5 g/dL for adult females and 13.5 g/dL for adult males. When patients become anemic due to the effects of myelosuppressive chemotherapy, the hemoglobin level may fall precipitously. ESAs can take from 4 to 6 weeks to have their intended effect (Aranesp<sup>®</sup> prescribing information, 2007); thus, waiting until the hemoglobin falls to below 10.0 g/dL will expose cancer patients to more severe and prolonged anemia symptoms, as the hemoglobin will likely fall further before the ESA takes effect. Therefore, defining the hemoglobin value to initiate therapy is critical.

- First, almost all randomized clinical trials have initiated ESA therapy when the hemoglobin level is less than 11.0 g/dL. As a result, evidence-based clinical practice guidelines have recommended the initiation of ESA therapy in cancer patients when the hemoglobin level is less than 11.0 g/dL.
- In placebo-controlled trials, when ESA-treated patients initiate therapy at hemoglobin < 9.0 g/dL, 68 percent receive at least one transfusion; however, if the hemoglobin is between 10.0 and 11.0 g/dL, only 26 percent receive at least one transfusion. Thus, the agency's proposed policy would significantly increase the percentage of patients who receive at least one transfusion. Importantly, the treatment effect regarding the reduction in red blood cell transfusions between ESA-treated patients and patients who received placebo is similar (*i.e.*, comparable hazard ratios) when hemoglobin is between 9.0 and 10.0 g/dL or when hemoglobin is between 10.0 and 11.0 g/dL (Table 13).

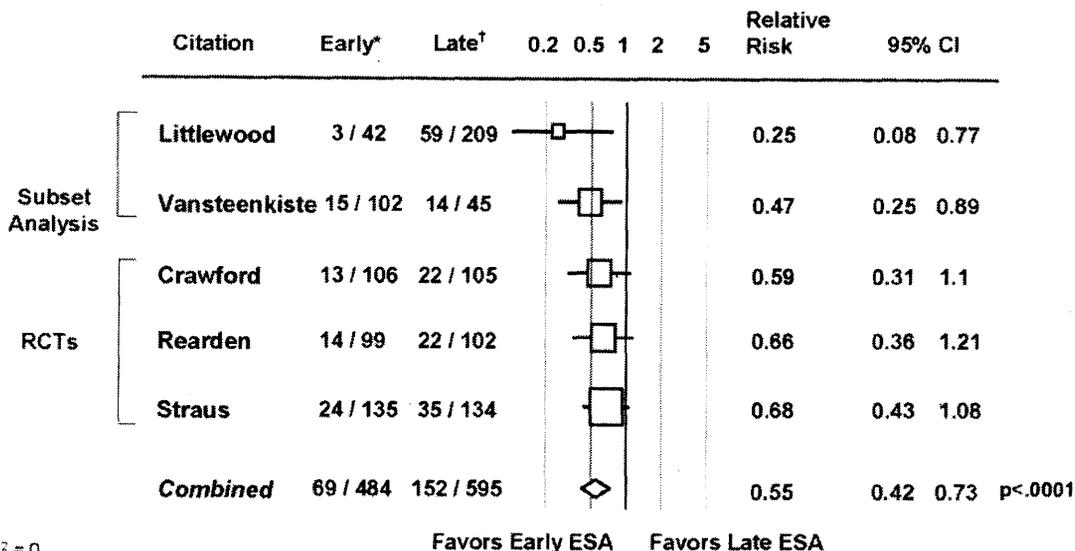
- Comparison of strategies for early intervention (generally initiation of therapy at approximately 12.0 g/dL) and later intervention (generally, initiation of therapy when hemoglobin level drops below 10.0 g/dL) have been evaluated in a number of RCTs. A meta-analysis of these studies has demonstrated an approximate 50 percent reduction in the risk of transfusion favoring the early intervention approach (relative risk, 0.55, 95 percent CI 0.42 – 0.73). This indicates that a 27 to 58 percent reduction in transfusions may be achievable when ESAs are used earlier (Chart 11).
- The hemoglobin initiation levels proposed by CMS will significantly reduce the effectiveness of ESAs in preventing transfusion, as the risk of transfusion when the hemoglobin level is < 9.0 g/dL is 68 percent.
- A meta-analysis of studies with an average hemoglobin level at baseline between 10 and 12.0 g/dL showed neutral outcomes with respect to overall survival (odds ratio, 0.86; 95 percent CI 0.69 – 1.08) (Amgen data on file).
- Finally, the current FDA label does not include an initiation threshold, and CMS has not provided any clinical or scientific rationale for including this as a basis for coverage policy.

**Table 13: Initiation of ESA at Hemoglobin > 11.0 g/dL  
 Results in Lowest Absolute Transfusion Risk and Lowest Hazard Ratio**

Baseline Hb	Patients receiving transfusion (% , N)				HR (95% CI)
	Darbepoetin alfa (n = 822)		Placebo (n = 819)		
Missing	27%	(6/22)	65%	(20/31)	
< 9 g/dL	68%	(65/96)	83%	(66/80)	0.68 (0.48, 0.97)
9 - < 10 g/dL	35%	(51/144)	61%	(103/170)	0.52 (0.37, 0.72)
10 - < 11 g/dL	26%	(56/212)	41%	(99/239)	0.58 (0.42, 0.81)
≥ 11 g/dL	14%	(49/348)	35%	(104/299)	0.38 (0.27, 0.53)
<b>Total</b>	<b>28%</b>	<b>(227/822)</b>	<b>47%</b>	<b>(392/819)</b>	

Amgen data on file

**Chart 11: Higher Hemoglobin Initiation Results in an Approximately 50 Percent Relative Risk Reduction of Transfusions (Adapted from Lyman and Glaspy, 2006)**



I<sup>2</sup> = 0

\* Early intervention is generally initiation of ESA therapy at Hb levels of approximately 12 g/dL.  
 † Late intervention is generally initiation of ESA therapy when the Hb levels drop to ≤ 10 g/dL.

***CMS has not provided any clinical or scientific rationale for setting an implicit hemoglobin upper limit at 9.0 g/dL (i.e., initiation at < 9.0 g/dL in each month) when the recently revised FDA label states that hemoglobin is not to exceed 12.0 g/dL.***

The goal of ESA treatment is to reduce and eliminate symptoms of anemia, by raising hemoglobin values and avoiding red blood cell transfusions. Treating anemia by raising hemoglobin levels using ESA therapy has also been shown to improve fatigue, energy, and other domains of health-related QOL in anemic patients with cancer (Glaspy et al., 1997; Demetri et al., 1998; Gabrilove et al., 2001; Littlewood et al., 2001; Hedenus et al., 2002; Vansteenkiste et al., 2002; Osterborg et al., 2002). Therefore, the clinical goals of therapy should reflect the range of important health benefits achieved through transfusion avoidance and improved symptoms and consider the individual patient-specific needs.

- Most of the RCTs conducted to define the efficacy and safety of the ESAs targeted hemoglobin levels of 11.0 to 13.0 g/dL, with dose withholding hemoglobin threshold greater than or equal to 13.0 g/dL. A few of the initial registration trials of darbepoetin alfa in CIA actually withheld treatment at higher hemoglobin levels of 14.0 to 15.0 g/dL, and no additional risk was identified in long-term follow-up. Thus, the evidence base that exists to inform CMS coverage policy of the improved net health outcomes of ESA therapy comprises studies where the protocol specified that patient hemoglobin levels be managed in this manner. This represents the highest level of evidence upon which CMS bases its coverage policies.<sup>12</sup>

- Current evidence-based clinical practice guidelines recommend targeting hemoglobin levels in the range of 11.0 to 13.0 g/dL, with ASH/ASCO recommending maintaining hemoglobin near 12.0 g/dL (Lichtin et al., 2005); NCCN recommending maintaining hemoglobin between 11.0 to 12.0 g/dL for the longest duration during therapy (Rodgers et al., 2007) and EORTC recommending a target hemoglobin range of 12.0 to 13.0 g/dL (Bokemeyer et al., 2006). These recommendations are based on trials that have demonstrated that anemia correction aimed at reaching a target hemoglobin of 11.0 to 12.0 g/dL maximizes health benefits, avoidance of red blood cell transfusions and improving symptoms and QOL (Glaspy et al., 1997; Demetri et al., 1998; Vahdan-Raj et al., 2003, Lyman and Glaspy 2006; Crawford et al., 2002).
- The recent FDA label change, in response to safety findings, includes a change from a target hemoglobin of 10.0 and 12.0 g/dL to a hemoglobin limit of 12.0 g/dL. **The recent FDA ODAC panel voted that this level should not be changed in further label revisions based on a review of existing data.**
- When survival outcomes are evaluated through meta-analysis in CIA, the hemoglobin thresholds of 12.0 g/dL to 13.0 g/dL are not associated with an increase in mortality, with an odds ratio for overall survival of 0.87 (95 percent CI: 0.54-1.38). (Amgen data on file).
- Finally, in a recent AHRQ meta-analysis of ESA safety, the relative risk of VTE does not vary when hemoglobin thresholds range from > 13.0 g/dL to 16.0 g/dL (Seidenfeld et al., 2006).

A hemoglobin limit of 12.0 g/dL is currently in the FDA-approved label for both marketed ESAs. However, the ability of physicians to effectively manage hemoglobin within target and threshold values is particularly important, given the variability in hemoglobin during repeated cycles of chemotherapy. If a patient experiences a single, transient, hemoglobin concentration > 12.0 g/dL, providers need discretion to determine for the individual patient whether to reduce the dose or withhold the dose. Moreover, in some patients, the abrupt withdrawal of ESA treatment in response to a single hemoglobin level > 12.0 g/dL may not represent optimal management. Many individual factors must be considered in this decision, including the underlying comorbidities, the severity of anemia symptoms, degree of ongoing myelosuppression imposed by the chemotherapy regimen, and the timing of the hemoglobin level assessment relative to the planned dosing of chemotherapy and ESA regimen being employed.

There are several reasons a physician may determine it is appropriate and necessary medical care to administer a reduced dose of ESA to a patient with a hemoglobin level greater than 12.0 g/dL rather than to withhold the dose. Some examples include the following:

- Imminent myelosuppressive chemotherapy in a patient who, based on previous experience, is predicted to have a significant subsequent decline in hemoglobin levels, resulting in significant anemia symptoms, or the need for transfusion.
- Significant anemia symptoms at hemoglobin levels at or near 12.0 g/dL.
- Prolonged duration of planned chemotherapy with expected cumulative myelotoxicity.
- Comorbid illnesses, such as impaired cardiac or pulmonary disease, associated with low physiologic tolerance for anemia.

Importantly, Amgen does not recommend that physicians target a hemoglobin > 12.0 g/dL in anemic cancer patients. However, we recognize the practical importance of a target hemoglobin level, allowing appropriate physician flexibility in the management of individual patients, as opposed to a limit for the purposes of coverage or payment. CMS should also recognize that based on current data there is no evidence to suggest that ESA doses are administered frequently to cancer patients with hemoglobin > 12.0 g/dL. In fact, a recent analysis of one of the largest electronic medical record (EMR) databases in oncology, representing more than 13,069 CIA patients, found that 96.5 percent of all patients receiving ESAs had a hemoglobin level < 12.0 g/dL at the time of administration.<sup>13</sup> Moreover, a recent chart audit showed 94 percent of patients with CIA receiving ESAs had a hemoglobin under 12.0 g/dL at ESA administration.<sup>14</sup>

If CMS simply limits coverage or payment to hemoglobin values < 12.0 g/dL, physicians may believe that they do not have the discretion to adequately treat patients with hemoglobin levels between 11.0 g/dL and 12.0 g/dL, the range where patient benefit is optimized.

Finally, CMS will soon be able to more effectively monitor the care delivered to cancer patients with anemia. Based on the recently passed Tax Relief and Health Care Act of 2006 (TRHCA), CMS will develop a system to collect hemoglobin levels in cancer patients, beginning in 2008.<sup>15</sup> At that time, data may be adequately compiled and analyzed to determine the need to introduce hemoglobin levels into medical review or claims processing guidelines.

### III. BENEFITS OF ESA TREATMENT

---

***In issuing the PDM, CMS appears not to weigh fully the well-documented benefits of ESA treatment, which include increased hemoglobin levels and avoidance of transfusion. Additionally, clinical studies report improvement in patient-reported outcomes (PROs) in patients undergoing cancer treatment with chemotherapy.***

ESAs demonstrate clear benefit in terms of avoidance of red blood cell transfusions required to treat signs and symptoms of anemia. Indeed, objective evidence of red blood cell transfusion reduction served as the basis for registration of ESAs in the treatment of CIA. Systematic reviews of randomized clinical studies through meta-analysis show that ESAs significantly increase the likelihood of hemoglobin response by more than three-fold, reduce the risk of transfusion by 36 to 59 percent (Bohlius et al., 2006b; Seidenfeld et al., 2006; Ross et al., 2006) and improve PROs based on the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) (Cella et al., 2002) and Linear Analog Scale Assessment (LASA) tools (Farrar et al., 2001), instruments that assess a patient's functionality, weakness/energy/tiredness, and ability to engage in daily activities. While these studies make use of clinical instruments that may not meet today's FDA standards for the registration of PROs in product labeling, the impact of ESA therapy on these PROs should not be discounted. Importantly, the clinical trials in the above-referenced meta-analysis included a large proportion of patients aged 65 and older, providing important evidence of benefit relevant to the Medicare beneficiary population.

Additionally, with ESA treatment, more consistent hemoglobin levels are maintained, helping to prevent the anemia from recurring. Following a transfusion, hemoglobin levels rise only temporarily, and patients may require multiple transfusions to treat the anemia as their hemoglobin levels inevitably decline.

Analysis of four randomized placebo-controlled Phase 3 clinical trials in CIA shows that starting ESA treatment at lower hemoglobin levels is associated with higher risk of transfusion. Among patients randomized to ESA treatment, 68 percent of all patients had at least one transfusion when the baseline hemoglobin was < 9.0 g/dL. In contrast, 35 percent of patients had at least one transfusion when baseline hemoglobin was between 9.0 and < 10.0 g/dL (Amgen data on file).

Further, shifting medical practice away from ESAs to transfusion will impose a significant burden on cancer patients and the health care delivery system. Access to transfusion is limited and cumbersome for the greater than 80 percent of cancer patients receiving chemotherapy in the community clinic. This was noted at the recent ODAC meeting on May 10, 2007 (Table 14).

**Table 14: Reaction from Clinical Oncology Expert at ODAC 2007**

Roy Beveridge, MD; Medical Oncologist at US Oncology

“Resorting to transfusion in this cancer population is very problematic in today’s world. There are the obvious safety issues that have been discussed earlier today. There is a taxing of the limited supply of blood that we have. But there is also a very significant taxing of the delivery system. I was actually at Fairfax Hospital this morning before I came here. It opens at 6 am in the morning. It closes 13 hours later. It’s open 7 days a week. The next time that we can schedule a blood transfusion if one wanted to do it today would be 13 days from now. The system is very saturated.” (Beveridge, 2007)

If the PDM is finalized without changes, these patients would be forced by CMS to travel from the clinic to a hospital to receive transfusions.

An actual transfusion typically takes more than four hours to administer, requires specialized equipment and trained personnel, and, in some cases, must be done before chemotherapy can be given. This is an important fact because the typical transfused patient receives over five units of red blood cells from different donors, and some cancer patients are transfused much more than this.

Additionally, CMS may not have fully considered the following important issue: the inability of red blood cell transfusions to maintain patient hemoglobin at appropriate levels unless patients are subjected to chronic hypertransfusion. On the other hand, clinical evidence strongly supports the finding that prevention of transfusion and improvements in PROs are optimized when ESAs are used to target hemoglobin levels between 11.0 and 12.0 g/dL (Crawford et al., 2002). CMS should recognize that the safety of red blood cell transfusions in these patients has not been rigorously tested at these levels.

***The real risks of red blood cell transfusions are significant and may not have been fully considered by CMS at the time the agency released the PDM.***

CMS should consider the following risks before finalizing a policy that could have a significant impact on the safety and health of the beneficiaries that the agency serves:

- Transfusions are a proven transmission route for serious infections. The human immunodeficiency virus (HIV) and hepatitis virus plagued the blood supply for years before they were recognized and testing developed (Dodd et al., 2003). Further, current testing procedures and technologies for detecting these and other viruses before they enter the U.S. blood supply are not perfect (Busch et al., 2003; Busch et al., 2005).
- Simply put, the blood supply is, at best, safe until the next pathogen emerges. The question is not whether a new pathogen will emerge but when. As characterized by the Centers for Disease Control and Prevention, “numerous pathogens have emerged in the United States and worldwide with the potential to affect the safety of the blood supply.” (Chamberland et al., 1998).

- Transfusion Related Acute Lung Injury (TRALI) is the leading cause of transfusion-related death according to the FDA and could occur at frequencies exceeding 1 in 10,000 patients (Bux and Sachs, 2007).
- Bacterial contamination has resulted in 1 in 10 transfusion-related deaths in the US (Kuehnert et al., 2001).
- Febrile reactions (e.g., sweating, rapid heart rate, nausea, or headache) occur in 5 to 10 percent of patients receiving transfusion because of antibodies in the transfused blood (King et al., 2004).
- Potentially fatal hemolytic reactions and graft versus host disease are rare, but the associated sequelae are very serious (Sazama et al., 1990; Linden et al., 1997).
- Clerical errors resulting in a person's receiving the wrong blood occur every 1 in 14,000 to 18,000 transfusion and are often fatal (Goodnough et al., 1999; Williamson et al., 1999).
- Iron overload occurs in patients who must receive repeated and prolonged transfusion, such as in MDS (Franchini and Veneri, 2004).

Further, the U.S. blood supply does not meet current clinical needs. Notably, the U.S. Department of Health and Human Services' Advisory Committee on Blood Safety and Availability (ACBSA) noted in its most recent (2005) report on blood availability that "the mean number of days of unmet nonsurgical blood need increased significantly from 2.1 days in 2001 to 19.27 days in 2004 ( $p < 0.001$ )."

(Whitaker et al., 2006). Such shortages lead to substantial problems for the health care system and Medicare beneficiaries, including the cancellation of vital surgical procedures. Therefore, CMS must carefully evaluate the impact of its proposed coverage policy on the U.S. blood supply. We recommend that the agency consult with the ACBSA to understand what effects the proposed coverage policy would have on an already limited national blood supply.

#### **IV. ANALYSIS OF THE POLICY IMPLICATIONS OF THE PROPOSED NON-COVERED AND COVERED CLINICAL INDICATIONS**

---

***Some of the agency's proposals appear to be clinically appropriate, and we recommend that CMS consider finalizing certain proposed non-covered indications.***

CMS has proposed to consider the following eight uses of ESAs as non-covered:

1. Anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis
2. Anemia of myeloid cancers, *specifically AML and CML*
3. Anemia associated with the treatment of myeloid cancers or erythroid cancers
4. Anemia associated with *primary treatment with radiotherapy*
5. Prophylactic use to prevent chemotherapy-induced anemia *in patients who have never suffered from CIA*
6. Prophylactic use to reduce tumor hypoxia *in non-anemic patients*
7. Patients with erythropoietin-type resistance due to neutralizing antibodies
8. Anemia due to cancer treatment if patients have uncontrolled hypertension

We note that the italicized text above represents specific clarifications that would make the proposed policy clearer.

**Recommendation:**      **Amgen recommends that CMS finalize these restrictions with the clarifications noted in italics. In our view, these uses are not supported by the current clinical evidence and there is no significant use of ESAs in current practice for these settings. As clinical evidence may evolve over time, we suggest that CMS review data on these clinical conditions periodically to reassess the appropriateness of non-coverage.**

Below, we review the proposed covered and non-covered indications outlined in the PDM.

***Some of the proposed non-covered indications are overly restrictive, when viewed against the available clinical evidence, and should not be implemented.***

In the cases below, we review the instances in which the clinical data do not support the agency's proposed non-coverage determination and review the clinical evidence that supports coverage.

##### Anemia of Cancer Not Related to Cancer Treatment

In the PDM, CMS has proposed non-coverage of ESAs for all patients with AOC. This proposal does not appropriately recognize that there is published evidence of benefit from controlled clinical trials, without evidence of detrimental survival outcomes, in

certain subgroups of patients receiving ESAs for AOC. For this reason, CMS should not restrict coverage for the entire patient population.

In response to the NCA for ESAs, Amgen previously has recommended that CMS consider restricting coverage in a specified subpopulation of AOC patients until further data clarify the benefit-to-risk profile in these patients. Specifically, we noted that the agency should consider restricting coverage in the subgroup of AOC patients with active cancer not receiving or planning to receive additional chemotherapy or radiation therapy with a poor prognosis, as these are the patients for whom evidence suggests that the benefit-to-risk profile could be negative and is at best neutral. Data from a recent clinical study of this patient population suggest that coverage for these patients may not be warranted at this time (Glaspy et al., 2007).

**Recommendation:** For these reasons, Amgen recommends that CMS not finalize the coverage exclusion for all AOC patients. Instead, CMS should consider restricting coverage for ESAs in only a subset of patients with AOC who have active disease and are not receiving or planning to receive chemotherapy or radiation therapy.

Patients with Treatment Regimens Including Anti-angiogenic Drugs and Monoclonal / Polyclonal Antibodies Directed Against the Epidermal Growth Factor Receptor

CMS proposes to implement a coverage restriction of ESAs for all patients with cancer-related anemia who are receiving anticancer therapy with biologic agents such as Avastin<sup>®</sup> (bevacizumab), Erbitux<sup>®</sup> (cetuximab), and Vectibix<sup>™</sup>. The CMS proposal appears to be based on three points:

1. A "colon cancer study" showing that patients treated with the anti-EGF-R monoclonal antibody, Vectibix<sup>™</sup>, and an ESA experienced decreased survival within 16 weeks;
2. A single study that used a chimeric receptor (*i.e.*, extracellular EGFR and intracellular EPO-R) transfected into a hematopoietic cell line to study the EPO-R signaling pathway in hemoglobin synthesis; (Wakao et al., 1997); and
3. Preclinical studies suggesting a possible role for EPO-R signaling in angiogenesis (Ribatti et al., 2007a; Ribatti et al., 2007b; Batra et al., 2003; Yasuda et al., 1998; Yasuda et al., 2002).

*Point 1 references research that does not appear to exist.* This point appears to result from blending the results from two separate studies: a study of Vectibix<sup>™</sup> in colon cancer patients (Amgen press release for PACCE, March 22, 2007) and a study of darbepoetin alfa in patients with anemia of cancer (Amgen press release for Study 20010103, April 16, 2007). Point 1, therefore, has no basis in evidence.

*Point 2 cites an irrelevant study.* The cited study demonstrated that the Stat5 protein is important for erythropoietin to stimulate hemoglobin synthesis. It does not bear on the question of whether ESAs will interfere with EGFR signaling (Wakao et al., 1997).

*Point 3 represents speculation.* This point has no supporting preclinical data and no relevant clinical data. The evidence cited included a letter to the editor (Ribatti et al.,

2002) speculating that angiogenesis stimulated by EPO may have contributed to the emergence of AML in an MDS patient as described in a case report (Bunworaste et al., 2001). The emergence of AML in patients with MDS is not uncommon, but angiogenesis is not believed to play a role in this pathologic evolution (Lundberg et al., 2006; Keith et al., 2007).

The ability of EPO itself to stimulate angiogenesis is highly speculative. The PDM cited a recent study (Zwezdaryk et al., 2007) using mesenchymal stem cells (MSCs) to show that erythropoietin elicited a pro-angiogenic response. However, the role of MSCs in tumor angiogenesis has not been well established; the study used the MAB307 antibody that does not specifically detect EPO-R; and a superphysiological concentration of erythropoietin (40-80 U/ml, 40-160-fold higher than levels achievable in clinical ESA therapy) was applied. Thus, the relevance of the findings from this study is unclear. Finally, EPO, even at huge concentrations, has no angiogenic activity in a rat corneal angiogenesis model, (Amgen Inc., ODAC Briefing Book 2007) which represents the most sensitive assay devised.

**Recommendation:**        **For these reasons, Amgen recommends that CMS not exclude coverage for patients who are also receiving antiangiogenic and anti-EGFR therapies. The agency's recommendation against use of ESAs with EGFR inhibitors or antiangiogenic agents lacks a scientific foundation. For the vast majority of patients, EGFR inhibitors and antiangiogenic agents are administered in combination with myelosuppressive regimens, for which anemia is a known and well-characterized complication. Therefore, the proposed restrictions should be reconsidered in order to protect a patient population with a demonstrated clinical need for ESA therapy.**

#### Patients with Thrombotic Episodes Related to Malignancy

In the PDM, CMS proposed to exclude coverage of ESAs for all patients with a history of thrombotic episodes related to malignancy. Patients exposed to ESAs have an increased risk of thrombotic vascular events (TVEs), reported by the Cochrane group as a relative risk of 1.67 (95 percent CI: 1.35, 2.06). This risk is well-described in the FDA-approved labels for ESAs. The absolute increase in the rate of TVEs is about two to three percent. Integrated analysis of all placebo-controlled randomized studies of darbepoetin alfa showed a relative risk of 1.57 (95 percent CI: 1.10, 2.26), similar to that reported by the Cochrane study level meta-analysis of all randomized controlled trials of ESA.

Importantly, the integrated analysis also demonstrated that the actual TVE rate was five percent in the placebo group, and eight percent in the darbepoetin alfa group. The increase in the rate of TVE remains at about three percent (absolute difference) regardless of whether patients had a prior history of TVE or not. In placebo-controlled CIA studies of darbepoetin alfa, for patients without a prior history of a TVE, the rate of TVE is 4.3 percent in the placebo patients and 7.3 percent in the darbepoetin alfa-treated patients; for patients with a history of prior TVE, the rate of TVE is 15.8 percent

in the placebo patients, and 18.9 percent in darbepoetin alfa-treated patients, thus indicating about a three percent increase above baseline with ESA therapy regardless of whether patients had a history of TVE (Amgen data on file). These clinical data suggest a lack of interaction between ESA treatment and prior TVE in terms of ongoing TVE risk, and therefore there is no scientific basis to recommend against the use of ESAs in patients with a history of prior TVE. Finally, ESA use in patients with thrombotic episodes is not a contraindication or a warning in the prescribing information for these products.

**Recommendation:** For these reasons, Amgen recommends that CMS not exclude coverage for patients who have had thrombotic episodes related to malignancy. The agency's recommendation against use of ESAs in this sub-population lacks a scientific foundation, as the clinical evidence shows a lack of interaction between ESA treatment and prior TVE in terms of ongoing TVE risk.

#### Treatment of MDS

CMS proposes non-coverage of ESAs for all patients with MDS, a chronic bone marrow disorder most frequent in patients over 65 years of age that leads to chronic anemia and transfusion dependence in the absence of ESA therapy (Balducci et al., 2006). Finalizing this proposal would reject the body of evidence that supports the benefit conferred by ESA treatment in this setting, without evidence of detrimental survival outcomes. Further, the proposal is contrary to the agency's own Physicians Quality Reporting Initiative (PQRI) mandated by Congress under TRHCA. Under PQRI, CMS recognizes MDS as a condition for which ESA treatment plays a valuable role and encourages physicians to report iron store levels in patients receiving ESA therapy (Available at: <http://www.cms.hhs.gov/PQRI/Downloads/PQRIMeasuresList.pdf>).

Further, while large, placebo-controlled randomized studies are not available, numerous clinical trials have been conducted with ESAs in MDS patients, and the extensive published evidence (Balducci et al., 2006; Casadevall et al., 2004; Hellstrom-Lindberg et al., 1995; Kurtin et al., 2006; Negrin et al., 1996; Spiriti et al., 2005) supports the efficacy of ESAs in reducing transfusions in MDS patients. Amgen summarized these data in our submission to CMS on April 13, 2007. This body of evidence has been recognized in the compendium-listed acceptance for MDS and in evidence-based guidelines (Greenberg et al., 2007).

With regard to safety in MDS patients, Jadersten and colleagues (Jadersten et al., 2005) reported the long-term outcome of 129 MDS patients treated with epoetin alfa and granulocyte-colony stimulating factor (G-CSF) who were followed for up to 45 months. Erythroid response rate was 39 percent and median response duration 23 months (range, 3-116 months or more). Complete responders showed longer response duration than partial responders (29 versus 12 months,  $P = 0.006$ ). There was no difference in survival (odds ratio [OR], 0.9; 95 percent CI: 0.7, 1.2;  $P = 0.55$ ) or risk of AML evolution (OR, 1.3; 95 percent CI: 0.7-2.2;  $P = 0.40$ ) between the ESA-treated patients in comparison to untreated patients selected from the IPSS database using multivariate Cox regression, adjusting for major prognostic variables.

Additionally, a matched case-control study of transfusion-dependent MDS patients treated with ESAs and a granulocyte-colony stimulating factor (n=123) compared to control MDS patients (n=240) showed that 41 percent of ESA-treated patients achieved transfusion independence (Jadersten et al., 2006). Multivariate Cox regression analysis showed that treated patients with (historical) transfusion need of less than 2 units of red blood cells per month had a survival benefit, with HR 0.57 (p = 0.015), while no difference in survival was observed in patients with higher transfusion need (p = 0.36). There was no significant impact on risk of leukemic transformation in patients with either a low (p = 0.75) or high (p = 0.21) transfusion need. These retrospective analyses support the use of ESAs to reduce transfusion dependence in MDS patients. This population is particularly vulnerable given the risk of allo-immunization from repeated transfusions.

A systematic review of 59 ESA studies (2106 patients) including 4 RCTs support the safety and efficacy of ESAs in the treatment of anemia associated with MDS (Ross et al., 2007).

In the May 10, 2007, meeting of the FDA's ODAC, numerous participants recognized MDS as a condition that warrants Medicare coverage. In comment at the ODAC meeting, the Director of the FDA's Office of Oncology Drug Products noted the need to separate MDS from other clinical conditions, as noted in Table 15.

**Table 15: FDA Statement on Need to Have Distinct Separation between MDS and Other Clinical Conditions for Coverage Purposes**

Dr. Richard Pazdur, Director, Office of Oncology Drug Products, FDA

"Those are two different things. I do not want them [MDS patients] to get swept away with this. We will discuss this with our colleagues at CMS to make sure that does not occur." (Pazdur, 2007)

**Recommendation:** For these reasons, Amgen recommends that CMS not exclude coverage for MDS. Given the well-recognized role of ESA therapy in MDS and the available clinical evidence that supports the use of ESA, CMS should not restrict coverage to Medicare beneficiaries for this indication.

## **V. PROPOSED COVERAGE LIMITATIONS**

---

***The proposed restriction to limit coverage for patients with hemoglobin levels less than 9.0 g/dL is not based in the clinical evidence.***

In this aspect of the PDM, CMS has blended the two following important but distinct clinical issues: (1) when to initiate ESA therapy and (2) when to withhold ESA treatment based on hemoglobin levels.

CMS states that the ESA should only be used when the hemoglobin falls below 9.0 g/dL, during each month for patients without known cardiovascular disease. Such a restriction is a serious concern because it is not based on the evidence of clinical efficacy of ESAs from randomized controlled trials. Most patients in randomized controlled trials had hemoglobin levels > 9.0 g/dL at study entry. For Amgen-sponsored darbepoetin alfa studies involving more than 10,000 patients, 88 percent had baseline hemoglobin of 9.0 g/dL or higher. The limitations as proposed by CMS will effectively set a hemoglobin target of 9.0 g/dL, a level that will negate the goal of avoiding transfusion with ESA therapy. This limitation is inconsistent with the FDA approved product label, and is in conflict with the current practice guidelines from major professional societies. This limitation also confuses two important aspects of optimal ESA treatment (*i.e.*, the hemoglobin level at which to initiate treatment, and the hemoglobin level to target once ESA treatment begins). For the purpose of avoiding transfusion and alleviating the signs and symptoms of anemia, it is important to set an initiation level at which the risk of transfusion is low. After initiation of therapy, the dose of ESAs should then be adjusted to achieve a target hemoglobin that is optimal to keep the patient free from the risk of transfusion as well as the signs and symptoms of anemia. Clinical trials to assess ESAs have been conducted with explicit levels of hemoglobin for initiation, and a clear guidance on dose adjustment to achieve and maintain a hemoglobin level considered appropriate for the well being of the patients.

This proposed restriction appears to be based on the cited "tradition" and critical care model of reserving transfusion for patients with hemoglobin levels less than 7 or 8 g/dL, and does not consider the current practice regarding transfusions in patients treated in the community-based outpatient clinic for CIA. Such evidence is available from clinical trials, community practice surveys, and claims database analyses. These analyses show that the hemoglobin level before transfusion varies over a wide range, but is consistent across multiple data sources. In the five randomized, phase 3 trials of darbepoetin alfa in CIA, 71 percent of the transfusions received by ESA-treated patients were preceded by a hemoglobin of < 9.0 g/dL. These results were similar to the 80 percent rate observed for two Amgen-sponsored, retrospective, observational studies.

These data clearly show that physicians prescribe red blood cell transfusions to treat the signs and symptoms of anemia, rather than relying on arbitrary hemoglobin level transfusion triggers. If CMS restricts ESA use with a 9.0 g/dL initiation level (which would also become the target level), it would lead to the replacement of ESA use with red blood cell transfusions for most patients.

The current product label for ESAs recommends that a hemoglobin level of no higher than 12.0 g/dL be used to avoid transfusion. This is a critical element in the current revised FDA label, which reflects a conservative approach, as most randomized clinical trials specified a target hemoglobin of 13.0 g/dL or higher and prior to the recently modified label, ESA treatment in cancer uses was withheld at 13.0 g/dL whereas now withholding occurs at 12.0 g/dL. The importance of this approach has been validated as the appropriate restriction by the recent ODAC panel, who recommended against a change in the labeled hemoglobin limit of 12.0 g/dL, which is essential to achieve the goals of transfusion avoidance. Under the proposed coverage restrictions, an arbitrary upper threshold for ESA therapy is set at a hemoglobin level of 9.0 g/dL, which will lead to transfusion in most patients *before* they can be qualified for ESA therapy, practically rendering the ESA ineffective in the FDA-defined primary objective of therapy— to reduce the risk of receiving a red blood cell transfusion (Aranesp® [darbepoetin alfa] prescribing information, Amgen). CMS should not implement a policy that conflicts with the ESA product label and the ODAC recommendation.

**Recommendation:** For these reasons, Amgen recommends that CMS include no initiation limit for ESAs. However, if CMS decides to implement an initiation threshold, we recommend a threshold of 11.0 g/dL and to allow treatment until a patient's hemoglobin reaches 12.0 g/dL. CMS should consider the need for physician discretion to dose reduce rather than withhold when hemoglobin exceeds 12.0 g/dL during chemotherapy.

***CMS has proposed a timeframe of 12 weeks per year for ESA treatment. This limit is without support in the clinical evidence and should be re-evaluated carefully in light of the best available data.***

Chemotherapy regimens in cancer patients are frequently prolonged and last beyond 12 weeks. For instance, in the adjuvant setting, colorectal cancer and breast cancer patients are typically treated with chemotherapy for six months. For patients with metastatic cancer, chemotherapy regimens are commonly administered until disease progression, at which time the second-line treatment may begin, and multiple lines of chemotherapy are often administered with the total treatment duration well over 12 weeks for patients who survive beyond 12 months. Clearly, the number of courses of chemotherapy in a year is highly variable depending on tumor type, extent of disease and response to therapy. Based on data from the Tandem Cancer audit (Amgen, data on file) the duration of chemotherapy is outlined in Table 16 for common tumor types.

**Table 16: Common Cancer Types and Treatment Durations**

<b>Cancer Type</b>	<b>Average Chemotherapy Duration</b>
Colorectal Cancer	23 weeks
Breast Cancer	16 weeks
Hodgkin's Disease	24 weeks
Non-Hodgkin's Lymphoma	20 weeks
Non-Small Cell Lung Cancer	17 weeks
Small Cell Lung Cancer	18 weeks
Ovarian Cancer	22 weeks
Prostate Cancer	26 weeks

Tandem Cancer Audit, Amgen data on file

Thus, it is clear that anemia in patients receiving myelosuppressive chemotherapy commonly lasts more than 12 weeks. As such, this proposal would inadvertently discriminate against Medicare beneficiaries who are prescribed chemotherapy regimens in excess of 12 weeks.

Further, patients with cancer are at risk of developing anemia not only when they are receiving myelosuppressive chemotherapy but also for a variable time period after the completion of their chemotherapy. The time necessary for bone marrow recovery after cessation of chemotherapy varies widely based on individual patient factors such as age, type of chemotherapy, type of disease, and effects of the chemotherapy on renal endocrine function. Additionally, expert medical societies, including ASH, have recommended that the duration of ESA therapy might need to be up to 90 days after completion of chemotherapy with longer durations depending on individual patient circumstances (ASH Statement to CMS).

For all of these reasons, a specific recommendation regarding the maximum duration of ESA treatment should not be made, as any time limit would be, quite simply, arbitrary.

**Recommendation:** For these reasons, Amgen recommends that CMS include no time limit for ESA treatment given the wide variations in treatment regimens for chemotherapy courses and need for multiples cycles and lines in cases of progression. Further, for purposes of coverage policy, CMS should define CIA as (1) patients with cancer and anemia who are receiving concomitant chemotherapy and (2) patients with anemia who have completed myelosuppressive chemotherapy within the prior three months.

***CMS has proposed a coverage limit of 126,000 units for epoetin alfa and 630 mcg for darbepoetin alfa per four week period. This proposal is not supported by the clinical evidence and should be reconsidered.***

This proposed restriction is inconsistent with the FDA-approved dosing regimen for ESAs. The ESAs are titratable drugs used to achieve specific hemoglobin levels. The starting doses and dose adjustment guidelines are clearly delineated in the product label and clinical practice guidelines. Further, the currently proposed coverage policy appears to be drafted to carefully control hemoglobin initiation and target levels. As such, restricting the dosing as well would not result in effective clinical care.

Moreover, the FDA-approved labeling for darbepoetin alfa states that one of the product's dosing regimens allows for administration at a dose of 500 mcg every three weeks (*i.e.*, up to 1,000 mcg per six weeks unless there are dose reductions). Limiting the total dose of darbepoetin alfa to 630 mcg per 4 weeks will limit the ability for physicians to effectively manage anemia in patients who may require a higher than average dose to respond and disadvantage patients who are prescribed every-three-week dosing given with their chemotherapy regimens. Similarly, the labeled dose of epoetin alfa is 40,000 U per week and the product label recommends an increase to 60,000 U per week (*i.e.*, 360,000 U per six weeks), if patients who do not have satisfactory response after 4 weeks of therapy.

**Recommendation:** For these reasons, we recommend that CMS not limit the doses for ESAs. If the agency chooses a dose limit, we recommend that CMS use the maximum approved doses for ESAs, per their product labels, in the finalized NCD. Additionally, CMS should adjust the timeframe to six weeks (versus four) because one ESA can be dosed on a three-week basis. Therefore, the maximum allowed doses should be 1,000 mcg per six weeks for darbepoetin alfa and 360,000 U per six weeks for epoetin alfa.

***In the PDM, CMS has proposed to limit access to ESAs if there is evidence of poor drug response (*i.e.*, hemoglobin rise < 1.0 g/dL or hematocrit rise < 3 percent) after 4 weeks of treatment. This proposal lacks necessary scientific support.***

Patients considered to be hypo-responsive, in the absence of other factors such as intestinal bleeding or functional iron deficiency, have typically been administered increased doses of ESAs after either 4 or 6 weeks, an approach used in the majority of licensing studies which have demonstrated positive risk/benefit for ESAs and have formed the basis of the current FDA label (Witzig et al., 2005; Vansteenkiste et al., 2002, Hedenus et al., 2002). In this regard it is important to note that although hemoglobin changes (as opposed to a bona fide clinical response) can be seen in as little as 2 weeks, the median time to a rise in hemoglobin of > 1.0 g/dL is 28 days (Amgen data on file). The current FDA label of Aranesp states "Increased hemoglobin levels are not generally observed until 2 to 6 weeks after initiating treatment" and refers the reader to the dosage and administration section. For weekly administration, this section recommends that if a patient has an inadequate initial response to therapy (defined as a less than 1.0 g/dL increase in 6 weeks) the weekly dose should be increased as

opposed to recommending cessation of therapy (Aranesp<sup>®</sup> prescribing information). Additionally, the NCCN clinical practice guidelines recommend discontinuation of ESA treatment only if no response is observed after 8 to 12 weeks of therapy (Rodgers et al., 2007). While different dose titration rules have been used in different studies, these dose titration rules have not been demonstrated to be valid predictors of clinical benefit, or surrogates for possible risk. In clinical trials the formal protocol-specified assessment of hemoglobin response to ESAs is typically performed after 8, 12, or 16 weeks of treatment. Amgen believes that an evaluation of hypo-responsiveness or non-response should be based on the clinical assessment based on the individualized treatment goals for a particular patient rather than on a broad laboratory based assessment that is inconsistent with current guidelines on clinical trial evidence.

**Recommendation:** For these reasons, Amgen recommends that CMS not include a specified time limit to assess ESA therapy response in the final policy. If the agency chooses to implement such a policy, we recommend that it be in line with the product label and clinical practice guidelines by extending the coverage parameters for an adequate trial of therapy to 12 weeks of therapy (instead of four).

***In the PDM, CMS has proposed restrictions on the administration of ESAs if there is a rapid rise in hemoglobin greater than 1.0 g/dl or hematocrit greater than 3 percent after 2 weeks of treatment.***

A potential safety concern with erythropoietic therapy is that rapid increases in hemoglobin or high hemoglobin concentrations may be associated with an increased rate of cardiovascular or thromboembolic adverse events. Using the data from previous Aranesp studies, a Cox Proportional-Hazard time-dependent analysis was conducted to examine the association between the rate of rise in hemoglobin and the risk of thromboembolic events. The time at-risk following a hemoglobin concentration of  $\geq 1.0$  g/dL within a 2-week period was not associated with an increased risk of a thromboembolic event, although similar analyses of patients who had an increase in hemoglobin concentration of  $\geq 2.0$  g/dL within a 28-day period suggested that the increase may be associated with an increased risk for thromboembolic events (Amgen ODAC Briefing Book 2004). Although early studies of darbepoetin alfa in the oncology setting did not use dose titration rules to address rapidly rising hemoglobin concentrations, based on the data indicating the potential for increased risk of thromboembolic events with a 2.0 g/dL increase in 28 days and the lack of clinical need to increase hemoglobin more rapidly, a precautionary approach was adopted in the US package insert (Aranesp<sup>®</sup> prescribing information). The current label information recommends a dose reduction for patients with a  $\geq 1.0$ -g/dL increase in hemoglobin within 14 days.

However, the CMS recommendation to withhold therapy from patients with a  $> 1.0$  g/dL increase in hemoglobin within 14 days is not based on evidence from clinical trials and will have an important negative impact on the benefit derived from ESA therapy in the cancer setting. Hydration therapy, chemotherapy, individual patient factors, and variation in laboratory values in patients with cancer theoretically make significant contributions to the natural variability in hemoglobin concentrations during the course of

each chemotherapy cycle. These factors may result in a significant rate of “false positives” when applying the 1.0 g/dL increase within 14 days rule, even in the absence of erythropoietic therapy. In fact, due to the natural variability of hemoglobin in cancer patients receiving chemotherapy in an analysis of placebo-controlled trials, the number of placebo-treated patients who had a > 1.0 g/dL increase in hemoglobin over 14 days was estimated to be 52% (excluding the effect of transfusions).

Given the inherent variability of hemoglobin concentrations and the lack of evidence suggesting an association between thrombotic events and a 1.0-g/dL increase in hemoglobin concentration within 14 days, a recommendation regarding cessation of therapy based on this algorithm is inappropriate for patients with cancer who are receiving chemotherapy. Coverage policy should adhere to the FDA-approved dosing recommendation and current treatment guidelines which recommend a dose reduction if a patient achieves a rapid rise in hemoglobin.

**Recommendation:** Therefore, Amgen recommends that CMS not include a specified time limit in this regard as part of the final policy. If the agency chooses to implement such a policy, we recommend that CMS revise its proposed NCD and implement a policy in line with prescribing information, by requiring a dose reduction of 40 percent for an approved ESA when the levels of hemoglobin increase by more than 1.0 g/dL in a two-week period.

*The agency has also proposed to restrict access to continued administration of ESAs if there is an increase in fluid retention or weight (5 kg) after 2 weeks of treatment.*

We find no evidence to support this proposed restriction.

**Recommendation:** Therefore, Amgen recommends that CMS cite specific data to support this proposal or explain how such a situation would constitute a medical problem. Otherwise, CMS should remove it from the finalized NCD.

## **VI. DISCUSSION OF LIMITATION OF COVERAGE TO ONLY BENEFICIARIES ENROLLED IN CLINICAL RESEARCH PROGRAMS**

---

***The agency commented that it is considering limiting coverage of ESAs to only those beneficiaries enrolled in clinical research studies.***

The implication of the agency's reference in the PDM to tying coverage to clinical studies is that the benefit-to-risk profile of ESAs in cancer patients does not support *any* use of an ESA outside of a purely investigative setting. As we have described throughout this document, the weight of evidence supports a neutral risk of adverse survival outcomes in CIA.

The hierarchy and weight of evidence already established for ESAs makes this type of restriction unnecessary. ESAs have been well studied, and appropriate analyses of the data are extremely reassuring. If the only mechanism for Medicare beneficiaries to access FDA labeled indications for ESA were in a clinical research study, beneficiaries who could not participate in such trials (*e.g.*, because of lack of trials in their locality) would lack treatments available to other beneficiaries who are fortunate enough to live near a clinical research site. This situation could prove common in rural areas and could appear to some as geographic discrimination. Furthermore, the great majority of community oncologists are not investigators. Limiting ESA access to investigational use would deny ESA access to many patients, leaving them with red blood cell transfusions as the only treatment option for anemia management.

Such a requirement for a Medicare Part B covered drug or biological would also be unprecedented and extraordinary, as CMS has never before imposed such a coverage limitation on any class of marketed products that has been used in clinical practice for nearly 20 years. To make cancer care the first area to have this type of experimental restriction is unwise and could pose a significant potential for worsening patient outcomes in anemia management.

For off-label uses, we suggest that CMS consider consultation with a broad group of stakeholders in the oncology community (*i.e.*, national medical societies, guideline organizations, community oncology groups, clinical and academic experts, patient groups, and manufacturers) to determine whether there are important questions that could be addressed in the context of ongoing clinical research.

**Recommendation:**      **For these reasons, Amgen recommends that CMS not implement a coverage restriction that would limit Medicare beneficiary access to ESAs only if they participate in a clinical research study.**

\* \* \* \*

Amgen appreciates the opportunity to share this information with CMS. We believe that our submission will help provide useful data for CMS to consider as its staff work to finalize an NCD for ESAs in non-renal disease indications (CAG-00383N). If you would like any further information, please contact me personally by phone at (805) 447-0787 or by email at [jofman@amgen.com](mailto:jofman@amgen.com). Alternatively, you may contact Sarah Wells Kocsis in Amgen's Global Government Affairs office at (202) 585-9713 or by email [wellss@amgen.com](mailto:wellss@amgen.com). Thank you for your attention to these important matters.

Regards,



Joshua J. Ofman MD, MSHS  
Vice President  
Global Coverage and Reimbursement  
Global Health Economics

Attachment: Appendix A (Review of the Science on the Hypothesis about the Putative Role of EPO-R in Tumor Growth)

cc: Barry Straube, MD, Director, Office of Clinical Standards and Quality (OCSQ),  
Chief Medical Officer, CMS  
Louis Jacques, MD, Director, Division of Items and Devices, Coverage and  
Analysis Group (CAG), CMS  
Elizabeth Koller, MD, FACE, Lead Medical Officer, CAG, CMS  
Shamiram Feinglass, MD, MPH, Lead Medical Officer, CAG, CMS  
Ross Brechner, MD, MS, MPH, CAG, CMS  
Maria Ciccanti, RN, Lead Analyst, CAG, CMS  
Leslye Fitterman, PhD, Analyst, CAG, CMS

## **REFERENCES**

- Aapro M, Barnadas A, Leonard R. Effects of epoetin beta treatment in patients with metastatic breast cancer receiving chemotherapy. Results of the BRAVE trial. *Breast Cancer Res Treat.* 2006;100. Abstract 6095.
- Abels, R. Erythropoietin for anaemia in cancer patients. *Eur J Cancer.* 1993. 29A;Suppl 2: S2-8.
- American Society of Clinical Oncology. ASCO Statement. May 15: Proposed National Coverage Policy on Erythropoiesis Stimulating Agents (ESAs). Available at <http://www.asco.org/portal/site/ASCO/menuitem.c543a013502b2a89de912310320041a0/?vgnnextoid=091d6f0fd7292110VqnVCM100000ed730ad1RCRD>. Accessed May 30, 2007.
- American Society of Hematology. ASH Statement on Medicare Proposed National Coverage Policy on Erythropoiesis-Stimulating Agents (ESAs). Available at: <http://www.hematology.org/policy/news/05182007.cfm>. Accessed May 24, 2007.
- Amgen Inc (2007). Safety of Erythropoiesis-Stimulating Agents (ESAs) in Oncology. Background Information for Oncologic Drugs Advisory Committee. Available at <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4301b2-01-01-Amgen.pdf>
- Amgen Inc. (2004). Aranesp<sup>(R)</sup> (darbepoetin alfa) safety, Oncologic Drugs Advisory Committee. Available at: <http://www.fda.gov/ohrms/dockets/ac/04/briefing/4037b2.htm>. Accessed July 22, 2005. Aranesp<sup>(R)</sup> (darbepoetin alfa) prescribing information, Amgen.
- Amgen Press Release. "Amgen Discontinues Vectibix<sup>(TM)</sup> Treatment In PACCE Trial Evaluating Vectibix<sup>(TM)</sup> As Part Of Triple Combination Regimen." March 22, 2007. Available at: [http://wwwext.amgen.com/media/media\\_pr\\_detail.jsp?year=2007&releaseID=977186](http://wwwext.amgen.com/media/media_pr_detail.jsp?year=2007&releaseID=977186)
- Amgen Press Release. "Aranesp<sup>(R)</sup> Phase 3 Study in Patients with Active Cancer Not Receiving Concurrent Chemotherapy or Radiotherapy Presented at AACR Annual Meeting". April 16, 2007. Available at: [http://wwwext.amgen.com/media/media\\_pr\\_detail.jsp?year=2007&releaseID=985366](http://wwwext.amgen.com/media/media_pr_detail.jsp?year=2007&releaseID=985366)
- Amgen Study 20010145.
- Aranesp<sup>(R)</sup> (darbepoetin alfa) prescribing information, Amgen Inc. 2007
- Balducci, L. Transfusion independence in patients with myelodysplastic syndromes: impact on outcomes and quality of life. *Cancer.* 2006;106:2087-2094.
- Bamias, A, Aravantinos, G, Kalofonos, C, et al. Prevention of anemia in patients with solid tumors receiving platinum-based chemotherapy by recombinant human

erythropoietin (rHuEPO): A prospective, open label, randomized trial by the Hellenic Cooperative Oncology Group. *Oncology*. 2003; 64 (2): 102-10.

Batra S, Perelman N, Luck L, Shimada H, Malik P. Pediatric tumor cells express erythropoietin and a functional erythropoietin receptor that promotes angiogenesis and tumor cell survival. *Lab Invest*. 2003;83:1477-87.

Beveridge, R. Quotation from United States Food and Drug Administration Oncology Drugs Advisory Committee on May 10, 2007.

Blohmer, J-U, Wurschmidt, F, Petry, U, et al. Results with sequential adjuvant chemoradiotherapy with vs without epoetin alfa for patients with high-risk cervical cancer: Results of a prospective, randomized, open and controlled AGO- and NOGGO-intergroup study. *Ann Oncol*. 2004; Abstract # 477PD.

Bohlius J, Wilson J, Seidenfeld J, et al. Erythropoietin or Darbepoetin for patients with cancer (Review). *Cochrane Database of Systematic Reviews* 2006;(3);CD003407.

Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. *J Natl Cancer Inst*. 2006;98:708-714.

Bokemeyer C, Aapro MS, Courdi A, et al. EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer. 2006 update. *Eur J Cancer* 2007;43:258-70.

Brown WM, Maxwell P, Graham ANJ, et al. Erythropoietin receptor expression in non-small cell lung carcinoma: a question of antibody specificity. *Stem Cells*. 2007;25:718-722.

Bunworasate U, Arnouk H, Minderman H, et al. Erythropoietin-dependent transformation of myelodysplastic syndrome to acute monoblastic leukemia. *Blood*. 2001;98:3492-3494.

Busch, MP, Caglioti, S, Robertson, EF, et al. Screening the blood supply for West Nile virus RNA by nucleic acid amplification testing. *N Engl J Med*. 2005; 353 (5): 460-7.

Busch, MP, Kleinman, SH and Nemo, GJ. Current and emerging infectious risks of blood transfusions. *JAMA*. 2003; 289 (8): 959-62.

Bux, J and Sachs, UJ. The pathogenesis of transfusion-related acute lung injury (TRALI). *Br J Haematol*. 2007; 136 (6): 788-99.

Casadevall et al. Health, economic, and quality-of-life effects of erythropoietin and granulocyte colony-stimulating factor for the treatment of myelodysplastic syndromes: randomized, controlled trial. *Blood* 2004;104:321-327.

Case, DC, Jr., Bukowski, RM, Carey, RW, et al. Recombinant human erythropoietin therapy for anemic cancer patients on combination chemotherapy. *Journal of the National Cancer Institute*. 1993; 85 (10): 801-806.

Cazzola, M, Messinger, D, Battistel, V, et al. Recombinant human erythropoietin in the anemia associated with multiple myeloma or non-Hodgkin's lymphoma: dose finding and identification of predictors of response. *Blood*. 1995; 86 (12): 4446-53.

Cella, D, Eton, DT, Lai, JS, et al. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *Journal of Pain & Symptom Management*. 2002; 24 (6): 547-561.

Centers for Medicare & Medicaid Services. Public Comments for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N) Centers for Medicare & Medicaid Services. Available at [http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca\\_id=203](http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca_id=203). Accessed May 23, 2007.

Centers for Medicare and Medicaid Services. Decision Memo for Anticancer Chemotherapy for Colorectal Cancer (CAG-00179N), Appendix B, General Methodological Principles of Study Design (Section VI of the Decision Memorandum). Available at <http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=90>. Accessed March 14, 2007.

Chamberland et al. Blood Safety. Centers for Disease Control and Prevention 1998. <http://www.cdc.gov/ncidod/eid/vol4no3/chambrln.htm>

Chang, J, Couture, F, Young, S, et al. Weekly epoetin alfa maintains hemoglobin, improves quality of life, and reduces transfusion in breast cancer patients receiving chemotherapy. *J Clin Oncol*. 2005; 23 (12): 2597-605.

Charu V, Belani CP, Gill AN, et al. A controlled, randomized, open-label study to evaluate the effect of every-2-week darbepoetin alfa for anemia of cancer. *Proc Am Soc Clin Oncol*. 2004; Abstract 8084 and poster.

ClinicalStudyResults.org Website. Results from a phase 3, randomized, double-blind, Placebo-controlled study of darbepoetin alfa in subjects with previously untreated extensive-stage small cell lung cancer (SCLC) treated with platinum plus etoposide chemotherapy. Available at: [http://www.clinicalstudyresults.org/documents/companystudy\\_2368\\_0.pdf](http://www.clinicalstudyresults.org/documents/companystudy_2368_0.pdf). Accessed May 23, 2007.

Coiffier B, Boogaerts M, Kainz C. Impact of Epoetin Beta versus Standard Care on Quality of Life in Patients with Malignant Disease. 6th Congress of the European Haematology Association. 2001: Abstract #194.

Constantinescu, S. Public Comments for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N). Posted 5/28/07; available at [http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?id=&cov\\_id=&state\\_id=&list\\_type=&goto=viewpubliccomment&nca\\_id=203&rangebegin=05\\_14\\_2007&rangeend=06\\_13\\_2007#0514200706132007C](http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?id=&cov_id=&state_id=&list_type=&goto=viewpubliccomment&nca_id=203&rangebegin=05_14_2007&rangeend=06_13_2007#0514200706132007C)

Crawford J, Cella D, Cleeland CS, et al. Relationship between changes in hemoglobin and quality of life during chemotherapy in anemic cancer patients receiving epoetin alfa therapy. *Cancer*. 2002;95:888-895

Crawford J, Robert F, Perry M, et al. A randomized trial comparing immediate versus delayed treatment of anemia with once-weekly epoetin alfa in patients with non-small cell lung cancer scheduled to receive first line chemotherapy. *J Thorac Oncol*. 2007;2:210-220.

DAHANCA-10 Interim Analysis, Danish Head and Neck Cancer Group. Available at: [http://www.dahanca.dk/get\\_media\\_file.php?mediaid=125](http://www.dahanca.dk/get_media_file.php?mediaid=125). Accessed May 23, 2007.

Dammacco F, Castoldi G, Rodger S. Efficacy of epoetin alfa in the treatment of anaemia of multiple myeloma. *Br J Haematol*. 2001;113:172-179.

Data on File, Amgen, Inc

Data on file, Johnson & Johnson Pharmaceutical Research and Development, LLC.

Del Maestro L, Venturini M, Lionetto R. Randomized phase III trial evaluating the role of erythropoietin in the prevention of chemotherapy-induced anemia. *J Clin Oncol*. 1997;15:2715-2721.

Delarue, R, Mounier, N, Haioun, C, et al. Safety of prophylactic use of darbepoetin alfa in patients with diffuse large b-cell lymphoma (DLBCL) treated with RCHOP14 or R-CHOP21: preliminary results of the LNH03-6B randomized GELA study. *Blood*. 2006; 108 (11): Abstract # 2436.

Demetri GD, Kris M, Wade J, et al. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: Results from a prospective community oncology study. Procrit Study Group. *J Clin Oncol*. 1998;16:3412-3425.

Dodd RY. Emerging infections, transfusion safety, and epidemiology. *New Engl J Med*. 2003;349:1205-1206.

Dunphy, FR, Harrison, BR, Dunleavy, TL, et al. Erythropoietin reduces anemia and transfusions: A randomized trial with or without erythropoietin during chemotherapy. *Cancer*. 1999; 86 (7): 1362-1367.

Eckhardt, GS. Quote in "Miracle-Gro?" ODAC Vents At Amgen, J&J Over ESAs' *The Cancer Letter*, May 18, 2007, Vol. 33 No. 19

Eckhardt, GS. Quote in 'CMS Proposal Restricting ESA Use Is Too Much, Too Fast, Critics Say' *The Cancer Letter*, May 18, 2007, Vol. 33 No. 19

EPOGEN® (Epoetin alfa) prescribing information, Amgen.

Farrar JT, Young JP, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical rating scale. *Pain*. 2001;94:145-158.

Franchini M, Veneri D. Iron-chelation therapy: an update. *Hematol J* 2004;5:287-292.

Gabrilove JL, Cleeland CS, Livingston RB, et al. Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: Improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. *J Clin Oncol*. 2001;19:2875-2882.

Glaspy J, Bukowski R, Steinberg D, et al. Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. *J Clin Oncol*. 1997;15:1218-1234.

Glaspy J, Smith R, Aapro M, et al. Results from a phase 3, randomized, double-blind, placebo-controlled study of darbepoetin alfa (DA) for the treatment of anemia in cancer patients not receiving chemotherapy or radiotherapy. *Proc Amer Assoc Cancer Res*. 2007. Abstract LB3 and presentation.

Goodnough, LT, Brecher, ME, Kanter, MH, et al. Transfusion medicine. First of two parts--blood transfusion. *N Engl J Med*. 1999; 340 (6): 438-47.

Gordon DH. Treating anemia of cancer with darbepoetin alfa administered every 4 weeks: final results from a phase 2, randomized, double-blind, placebo-controlled study in cancer patients not receiving chemotherapy and/or radiotherapy. *48th ASH Annual Meeting*. 2006;Abstract 1340 and poster.

Greenberg PL, Baer MR, Bennett JM, et al. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes. V.1.2007; 2007. Available at [www. NCCN.org](http://www.NCCN.org). Accessed May 31, 2007.

Grote T, Yeilding AL, Castillo R, et al. Efficacy and safety analysis of epoetin alfa in patients with small-cell lung cancer: a randomized, double-blind, placebo-controlled trial. *J Clin Oncol*. 2005;23:9377-9386.

Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al. Current methods of the U.S. Preventive Services Task Force: a review of the process. *Am J Prev Med*. 2001; 20(3 Suppl):21-35.

Hedenus M, Adriansson M, San Miguel J, et al. Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: a randomized, double-blind, placebo-controlled study. *Br J Haematol*. 2003;122:394-403.

Hedenus M, Hansen S, Taylor K, et al. Randomized, dose-finding study of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies. *Br J Haematol*. 2002;119:79-86.

Hellstrom-Lindberg. Efficacy of erythropoietin in the myelodysplastic syndromes: a meta-analysis of 205 patients from 17 studies. *Br J Haematol*. 1995;89:67-71.

Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: Randomised, double-blind, placebo-controlled trial. *Lancet*. 2003;362:1255-1260.

Henry, DH and Abels, RI. Benefits of epoetin alfa therapy in anemic cancer patients receiving chemotherapy. *J Clin Oncol*. 1995; 13 (9): 2473-4.

Higgins JPT, Thompson SG, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557.

Hirsh, V, Glaspy, J, Mainwaring, P, et al. Phase II study of two dose schedules of C.E.R.A. (Continuous Erythropoietin Receptor Activator) in anemic patients with advanced non-small cell lung cancer (NSCLC) receiving chemotherapy. *Trials*. 2007; 8:8.

Jadersten M, Malcovati L, Dybedal I et al. Treatment with Erythropoietin and G-CSF Improves Survival in MDS Patients with Low Transfusion Need. *Blood*. 2006;108. Abstract 521.

Jadersten, M, Montgomery, SM, Dybedal, I, et al. Long-term outcome of treatment of anemia in MDS with erythropoietin and G-CSF. *Blood*. 2005; 106 (3): 803-11.

Johnson & Johnson Pharmaceutical Research and Development, LLC. Safety of Erythropoietin Receptor Agonists (ERAs) in Patients With Cancer. Background Information for Oncologic Drugs Advisory Committee Meeting May 4 2004

Keith T, Araki Y, Ohyagi M. Regulation of angiogenesis in the bone marrow of myelodysplastic syndromes transforming to overt leukaemia. *Br J Haematol*. 2007;137:206-215.

King, KE, Shirey, RS, Thoman, SK, et al. Universal leukoreduction decreases the incidence of febrile nonhemolytic transfusion reactions to RBCs. *Transfusion*. 2004; 44 (1): 25-9.

Kotasek, D, Steger, G, Faught, W, et al. Darbepoetin alfa administered every 3 weeks alleviates anaemia in patients with solid tumours receiving chemotherapy; results of a double-blind, placebo-controlled, randomised study. *Eur J Cancer*. 2003; 39 (14): 2026-34.

Kuehnert, MJ, Roth, VR, Haley, NR, et al. Transfusion-transmitted bacterial infection in the United States, 1998 through 2000. *Transfusion*. 2001; 41 (12): 1493-9.

Kurtin SE. Advances in the management of low- to intermediate-risk myelodysplastic syndrome: Integrating the national comprehensive cancer network guidelines. *Clin J of Oncol Nursing*. 2006;10:197-208.

LaMontagne KR, Butler J, Marshall DJ, et al. Recombinant epoetins do not stimulate tumor growth in erythropoietin receptor–positive breast carcinoma models. *Mol Cancer Ther.* 2006;5:347-355.

Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining Normal Hemoglobin Levels With Epoetin Alfa in Mainly Nonanemic Patients With Metastatic Breast Cancer Receiving First-Line Chemotherapy: A Survival Study. *J Clin Oncol.* 2005;23:5960-5972.

Leyland-Jones, B. Breast cancer trial with erythropoietin terminated unexpectedly. *Lancet Oncol.* 2003;4:459-460.

Lichtin, A. The ASH/ASCO clinical guidelines on the use of erythropoietin. *Best Pract Res Clin Haematol.* 2005;18:433-438.

Linden, JV, Tourault, MA and Scribner, CL. Decrease in frequency of transfusion fatalities. *Transfusion.* 1997; 37 (2): 243-4.

Littlewood TJ, Bajetta E, Nortier JW, et al. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. *J Clin Oncol.* 2001;19:2865-2874.

Lundberg LG, Hellstrom-Lindberg E, Kanter-Lewensohn LK, et al. Angiogenesis in relation to clinical stage, apoptosis and prognostic score in myelodysplastic syndromes. *Leuk Res.* 2006;30:247-253.

Lyman GH and Glaspy J. Are There Clinical Benefits with Early Erythropoietic Intervention for Chemotherapy-Induced Anemia? A systematic review. *Cancer.* 2006;106:223-233.

Machtay M, Pajak TF, Suntharalingam M, et al. Radiotherapy with or without erythropoietin for anemic patients with head and neck cancer: a randomized trial of the radiation therapy oncology group (Protocol RTOG 99-03). Ortho Biotech Clinical Affairs. Data on file.

Möbus V. The impact of epoetin-alpha on anemia, red blood cell (RBC) transfusions, and survival in breast cancer patients (pts) treated with dose-dense sequential chemotherapy: Mature results of an AGO phase III study (ETC trial). *Proc of Am Soc Clin Oncol.* 2007. Abstract 0569.

Mystakidou K, Kalaidopoulou O, Katsouda E, et al. Evaluation of epoetin supplemented with oral iron in patients with solid malignancies and chronic anemia not receiving anticancer treatment. *Anticancer Res.* 2005;25:3495-3500.

NCCN Clinical Practice Guidelines in Oncology: Cancer- and Treatment-Related Anemia. Available at: [http://www.nccn.org/professionals/physician\\_gls/PDF/anemia.pdf](http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf). Accessed May 29, 2007.

NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes. Available at: [http://www.nccn.org/professionals/physician\\_gls/PDF/mds.pdf](http://www.nccn.org/professionals/physician_gls/PDF/mds.pdf). Accessed May 29, 2007.

Negrin RS, Stein R, Doherty K, et al. Maintenance treatment of the anemia of myelodysplastic syndromes with recombinant human granulocyte colony-stimulating factor and erythropoietin: evidence for in vivo synergy. *Blood*. 1996;87:4076-4081.

Nissen, SE and Wolski, K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. *N Engl J Med*. 2007; in press.

Nitz, U et al (principal investigator) Adjuvant therapy for breast cancer: Impact of erythropoiesis-stimulating factors on survival in high-risk breast cancer treatment. Prospective randomized comparison of CEF/TAC chemotherapy ± darbepoetin alfa (Aranesp®) for patients with positive lymph nodes. ARA PLUS study (DE-2002-0015)

O'Shaughnessy J, Vukelja S, Holmes F, et al. Feasibility of quantifying the effects of epoetin alfa therapy on cognitive function in women with breast cancer undergoing adjuvant or neoadjuvant chemotherapy. *Clin Breast Cancer*. 2005;5:439-446.

Oberhoff, C, Neri, B, Amadori, D, et al. Recombinant human erythropoietin in the treatment of chemotherapy-induced anemia and prevention of transfusion requirement associated with solid tumors: A randomized, controlled study. *Annals of Oncology*. 1998; 9 (3): 255-260.

Oncologic Drugs Advisory Committee May 10 2007. Open public hearing.

Ortho Biotech. ODAC Briefing Book, 2004.

Österborg A, Aapro M, Cornes P, et al. Review. Preclinical studies of erythropoietin receptor expression in tumour cells: Impact on clinical use of erythropoietic proteins to correct cancer-related anaemia. *Eur J Cancer*. 2007;43:510-519.

Österborg A, Brandberg Y, Molostova V, et al. Randomized, double-blind, placebo-controlled trial of recombinant human erythropoietin, epoetin beta, in hematologic malignancies. *J Clin Oncol*. 2002;20:2486-2494.

Österborg, A, Boogaerts, MA, Cimino, R, et al. Recombinant human erythropoietin in transfusion-dependent anemic patients with multiple myeloma and non-Hodgkin's lymphoma--a randomized multicenter study. The European Study Group of Erythropoietin (Epoetin Beta) Treatment in Multiple Myeloma and Non-Hodgkin's Lymphoma. *Blood*. 1996; 87 (7): 2675-82.

Österborg, A, Brandberg, Y and Hedenus, M. Impact of epoetin-beta on survival of patients with lymphoproliferative malignancies: long-term follow-up of a large randomized study. *Br J Haematol*. 2005; 129 (2): 206-9.

Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998;17:2815–2834.

Pazdur, R. Comments from United States Food and Drug Administration Oncology Drugs Advisory Committee on May 10, 2007.

Phurrough, S. Medicare Coverage Decisions: Balancing Competing Demands. Medicare National Coverage Determination.  
<http://www.academyhealth.org/nhpc/2005/phurrough.pdf>

Prozanto P, Cortesi E, van der Rijt K, et al. Early intervention with epoetin alfa in breast cancer (BC) patients (pts) undergoing chemotherapy (CT): results of a randomized, multicenter, phase IIIb study (EPO-INT-47 Study Group). *Annals of Oncology* 2002; Vol. 13 Suppl 5:168.

Razzouk, BI, Hord, JD, Hockenberry, M, et al. Double-blind, placebo-controlled study of quality of life, hematologic end points, and safety of weekly epoetin alfa in children with cancer receiving myelosuppressive chemotherapy. *J Clin Oncol.* 2006; 24 (22): 3583-9.

Ribatti D, Marzullo A, Gentili A, Longo V, Nico B, Vacca A, Dammacco F. Erythropoietin/erythropoietin-receptor system is involved in angiogenesis in human hepatocellular carcinoma. *Histopathology.* 2007b;50:591-6.

Ribatti D, Poliani P, Longo V, Mangieri D, Nico B, Vacca A. Erythropoietin/erythropoietin receptor system is involved in angiogenesis in human neuroblastoma. *Histopathology.* 2007a;50:636-41.

Ribatti D. A potential role of erythropoietin in angiogenesis associated with myelodysplastic syndromes. *Leukemia.* 2002;16:1890-1.

Rodgers GM III, Cella D, Chanan-Khan A, et al. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Cancer- and Treatment-Related Anemia. V.2.2007; 2007. Available at [www.NCCN.org](http://www.NCCN.org). Accessed May 31, 2007.

Rose, E, Rai, K and Revicki, D. Clinical and health status assessments in anemia chronic lymphocytic leukemia (CLL) patients treated with epoetin alfa (EPO). *Blood.* 1994; 84 (10 Suppl 1: 526a).

Rosenzweig MQ, Bengner CM, Lucke JP, et al. The decision to prematurely terminate a trial of R-HuEPO due to thrombotic events. *J Pain Symptom Manage.* 2004;27:185-190.

Ross, SD, Allen IE, Probst C, et al. Efficacy and safety of erythropoiesis-stimulating proteins in myelodysplastic syndrome: A systematic review and meta-analysis. Submitted, 2007.

Ross, SD, Allen, IE, Henry, DH, et al. Clinical benefits and risks associated with epoetin and darbepoetin in patients with chemotherapy-induced anemia: A systematic review of the literature. *Clin Therapeutics.* 2006;28:801-831.

Savonije, JH, van Groenigen, CJ, van Bochove, A, et al. Effects of early intervention with epoetin alfa on transfusion requirement, hemoglobin level and survival during platinum-based chemotherapy: Results of a multicenter randomised controlled trial. *Eur J Cancer*. 2005; 41 (11): 1560-9.

Sazama, K. Reports of 355 transfusion-associated deaths: 1976 through 1985. *Transfusion*. 1990; 30 (7): 583-90.

Seidenfeld J, Piper M, Bohlius J, et al. Comparative effectiveness of epoetin and darbepoetin for managing anemia in patients undergoing cancer treatment. Comparative Effectiveness Review No. 3. (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-02-0026.) Rockville, MD: Agency for Healthcare Research and Quality. May 2006. Available at: [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm). Accessed May 29, 2007.

Sinclair A, Busse L, Rogers N, et al. EPO receptor transcription is not elevated nor predictive of surface expression in human tumor cells. *Proc Amer Assoc Cancer Res*. 2005;46. Abstract 5457.

Sinclair, A, et al., Expression and function of erythropoietin receptors in tumors: Implications for the use of erythropoiesis-stimulating agents in cancer patients. *Cancer* 2007, in press

Smith R, Aapro M, Ludwig H., et al. Darbepoetin alfa for the Treatment of Anemia in Patients With Active Cancer not Receiving Chemotherapy or Radiotherapy: Results of a Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study. Submitted 2007.

Smith RE, Tchekmedyian NS, Chan D, et al. A dose-finding and schedule-finding study of darbepoetin alfa for the treatment of chronic anaemia of cancer. *Br J Cancer*. 2003;88:1851-1858.

Spiriti MA, Latagliata R, Niscola P, et al. Impact of a new dosing regimen of epoetin alfa on quality of life and anemia in patients with low-risk myelodysplastic syndrome. *Ann Hematol* 2005;84:167-176.

Strauss, H, Haensgen, G, Dunst, J, et al. Effects of anaemia correction with epoetin beta in patients with advance cervical cancer and radiochemotherapy. *Proc Am Soc Clin Oncol*. 2005; 23 (16S): Abstract # 5121.

Tandem Cancer Audit, Amgen data on file.

Taylor, K, Ganly, P and Charu, V. Randomized, Double-Blind, Placebo-Controlled Study of Darbepoetin alfa Every 3 Weeks for the Treatment of Chemotherapy-induced Anemia *Blood*. 2005; 106 (11): Abstract # 3556.

Ten Bokkel Huinink, WW, de Swart, CAM, van Toorn, DW, et al. Controlled multicentre study of the influence of subcutaneous recombinant human erythropoietin on anaemia and transfusion dependency in patients with ovarian carcinoma treated with platinum-based chemotherapy. *Med Onc.* 1998; 15(3) 174-182.

Thatcher, N, De Campos, ES, Bell, DR, et al. Epoetin alpha prevents anaemia and reduces transfusion requirements in patients undergoing primarily platinum-based chemotherapy for small cell lung cancer. *Br J Cancer.* 1999; 80 (3-4): 396-402.

Throuvalas, N, Antonadou, D, Boufi, M, et al. Erythropoietin decreases Transfusion Requirements during Radiochemotherapy. *Proc Am Soc Clin Oncol.* 2000; Abstract # 1558.

Title 21 Code of Federal Regulations, Pt. 314. International Conference on Harmonisation (ICH): E9 Statistical Principles for Clinical Trials

United States Food and Drug Administration Oncology Drugs Advisory Committee on May 10, 2007. Amgen, Inc. ODAC core presentation

United States Food and Drug Administration Oncology Drugs Advisory Committee on May 10, 2007. FDA Briefing Material: Continuing Reassessment of the Risks of Erythropoiesis-Stimulating Agents (ESAs) Administered for the Treatment of Anemia associated with Cancer Chemotherapy. Available at: <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4301b2-02-FDA.pdf>. Accessed May 23, 2007.

United States Food and Drug Administration Oncology Drugs Advisory Committee on May 10, 2007. Amgen, Inc. Briefing Material: Safety of Erythropoiesis-Stimulating Agents (ESAs) in Oncology. Available at: <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4301b2-01-01-Amgen.pdf>. Accessed May 23, 2007.

United States Food and Drug Administration Oncology Drugs Advisory Committee on May 14, 2004. Johnson and Johnson Pharmaceutical Research and Development. Briefing Material: Safety of Erythropoiesis-Receptor Agonists (ERAs) in Patients With Cancer. [http://www.fda.gov/ohrms/dockets/ac/04/briefing/4037B2\\_02\\_JohnsonJohnson-Procrit.pdf](http://www.fda.gov/ohrms/dockets/ac/04/briefing/4037B2_02_JohnsonJohnson-Procrit.pdf). Accessed May 23, 2007.

Untch M, Jackish C., Lenhard MS. Epoetin-alpha reduces red blood cell transfusions (RBC) in high-risk breast cancer patients with adjuvant dose-dense, sequential chemotherapy with epirubicin (E), paclitaxel (T) and cyclophosphamide (C) (ETC). *J Clin Oncol.*, 2005 ASCO Annual Meeting Proceedings. Vol 23, No. 16S, 2005: 613

Untch, M et al (principal investigator) Randomized comparison of a preoperative, dose-intensified, intervalshortenedsequential chemotherapy with epirubicin, paclitaxel and CMF ± darbepoetin alfa versus a preoperative, sequential chemotherapy with epirubicin and cyclophosphamide followed by paclitaxel in standard dosage ± darbepoetin alfa in patients with primary breast cancer. PREPARE study (DE-2001-0033)

Untch, M, Jackisch, C, Lenhard, M, et al. Epoetin-alpha reduces red blood cell transfusions (RBC) in high-risk breast cancer patients with adjuvant dose-dense, sequential chemotherapy with epirubicin (E), paclitaxel (T) and cyclophosphamide (C) (ETC). *Proc Am Soc Clin Oncol*. 2005; 23(16S). Abstract 613.

Vadhan-Raj S, Hong JJ, Gregory SA, et al. An open-label, randomized study to develop a screening tool for functional capacity in anemic subjects with nonmyeloid malignancies receiving chemotherapy and darbepoetin alfa. *Proc Am Soc Hematol*. 2003;102. Abstract 1814 and poster.

Vadhan-Raj S, Skibber JM, Crane C, et al. Randomized, Double-Blind, Placebo-Controlled Trial of Epoetin Alfa (Procrit) in Patients with Rectal and Gastric Cancer Undergoing Chemo-Radiotherapy (CT/RT) Followed by Surgery: Early Termination of the Trial Due to Increased Incidence of Thrombo-Embolic Events (TEE). *Blood*. 2004;104. Abstract 2915.

Vansteenkiste J, Pirker R, Massuti B, et al. Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. *J Natl Cancer Inst*. 2002;94:1211-1220.

Wakao H, Chida D, Damen JE, et al. A possible involvement of Stat5 in erythropoietin-induced hemoglobin synthesis. *Biochemical & Biophysical Research Communications* 1997;234:198-205.

Warm M, Schütt G, Ziegler K, et al. Second interim analysis of the ARA Plus study: Breast Cancer (BC) adjuvant chemotherapy (CT) with and without darbepoetin- alpha, analysis of serious adverse events. Presented at the 43rd Annual Meeting of the American Society of Clinical Oncology, Chicago, Ill; June 1-5, 2007; Abstract No: 564

Whitaker, B and Sullivan, M. The 2005 Nationwide Blood Collection and Utilization Survey Report. 2006; Bethesda, MD.

Wilkinson, PM, Antonopoulos, M, Lahousen, M, et al. Epoetin alfa in platinum-treated ovarian cancer patients: results of a multinational, multicentre, randomised trial. *Br J Cancer*. 2006; 94 (7): 947-54.

Williamson, LM, Lowe, S, Love, EM, et al. Serious hazards of transfusion (SHOT) initiative: analysis of the first two annual reports. *Bmj*. 1999; 319 (7201): 16-19.

Witzig, TE, Silberstein, PT, Loprinzi, CL, et al. Phase III, randomized, double-blind study of epoetin alfa compared with placebo in anemic patients receiving chemotherapy. *J Clin Oncol*. 2005; 23 (12): 2606-17.

Wright JR, Ung YC, Julian JA, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. *J Clin Oncol*. 2007;25:1027-1032.

Yasuda Y, Fujita Y, Masuda S, Musha T, Ueda K, Tanaka H, Fujita H, Matsuo T, Nagao M, Sasaki R, Nakamura Y. Erythropoietin is involved in growth and angiogenesis in malignant tumors of female reproductive organs. *Carcinogenesis*. 2002;23:1797-805.

Yasuda Y, Masuda S, Chikuma M, Inoue K, Nagao M, Sasaki R. Estrogen-dependent production of erythropoietin in uterus and its implication in uterine angiogenesis. *J Biol Chem*. 1998;273:25381-7.

Zwezdaryk K, Coffelt S, Figueroa Y, Liu J, Phinney D, LaMarca H, Florez L, Morris C, Hoyle G, Scandurro A. Erythropoietin, a hypoxia-regulated factor, elicits a pro-angiogenic program in human mesenchymal stem cells. *Exp Hematol*. 2007;35:640-52.

## ENDNOTES

1. See "Proposed Decision Memorandum for Erythropoiesis Stimulating Agents for Non-Renal Disease Indications (CAG-00383N)." Available at <http://www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?id=203> (Accessed May 14, 2007).
2. We note that the class of biologicals known as ESAs includes Amgen's products, Aranesp<sup>®</sup> (darbepoetin alfa) and EPOGEN<sup>®</sup> (epoetin alfa). These biologicals have been studied for more than 15 years in a variety of clinical uses. Aranesp<sup>®</sup> and EPOGEN<sup>®</sup> have improved anemia management in approximately 4 million patients worldwide. Amgen was the first to clone the gene encoding erythropoietin and is the sponsor of the epoetin alfa Biologics License Application. In the United States, epoetin alfa is marketed under the trade names EPOGEN<sup>®</sup> and Procrit<sup>®</sup>. Amgen clinically developed, manufactures, markets, and distributes EPOGEN<sup>®</sup> for the treatment of anemia associated with chronic renal failure in patients who are receiving dialysis. While Amgen manufactures both Procrit<sup>®</sup> and EPOGEN<sup>®</sup>, Ortho Biotech Products, L.P., a subsidiary of Johnson & Johnson (J&J), is responsible for the clinical development, marketing, and distribution of Procrit<sup>®</sup> in the United States under license from Amgen.
3. In the PDM, CMS discusses and requests information about the benefits and risks of ESAs across a variety of cancer and cancer-related clinical conditions for which these products are currently used in clinical practice. We note that Amgen only markets and promotes its ESA products with their FDA-approved product labels. However, in response to the agency's specific request for information, we provide a robust summary of the evidence in labeled and non-labeled indications for ESAs.
4. We note that the labeled indications for ESAs include the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. For the sake of clarity and brevity, we have termed any study that evaluated ESAs in combination with chemotherapy as "chemotherapy-induced anemia" or "CIA."
5. As disclosed in Amgen's Form 10-K and noted in CMS' request, Amgen has received an informal inquiry from the SEC regarding the DAHANCA-10 study. Amgen intends to cooperate fully with the SEC inquiry.
6. We note that the labeled indications for ESAs include the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. For the sake of clarity and brevity, we refer to this indication in our submission using the clinically accepted reference "chemotherapy-induced anemia" or "CIA."
7. As disclosed in Amgen's Form 10-K and noted in CMS' request, Amgen has received an informal inquiry from the SEC regarding the DAHANCA-10 study. Amgen intends to cooperate fully with the SEC inquiry.
8. There are two commonly used meta-analysis models: the fixed-effects model and the random-effects model. Fixed-effects models assume that the true effect of treatment is the same in every study. This assumption implies that the observed differences among study results are due solely to chance. Random effect-models assume that the treatment effects are not identical in all studies, but follow some distribution. In general, random-effect models are preferred because they acknowledge heterogeneity from study-to-study. When heterogeneity is suspected, random-effects models are preferable to fixed-effects models as they explicitly incorporate the added

variability. For this reason, results of the random-effects model will be presented. It is important to consider the consistency of results between studies included in a meta-analysis. One statistic for quantifying inconsistency is the inconsistency statistic,  $I^2$ , which describes the percentage of the variability is due to heterogeneity rather than sampling error (chance) (Higgins et al., 2003.)  $I^2$  can range from 0 percent to 100 percent; values > 50 percent indicate a moderate to high level of heterogeneity. Tests for heterogeneity are commonly used to decide on methods for combining studies and for concluding consistency or inconsistency of findings. When  $I^2 = 0$ , then the results of the fixed-effects model equals that for the random-effects model. However, the confidence interval calculated for the random-effects model may be slightly wider than for the fixed-effects model.

9. See 1862(a)(1)(A) of the Social Security Act.
10. See "Factors CMS Considers in Commissioning External Technology Assessments" ([http://www.cms.hhs.gov/mcd/ncpc\\_view\\_document.asp?id=7](http://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=7)). The principles of evidence-based medicine should be used to derive coverage positions, avoiding the broad extrapolation of clinical and safety data beyond the defined patient groups studied.
11. S. Phurrough. "Medicare Coverage Decisions: Balancing Competing Demands." National Health Policy Conference Presentation (Feb. 2, 2005). Available at <http://www.academyhealth.org/nhpc/2005/phurrough.pdf>.)
12. "CMS considers whether reported benefits translate into improved net health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses." See CMS. "Decision Memo for Anticancer Chemotherapy for Colorectal Cancer (CAG-00179N), Appendix B, General Methodological Principles of Study Design (Section VI of the Decision Memorandum)." Available at <http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=90> (Accessed March 14, 2007).
13. Luo W, et al. Adherence to guidelines for use of erythropoiesis stimulating proteins in patients with chemotherapy-induced anemia: Trends from Electronic Medical Records. Abstract submitted to *International Society for Pharmacoeconomics and Outcomes Research. Value in Health*. 2007;in press.
14. Anemia Insights, Time frame: 1/1/04-3/31/06. Data on file at Amgen.
15. See Section 110 (Reporting of Anemia Quality Indicators for Medicare Part B Cancer Anti-Anemia Drugs) of TRHCA.

**Note to June 11 version:**

This version incorporates corrections to minor typographical errors in text and tables; these corrections do not substantively change the content or meaning of this document. A full listing of these corrections is available from Amgen on request [Contact Ashley Koss, 805 313-6151, [akoss@amgen.com](mailto:akoss@amgen.com)].



**Appendix A**

**Review of the Science on the Putative Role of  
EPO-R in Tumor Growth**

**June 1, 2007**

Amgen recognizes the critical importance of the question of the potential role of the erythropoietin (EPO) receptor (EPO-R) in human tumors and is concerned that the agency's review of the scientific evidence has led to a proposed coverage policy that is not science-based and would needlessly restrict access to ESAs for the vast majority of Medicare beneficiaries who could safely benefit from these important medicines.

Careful, critical assessment of the complete literature and evidence base leads to only one conclusion, namely, that EPO-R and EPO play no discernable role in the development or progression of human tumors. While there are indeed published papers that provide data which at first blush appear consistent with the hypothesis of EPO-R involvement in tumor progression, more recent studies make plain that EPO-R is not expressed at significant levels in human cancer cells, and that EPO does not stimulate tumor growth.

We note the following:

- The EPO-R gene is not significantly amplified or overexpressed in solid tumors (Sinclair et al 2005). Hence the EPO-R gene does not behave as an oncogene in this respect. Expression of constitutively active forms of EPO-R does not transform non-hematopoietic cells (Longmore and Lodish, 1991).
- Conditions in humans that have hyperactivating mutations of EPO-R (truncations) or overexpress EPO (Chuvash Polycythemia) result in erythrocytosis and not increased tumor incidence (Arcasoy et al., 2002; Gordeuk et al., 2004; de la Chapelle et al., 1993).
- While the EPO-R gene is transcribed in most tissues and cell lines at low to moderate levels (Sinclair et al 2005), high level transcription of EPO-R is restricted to known EPO responsive erythroid precursor cells (Ulich et al., 1991; Ashihara et al., 1997; Billia et al., 2001)
- In addition, steady-state levels of EPO-R mRNA mirror those seen in normal tissues from which the tumor originates (Winter et al, 2005; Feldman et al 2006; Sinclair et al., 2005). Hence there is no evidence that augmented expression of EPO-R mRNA confers a survival advantage.
- Detection of EPO-R protein on the surfaces of cells is technically challenging because no satisfactory antibody reagents for detecting EPO-R exist. Indeed the most commonly used "anti-EPO-R" polyclonal antibody (*i.e.*, Santa Cruz C-20) was shown to detect heat shock protein HSP70 (Elliott et al 2006, Brown et al 2007; Ragione et al, 2007), in tumor cell lines and samples. Hence there are no well-founded data to suggest that cancer cells express immunologically detectable EPO-R molecules on their cell surface.

**Amgen Response to Proposed Decision Memorandum  
on ESA for Non-Renal Disease Indications (CAG-00383N)**

---

- Gold-standard experiments designed and conducted to detect cell surface EPO-R on tumor cell lines by measuring binding of radiolabeled EPO showed no evidence of EPO binding, and therefore no evidence that EPO-R is present on the surface of these cells, even though EPO-R protein was synthesized (Sinclair et al., 2005; LaMontagne et al., 2006). A few studies have reported surface EpoR expression on tumor lines using EPO binding studies (Westenfelder and Baranowski, 2000; Masuda et al., 1993; Okuno et al., 1990; Um et al., 2007) but receptor number or affinity was very low where measured, raising questions about the significance of the findings. In contrast, the same experimental method easily detects high affinity binding of EPO in normal red blood cell progenitor cells from human bone marrow (Fraser et al., 1988; Sawada et al., 1988; Broudy et al., 1991).
- Many groups have reported that tumor cell lines do not proliferate in response to ESAs (Mundt et al, 1992; Pedrazzoli et al, 1992a; Berdel et al, 1991; Rosti et al, 1993; Westphal et al, 2002; Liu et al, 2004; Dunlop et al, 2006; Rossler et al, 2004; LaMontagne et al, 2006; Gewirtz et al, 2006; Abdalla et al, 2005; poster abstract). Those in vitro studies that claim a response report modest (*i.e.*, 1.15- to 4.0-fold) effects on proliferation that are similar to background experimental noise, and only after exposure to high levels of EPO, far beyond those that can be attained in patients (Takeshita et al, 2000; Acs et al, 2001; Westenfelder and Baranowski, 2000; Feldman et al, 2006; Lai et al, 2005; Ogilvie et al, 2000).
- All rodent in vivo tumor models (23 independent studies with 31 cell lines and 1 primary tumor graft from a broad range of tumor types, including head and neck tumor cell lines) have demonstrated that ESAs alone do not enhance tumor growth or survival (Kelleher et al, 1996; Golab et al, 1998; Thews et al, 1998; Silver and Piver, 1999; Mittleman et al, 2001; Stuben et al, 2001; Thews et al, 2001; Golab et al, 2002; Blackwell et al, 2003; Kirkpatrick et al, 2006; Mittleman et al, 2003; Stuben et al, 2003; Sigounas et al, 2004; Van Halteren et al, 2004; Pinel et al, 2004; Ning et al., 2005; Shannon et al, 2005; Hardee et al, 2005; Hardee et al, 2006; LaMontagne et al, 2006; Kjellen et al, 2006; Bianchi et al, 2007; Tovari et al, 2005). Indeed in some studies ESAs have been shown to increase sensitivity of tumor cells to radiation or chemotherapy (tumor studies performed with chemotherapeutic agents, including cisplatin, cyclophosphamide, mitomycin C, gemcitabine, paclitaxel, and 5-FU) (Thews et al, 1998; Silver and Piver, 1999; Stuben et al, 2001; Thews et al, 2001; Kirkpatrick et al, 2006; Stuben et al, 2003; Sigounas et al, 2004; Pinel et al, 2004; Ning et al, 2005; Shannon et al, 2005; Tovari et al, 2005).

Taken together, these observations demonstrate that there is no compelling scientific evidence that ESAs promote tumor growth or survival. Importantly, Amgen is not alone in its assessment of the evidence regarding the putative role of EPO-R in tumor growth. As outlined in Table 1, the U.S. Food and Drug Administration's (FDA's) Oncologic Drug Advisory Committee (ODAC) Chair as well as the FDA shared concerns in this regard.

**Table 1: Views of Clinical  
Oncology Experts on the EPO-R Hypothesis**

Dr. S. Gail Eckhardt, Chair, FDA's ODAC 2007 (Eckhardt, 2007)

*With respect to CMS basing its proposed policy on the EPO receptor hypothesis, "there is a huge amount of conflicting science on that issue, so I don't think that anybody can say definitively one way or the other, certainly not at ODAC."*

FDA (FDA, 2007)

*".. a direct relationship between the presence of erythropoietin receptors on tumor and tumor proliferation in response to exogenous erythropoietin has not been established. In vitro and in vivo data do not provide convincing evidence that erythropoietin promotes tumor growth and proliferation."*

Stefan Constantinescu, MD, PhD; Ludwig Institute for Cancer Research and Institut de Duve, Brussels, Belgium (Constantinescu, 2007)

*"In your document, data claiming a role for EpoR in tumor progression, angiogenesis and decreased survival are presented as established, accepted and valid, while they are preliminary, poorly controlled, insufficiently demonstrated and quoted due to the notoriety of the subject, and not because of their intrinsic quality. For many of those studies, others with opposing conclusions have been published, yet that data appears to have been overlooked."*

Clive R Taylor, MD D.Phil., Department of Pathology and Laboratory Medicine, Keck School of Medicine, University of Southern California (Taylor, 2007)

*"In summary, CAG #000383N – The Use of Erythropoiesis Stimulating Agents in Cancer and related Neoplastic Conditions, is a complex document, extensively researched, with an extensive bibliography, but it is incomplete in important areas, giving great credibility to preliminary and unproved work, and importantly not citing work that is contradictory to the preconceived position that the use of ESAs should be restricted in cancer sufferers."*

If the clinical and scientific experts at the FDA and on the FDA's ODAC and at leading university laboratories do not find the data on EPO-R to be compelling in proving a link to tumor progression, it stands to reason that CMS should not restrict ESA coverage based on a hypothesis for which there is so little experimental support. After a thorough review of the evidence, we expect that CMS will revise this aspect of its proposed coverage policy in the final national coverage determination (NCD).

## REFERENCES

- Abdalla A, Kokhaei P, Hansson L, et al. Expression of erythropoietin receptor (EPO-R) and in vitro functional effects of Epoetin in B-cell malignancies. *Blood*. 2005;106:Abstract 4278.
- Acs G, Acs P, Beckwith SM, et al. Erythropoietin and erythropoietin receptor expression in human cancer. *Cancer Res*. 2001;61:3561-3565.
- Arcasoy MO, Karayal AF, Segal HM, Sinning JG, Forget BG. A novel mutation in the erythropoietin receptor gene is associated with familial erythrocytosis. *Blood*. 2002;99:3066-3069.
- Ashihara E, Vannucchi AM, Migliaccio G, Migliaccio AR. Growth factor receptor expression during in vitro differentiation of partially purified populations containing murine stem cells. *J. Cell. Physiol*. 1997 171(3):343-56.
- Berdel WE, Danhauser-Riedl S, Oberberg D, Zafferani M. Effects of hematopoietic growth factors on malignant nonhematopoietic cells. *Semin Oncol*. 1992;19:41-45.
- Bianchi R, Gilardini A, Rodriguez-Menendez V, et al. Cisplatin-induced peripheral neuropathy: neuroprotection by erythropoietin without affecting tumour growth. *Eur J Cancer*. 2007;43:710-717.
- Billia F, Barbara M, McEwen J, Trevisan M, Iscove NN. Resolution of pluripotential intermediates in murine hematopoietic differentiation by global complementary DNA amplification from single cells: confirmation of assignments by expression profiling of cytokine receptor transcripts. *Blood*. 97(8):2257-68.
- Blackwell L, Kirkpatrick JP, Synder SA, et al. Human recombinant erythropoietin significantly improves tumor oxygenation independent of its effect on hemoglobin. *Cancer Res*. 2003;63:6162-6165.
- Broudy, VC, Lin, N, Brice, M, et al. Erythropoietin receptor characteristics on primary human erythroid cells. *Blood*. 1991; 77 (12): 2583-90.
- Brown WM, Maxwell P, Graham ANJ, et al. Erythropoietin receptor expression in non-small cell lung carcinoma: a question of antibody specificity. *Stem Cells*. 2007;25:718-722.

**Amgen Response to Proposed Decision Memorandum  
on ESA for Non-Renal Disease Indications (CAG-00383N)**

---

Constantinescu, S. Public Comments for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N). Posted 5/28/07; available at [http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?id=&cov\\_id=&state\\_id=&list\\_type=&goto=viewpubliccomment&nca\\_id=203&rangebegin=05\\_14\\_2007&rangeend=06\\_13\\_2007#0514200706132007C](http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?id=&cov_id=&state_id=&list_type=&goto=viewpubliccomment&nca_id=203&rangebegin=05_14_2007&rangeend=06_13_2007#0514200706132007C)

de la Chapelle A, Traskelin AL, Juvonen E. Truncated erythropoietin receptor causes dominantly inherited benign human erythrocytosis. *Proc Natl Acad Sci USA*. 1993;90:4495-4499.

Dunlop EA, Percy MJ, Boland MP, Maxwell AP, Lappin TR. Induction of signaling in non-erythroid cells by pharmacological levels of erythropoietin. *Neurodegenerative Dis*. 2006;3:94-100.

Eckhardt, SG. Comment to ODAC members, ODAC Meeting, May 10, 2007.

Elliott S, Busse L, Bass MB, et al. Anti-epo receptor antibodies do not predict Epo receptor expression. *Blood*. 2006;107:1892-1895.

FDA BRIEFING DOCUMENT, May 10, 2007 Oncologic Drugs Advisory Committee. Continuing Reassessment of the Risks of Erythropoiesis-Stimulating Agents (ESAs) Administered for the Treatment of Anemia associated with Cancer Chemotherapy; p.9. Available at <http://www.fda.gov/OHRMS/DOCKETS/AC/07/briefing/2007-4301b2-02-FDA.pdf>

Feldman L, Wang Y, Rhim JS, et al. Erythropoietin stimulates growth and STAT5 phosphorylation in human prostate epithelial and prostate cancer cells. *Prostate*. 2006;66:135-145.

Fraser J, Lin F, Berridge M. Expression of high affinity receptors for erythropoietin on human bone marrow cells and on the human erythroleukemic cell line, HEL. *Exp Hematol*. 1988;16:836-42.

Gewirtz DA, Di X, Walker TD, Sawyer ST. Erythropoietin fails to interfere with the antiproliferative and cytotoxic effects of antitumor drugs. *Clin Cancer Res*. 2006;12:2232-2238.

Golab J, Olszewska D, Mroz P, et al. Erythropoietin restores the antitumor effectiveness of photodynamic therapy in mice with chemotherapy-induced anemia. *Clin Cancer Res*. 2002;8:1265-1270.

Golab J, Zagozdzon R, Lasek W, Jakobisiak M. Erythropoietin prevents the development of interleukin-12-induced anemia and thrombocytopenia but does not decrease its antitumor activity in mice. *Blood*. 1998;91:4387-4388.

**Amgen Response to Proposed Decision Memorandum  
on ESA for Non-Renal Disease Indications (CAG-00383N)**

---

Gordeuk VR, Sergueeva AI, Miasnikova GY, et al. Congenital disorder of oxygen sensing: association of the homozygous Chuvash polycythemia *VHL* mutation with thrombosis and vascular abnormalities but not tumors. *Blood*. 2004;103:3924-3932.

Hardee ME, Kirkpatrick JP, Shan S, et al. Human recombinant erythropoietin (rEpo) has no effect on tumour growth or angiogenesis. *Br J Cancer*. 2005;93(12): 1350-1355.

Hardee ME, Rabbani ZN, Arcasoy MO, et al. Erythropoietin inhibits apoptosis in breast cancer cells via an Akt-dependent pathway without modulating in vivo chemosensitivity. *Mol Cancer Ther*. 2006;5:356-361.

Kelleher DK, Matthiensen U, Thews O, Vaupel P. Blood flow, oxygenation, and bioenergetic status of tumors after erythropoietin treatment in normal and anemic rats. *Cancer Res*. 1996;56:4728-4734.

Kirkpatrick JP, Hardee ME, Snyder SA, et al. The effect of darbepoetin alfa on growth, oxygenation, and radioresponsiveness of a breast adenocarcinoma. *Radiation Res*. 2006;165:192-201.

Kjellen E, Sasaki Y, Kjellstrom J, Zackrisson B, Wennerberg J. Recombinant erythropoietin  $\beta$  enhances growth of xenografted human squamous cell carcinoma of the head and neck after surgical trauma. *Acta Otolaryngol*. 2006;126:545-547.

Lai, SY, Childs, EE, Xi, S, et al. Erythropoietin-mediated activation of JAK-STAT signaling contributes to cellular invasion in head and neck squamous cell carcinoma. *Oncogene*. 2005; 24 (27): 4442-9.

LaMontagne KR, Butler J, Marshall DJ, et al. Recombinant epoetins do not stimulate tumor growth in erythropoietin receptor-positive breast carcinoma models. *Mol Cancer Ther*. 2006;5:347-355.

Liu WM, Powles T, Shamash J, et al. Effect of haemopoietic growth factors on cancer cell lines and their role in chemosensitivity. *Oncogene*. 2004;23:981-990.

Longmore GD, Lodish HF. An activating mutation in the murine erythropoietin receptor induces erythroleukemia in mice: a cytokine receptor superfamily oncogene. *Cell*. 1991;67:1089-1102.

Masuda, S, Nagao, M, Takahata, K, et al. Functional erythropoietin receptor of the cells with neural characteristics. Comparison with receptor properties of erythroid cells. *J Biol Chem*. 1993; 268 (15): 11208-16.

**Amgen Response to Proposed Decision Memorandum  
on ESA for Non-Renal Disease Indications (CAG-00383N)**

---

Mittelman M, Peled A, Haran-Ghera N. The anti myeloma effect of erythropoietin – studies in mice models, gender differences and insights into the immune mechanism. *Blood*. 2003;102:388b (Abstract).

Mittleman et al, 2001; Mittelman M, Neumann D, Peled A, Kanter P, Haran-Ghera N. Erythropoietin induces tumor regression and antitumor immune responses in murine myeloma models. *PNAS*. 2001;98:5181-5186.

Mundt D, Berger MR, Bode G. Effect of recombinant human erythropoietin on the growth of human tumor cell lines in vitro. *Drug Res*. 1992;42:92-95.

Ning S, Hartley C, Molineux G, Knox SJ. Darbepoietin alfa potentiates the efficacy of radiation therapy in mice with corrected or uncorrected anemia. *Cancer Res*. 2005;65:284-290.

Ogilvie M, Yu X, Nicolas-Metral V, et al. Erythropoietin stimulates proliferation and interferes with differentiation of myoblasts. *J Biol Chem*. 2000;275(50):39754-61.

Okuno, Y, Takahashi, T, Suzuki, A, et al. Expression of the erythropoietin receptor on a human myeloma cell line. *Biochem Biophys Res Commun*. 1990; 170 (3): 1128-34.

Pedrazzoli P, Rosti V, Ponchio L, et al. Effect of recombinant human erythropoietin on solid tumor and leukemia-derived cell lines. *Proc ASCO*. 1992;11:124 (Abstract).

Pinel S, Barberi-Heyob M, et al. Erythropoietin-induced reduction of hypoxia before and during fractionated irradiation contributes to improvement of radioresponse in human glioma xenografts. *Int J Radiat Oncol Biol Phys*. 2004;59(1): 250-259.

Ragione FD, Cucciolla V, Borriello A, et al. Erythropoietin receptors on cancer cells: A still open question. *J Clin. Oncol*. 2007;25:1812-1818.

Rosler J, Stolze I, Frede S, et al. Hypoxia-induced erythropoietin expression in human neuroblastoma requires a methylation free HIF-1 binding site. *J Cell Biochem*. 2004;93:153-161.

Rosti V, Pedrazzoli P, Ponchio L, et al. Effect of recombinant human erythropoietin on hematopoietic and non-hematopoietic malignant cell growth in vitro. *Haematologica*. 1993;78:208-212.

Sawada, K, Krantz, SB, Sawyer, ST, et al. Quantitation of specific binding of erythropoietin to human erythroid colony-forming cells. *J Cell Physiol*. 1988; 137 (2): 337-45.

**Amgen Response to Proposed Decision Memorandum  
on ESA for Non-Renal Disease Indications (CAG-00383N)**

---

Shannon AM, Bouchier-Hayes DJ, Condrón CM, Toomey D. Correction of anaemia through the use of darbepoetin alfa improves chemotherapeutic outcome in a murine model of Lewis lung carcinoma. *Br J Cancer*. 2005;93:224-232.

Sigounas G, Sallah S, Sigounas VY. Erythropoietin modulates the anticancer activity of chemotherapeutic drugs in a murine lung cancer model. *Cancer Lett*. 2004;214:171-179.

Silver DF, Piver MS. Effects of recombinant human erythropoietin on the antitumor effect of cisplatin in SCID mice bearing human ovarian cancer: a possible oxygen effect. *Gynecol Oncol*. 1999;73:280-284.

Sinclair A, Busse L, Rogers N, et al. EPO receptor transcription is not elevated nor predictive of surface expression in human tumor cells. *Proc Amer Assoc Cancer Res*. 2005;46:(Abstract 5457)

Stuben G, Pottgen C, Knuhmann K, et al. Erythropoietin restores the anemia-induced reduction in radiosensitivity of experimental human tumors in nude mice. *Int J Radiat Oncol Biol Phys*. 2003;55:1358-1362.

Stuben G, Thews O, Pottgen C, et al. Recombinant human erythropoietin increases the radiosensitivity of xenografted human tumours in anaemic nude mice. *J Cancer Res Clin Oncol*. 2001;127:346-350.

Takeshita A, Shinjo K, Higuchi M, et al. Quantitative expression of erythropoietin receptor (EPO-R) on acute leukaemia cells: relationships between the amount of EPO-R and CD phenotypes, in vitro proliferative response, the amount of other cytokine receptors and clinical prognosis. *Br J Haematol*. 2000;108:55-63.

Taylor, CR. Public Comments for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N). Posted 5/29/07; available at [http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?id=&cov\\_id=&state\\_id=&list\\_type=&goto=viewpubliccomment&nca\\_id=203&rangebegin=05\\_14\\_2007&rangeend=06\\_13\\_2007#0514200706132007T](http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?id=&cov_id=&state_id=&list_type=&goto=viewpubliccomment&nca_id=203&rangebegin=05_14_2007&rangeend=06_13_2007#0514200706132007T)

Thews O, Kelleher DK, Vaupel P. Erythropoietin restores the anemia-induced reduction in cyclophosphamide cytotoxicity in rat tumors. *Cancer Res*. 2001;61:1358-1361.

Thews, O, Koenig, R, Kelleher, DK, et al. Enhanced radiosensitivity in experimental tumours following erythropoietin treatment of chemotherapy-induced anaemia. *Br J Cancer*. 1998; 78 (6): 752-6.

**Amgen Response to Proposed Decision Memorandum  
on ESA for Non-Renal Disease Indications (CAG-00383N)**

---

Tovari, J., R. Gilly, et al. Recombinant human erythropoietin targets intratumoral blood vessels, improving chemotherapy in human xenograft models. *Cancer Res.* 2005;5(16): 7186-7193.

Ulich TR, del Castillo J, Yin SM, Egrie JC. The erythropoietic effects of interleukin 6 and erythropoietin in vivo. *Exp. Hematol.* 1991; 19(1):29-34.

Um, M, Gross, AW and Lodish, HF. A "classical" homodimeric erythropoietin receptor is essential for the antiapoptotic effects of erythropoietin on differentiated neuroblastoma SH-SY5Y and pheochromocytoma PC-12 cells. *Cell Signal.* 2007; 19 (3): 634-45.

van Halteren HK, Bongaerts GP, Verhagen CA, et al. Recombinant human erythropoietin attenuates weight loss in a murine cancer cachexia model. *J Cancer Res Clin Oncol.* 2004;130:211-216.

Westenfelder C, Baranowski RL. Erythropoietin stimulates proliferation of human renal carcinoma cells. *Kidney Intl.* 2000;58:647-657.

Westphal G, Niederberger E, Blum C, et al. Erythropoietin and G-CSF receptors in human tumor cells: expression and aspects regarding functionality. *Tumori.* 2002;88:150-159.

Winter, SC, Shah, KA, Campo, L, et al. Relation of erythropoietin and erythropoietin receptor expression to hypoxia and anemia in head and neck squamous cell carcinoma. *Clin Cancer Res.* 2005; 11 (21): 7614-20.

**Amgen Comment on CMS Proposed Decision Memorandum for ESAs  
For Non-Renal Disease Indications (CAG-00383N)**

**Errata List**

The below errata list largely represents either transcription or typographical errors and a few circumstances where incorrect values were mistakenly cited. It is important to note that none of these errata have a meaningful impact on the text discussion or conclusions reflected in Amgen's Comment Letter.

Ref	Page No.	Location	Transcription/ Typographical Error	Correction
1	4	3rd bullet under Key Points on Initiation Level	odds ratio, 0.86, 95 percent CI 0.69 - 10.8	odds ratio, 0.86, 95 percent CI 0.69 - 1.08
2	15	Table 4	lower limit for 145 study (0.88-1.21)	(0.86 - 1.21)
3	17	Table 5	I <sup>2</sup> listed as 8.6 for Heme tumor type	change to 8.7
4	18	Table 6	upper limit for BEST (1.07 - 0.74)	(1.07 - 1.74)
5	18	Table 6	upper limit for 161 PFS (1.27)	1.29
6	18	Table 6	CL for Wright missing	(1.01, 3.35)
7	18	Table 6	HR listed as endpoint in Henke	change to RR
8	19	Line 2	9 percent CI	95 percent CI
9	21	Line 6 after Chart 6	HR = 1.10, 95% CI (0.97-1.25)	HR = 1.04, 95% (0.87-1.24), I <sup>2</sup> =56.5
10	22	4th column heading - Table 8	HR/RR should be HR/OR	HR or OR
11	22	3rd row - 3rd column data; Table 7	heterogeneity, p=0.79, I <sup>2</sup> = 0%	heterogeneity, p=0.02, I <sup>2</sup> = 50%
12	22, 25	Table 8 & 9, Error	Table 8 for EPO-CAN-17 Study reports HR of 0.94 (0.55, 1.66)	correct CI from 1.66 to 1.60
13	28	Line 2	9.652 patients	9652 patients
14	3 (Executive Summary), 4, 33	Error with CI stated	meta-analysis reports OR 0.86 (0.69, 10.8)	CI should read: 1.08

Ref	Page No.	Location	Transcription/ Typographical Error	Correction
15	34	Chart 11	title reference incorrect	add reference "Adapted from ..." in chart title
16	4 (Executive Summary), 5, 35	Need ">" qualifier	risk of VTE does not vary when Hb thresholds range from 13.0 to 16.0 g/dL	range should read: > 13.0 to 16.0 g/dL
17	36	First paragraph	95.3% of all patients receiving ESA had Hb < 12 g/dL	change to 96.5%
18	36	First paragraph	a recent chart audit showed 86% of patients with CIA receiving ESAs had a Hb < 12.0 g/dL at ESA administration. The indicated reference actually shows 94%.	correct 86% to 94%
19	42	line 7 under Patients with Thrombotic Episodes...	1.59 (95% CI: 1.13, 2.23)	1.57 (95% CI: 1.10, 2.26)
20	43	2 <sup>nd</sup> paragraph in <u>Treatment of MDS</u> , line 7	there is no endnote numbered 21 listed in the endnotes (endnotes end at #15)	delete endnote indicator
21	49	Last line on page	66 percent	change to "estimated to be 52% (excluding the effect of transfusions)"
22	67	Endnote 10	quotation marks mistakenly used	delete "CMS states" and quotation marks.

On behalf of the International Myeloma Foundation (IMF), an organization dedicated to improving the quality of life of myeloma patients while working toward prevention and a cure, I am writing to express our serious concern about the content and timing of the proposed decision memo recently issued by the Centers for Medicare and Medicaid Services (CMS) that addresses the use of erythropoiesis stimulating agents (ESAs) in the management of patients with myeloma, other forms of cancer, and related neoplastic conditions. We respectfully suggest that the proposals in this decision memo are premature and recommend they be withdrawn until appropriate determinations about the safety and efficacy of ESAs in the management of cancer patients in general, and patients with myeloma patients in particular, are made by the US Food and Drug Administration (FDA).

The FDA has primary responsibility for determining the limits that are set forth in CMS's proposed decision memo. Furthermore, the ESA controversy is currently under active review by FDA. As CMS officials are certainly aware, the FDA's Oncologic Drugs Advisory Committee (ODAC) intensively reviewed the available data in a meeting on May 10. The FDA's Cardiovascular and Renal Drugs Advisory Committee (CRDAC) has also been asked to offer recommendations on the entire class of ESAs later in the year. Even prior to the ODAC meeting, FDA had taken action to require "black box" warnings for the products. FDA is currently considering the recommendations from ODAC, but the agency is not compelled to follow them, and certainly will make no decisions prior to receipt of comments from the CRDAC. Until FDA has made a decision to change the existing labeling of ESAs, Medicare should follow the labeling as it is currently configured, certainly taking into account the warnings required by FDA.

This result is necessary, not just as a matter of medical evidence and bureaucratic prudence but also because it is compelled by the laws that govern Medicare coverage policies. In 1993 Congress enacted legislation that was intended to resolve questions about the discretion of Medicare officials and contractors to limit coverage of medically appropriate cancer therapies. Accordingly, in §1861(t)(2) of the Social Security Act (42 U.S.C. §1395x(t)(2)), the term "drugs" is specifically defined to include "any drugs or biologicals used in an anticancer chemotherapeutic regimen for a medically accepted indication," which is further defined to include "any use which has been approved by the Food and Drug Administration"

as well as any compendia-supported use that has not been found by the Secretary to be medically inappropriate.

In light of these legal requirements, we believe that Medicare does not have discretion to restrict coverage to be inconsistent with the FDA-approved labeling. In addition, if off-label coverage of ESAs in patients with myeloma is to be restricted in a manner that conflicts with compendia references, there must be a specific determination by the Secretary that the restricted uses are medically inappropriate.

We take no position as to whether Medicare officials have identified appropriate limits on the use of these products in treatment of myeloma because we believe that determination should not be made prior to a determination on that issue by the Food and Drug Administration (FDA). It is our considered opinion that the proposed decision memo should be withdrawn to await the decision by FDA as to the medically appropriate uses of ESAs in myeloma and other forms of cancer, and any future coverage determination by Medicare should be made in strict conformity with the terms of §1861(t)(2) of the Act.

We would appreciate your early action on this issue.

Sincerely

Susie Novis  
President



Winning the fight against cancer, every day.<sup>®</sup>

**Regulation Title: Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N)**

**Author: Anthony Perre, MD, Cancer Treatment Centers of America; Eastern Regional Medical Center, 1331 Wyoming Ave.; Philadelphia, PA 19124.**

**Comments Summary: Proposed window of therapeutic use is too narrow; proposed maximum doses of erythropoietin is too low; CMS ESA usage proposal differs from manufacturer recommendations.**

**References:**

*Cancer and Treatment Related Anemia, v.3.2007*; NCCN Clinical Practice Guidelines in Oncology. Version 3.2007, 4/10/07. National Comprehensive Cancer Network.

*Aranesp—Prescribing Information, Dosage and Administration*; Issue Date: 5/2007. Amgen Inc.

[http://www.aranesp.com/professional/cia/prescribing\\_information/prescribing information.jsp#dosage.](http://www.aranesp.com/professional/cia/prescribing_information/prescribing_information.jsp#dosage)

Comment 1:

CMS states:

"...the maximum covered 4 week treatment dose is 126,000 units for erythropoietin and 630 µg for darbepoietin..."

See **Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N)** p. 4.

Our response:

The proposed max dose of erythropoietin is too low. The dose used weekly is 40,000 units, which would surpass the monthly proposed maximum of 126,000 units per month.

*Cancer and Treatment Related Anemia, v.3.2007*; NCCN Clinical Practice Guidelines in Oncology. Version 3.2007, 4/10/07. National Comprehensive Cancer Network,

*Aranesp—Prescribing Information, Dosage and Administration*; Issue Date: 5/2007. Amgen Inc.

[http://www.aranesp.com/professional/cia/prescribing\\_information/prescribing information.jsp#dosage](http://www.aranesp.com/professional/cia/prescribing_information/prescribing_information.jsp#dosage)

Comment 2:  
CMS states:

"...continued use of the drug is not reasonable and necessary if there is evidence of poor drug response (hemoglobin/hematocrit rise <1 g/dl/<3%) after 4 weeks of treatment..."

See **Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N)** p. 4.

Our response:

The proposed window of therapeutic use is too narrow. They propose discontinuation of the ESA if there is no therapeutic response within 4 weeks although it generally takes 2-6 weeks for response. In addition, normally the dose would be increased if there is lack of therapeutic response; the ESA would not be discontinued as EMS suggests.

***Cancer and Treatment Related Anemia, v.3.2007; NCCN Clinical Practice Guidelines in Oncology. Version 3.2007, 4/10/07. National Comprehensive Cancer Network.***

***Aranesp—Prescribing Information, Dosage and Administration; Issue Date: 5/2007. Amgen Inc.***

**[http://www.aranesp.com/professional/cia/prescribing\\_information/prescribing\\_infor  
mation.jsp#dosage](http://www.aranesp.com/professional/cia/prescribing_information/prescribing_information.jsp#dosage)**

Comment 3:

CMS states:

"For patients undergoing treatment for these cancers, we propose ESAs are reasonable and necessary with the following limitations:

the hemoglobin/hematocrit levels immediately prior to initiation of dosing for the month should be <9 g/dl/27% in patients without known cardiovascular disease and <10 g/dl/30% in patients with documented symptomatic ischemic disease that cannot be treated with blood transfusion (The latter patients should be alerted to the increased potential for thrombosis and sequelae.) (We suggest that patients, especially those in the latter category, be alerted to the increased potential for thrombosis and sequelae.) "

See **Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N)** p. 3.

Our response:

The manufacturer proposes that ESA's may be used if the hemoglobin <10 and the patient is symptomatic. EMS proposes cut-off of 9 for non-cardiac patients and 10 for cardiac patients with symptoms which is narrower than what the manufacturer recommends and is approved for.

***Cancer and Treatment Related Anemia, v.3.2007; NCCN Clinical Practice Guidelines in Oncology. Version 3.2007, 4/10/07. National Comprehensive Cancer Network,***

*Aranesp—Prescribing Information, Dosage and Administration; Issue Date: 5/2007.*  
Amgen Inc.

**[http://www.aranesp.com/professional/cia/prescribing\\_information/prescribing information.jsp#dosage](http://www.aranesp.com/professional/cia/prescribing_information/prescribing_information.jsp#dosage)**

West Clinic  
100 North Humphreys  
Memphis, TN 38120  
June 6, 2007

Steve Phurrough, MD, MPA  
Elizabeth Koller, MD, FACE  
Maria Ciccanti, RN  
Coverage Analysis Group  
Office of Clinical Standards and Quality  
Centers for Medicare and Medicaid Services  
Mail Stop C1-12-28  
7500 Baltimore, Maryland 21244-1849

Dear Sir and Madam:

Thank you for the opportunity to respond to the Center for Medicare & Medicaid Services proposed NCD regarding erythropoiesis stimulating agents (ESA's). I am a Hematologist-Oncologist who has been in practice for over 20 years and am the current Vice-President of TOPS, the Tennessee Oncology Practice Society, which represents oncologists all across Tennessee. I have grave concerns about the CMS proposal and what it will do to non-Medicare hematology and cancer patients not only here in America but potentially worldwide if private insurance and other countries endorse similar proposals. The proposal as it stands will set back the standard of care by at least 10 years leading to millions of patients being denied access to treatments that have significantly improved their quality of life all in the aim of controlling costs.

Let me be clear about this: Since the MMA, we do not make money off Medicare patients who receive ESA's. In fact, on the contrary, we strive to break even. Therefore, I have no ax to grind here except for the care and well-being of my patients.

I began my medical career well before ESA's were used. I clearly remember dialysis patients who survived (and I do mean survive in the worst sense of the word) with hematocrits in the mid-to-low 20's, rarely getting transfusions because of the risks, not only of transfusions reactions & fluid overload, but of infections, auto-immunization, and iron overload. The single most effective improvement in their quality of life in the late 20<sup>th</sup> century was the availability of ESA's which increased their hematocrits into the mid-30's and dramatically altered the severe fatigue they had lived with for years with no hope of improvement. Although the use of ESA's in renal failure patients is not curtailed by the proposed NCD (except to correctly cap use for hematocrits above 36), cancer patients also have severe fatigue which has been decreased significantly by the use of ESA's. It is cruel and unusual punishment to suggest that these patients go back to the dark ages again with periodic transfusions. Patient's fatigue *may* get somewhat better after each transfusion, but nowhere near the improvement we see daily with ESA's. There is no way to compare the improvement in quality of life with a sustained

100

hematocrit in the mid-30's to the life one leads with the use of intermittent transfusions whenever the hematocrit hits 25 or lower. CMS has said that ESA's do not increase survival, but what is important is what kind of survival you are talking about. The point is that patients with adequate hematocrits can be truly *living* whereas those with hematocrits of 25 are waiting to *die*. The difference is that stark.

I am also very concerned because many of the proposals to restrict ESA use show a clear disregard for a huge body of clinical experience about their safe and effective use whereas other decisions made have no basis in clinical experience at all (the proposal for 12 weeks total use per year is but one example) other than arbitrarily derived to contain costs. ESA's have been used safely in millions of patients around the world for many years—these are not new drugs! Although there are many questions that are unanswered by currently available trials, that does not mean we should throw out the use of ESA's in every situation where there is not solid evidence supporting its use (many of which have 15+ years of solid clinical experience backing their unequivocal but unfortunately underdocumented efficacy in improving QOL) just to save money. The repercussions of this proposal go far beyond the hematology/cancer/dialysis population as the strain on the already stressed blood banks will mean that blood will not be available for many, many other patients who need blood products. We frequently have to withhold transfusions at our hospital until hematocrits reach 22 due to blood shortages already. The cost of treatment for iron overload in patients who will require frequent transfusions is high, with unknown risks when used on such a massive scale, and will need to be factored in when estimating Medicare's "savings".

It is hard to understand how these proposals could come from experienced, caring physicians. It makes one feel as if the accountants who once ran managed care have been loosed in the Medicare program with potentially disastrous results. The decisions regarding the use of ESA's should at least have some guidance from a broad field of both university and community oncologists, with level-headed & dispassionate decisions that are *medically reasonable*. The fact that ASCO, ASH, US Oncology, and the Community Oncology Alliance all oppose the current CMS proposal should cause CMS to seriously consider how flawed its proposal really is.

I have reviewed comments from all of the above organizations and agree strongly with their points. Comments taken from US Oncology, printed below, are most succinct and I endorse all of them.

#### Key Points of Policy Disagreement with the Proposed NCD

1. Use of Hgb  $<9$ g/dl as a treatment initiation point is inadequate. Current data shows many of the patients who receive ESA's after Hgb drops to the  $<9$ g/dl level will require transfusions that are otherwise avoidable because their Hgb will continue to fall for several weeks after ESA use is initiated.
2. Evidence suggests that transfusion avoidance is better accomplished by early intervention at a higher Hgb level ( $<11$ g has been shown to be superior to  $<10$  by every measure in 6 different randomized studies).

3. A "stopping rule" at 4 weeks if a 1g/dl rise in Hgb is not achieved is not consistent with the clinical trial data. The clinical trials with both ESA agents demonstrate that 6-8 weeks may be required to achieve a 1 g/dl rise. Dose escalation has been a critical element of most of the clinical trials. A significant number of patients who failed to respond to initial ESA use will respond after administering a single dose 50% higher than the initial dose. Therefore, dose escalation has become part of the standard of care.
4. Maximum treatment duration of 12 weeks per year is grossly inadequate for many patients. Patients with metastatic disease may receive multiple courses of chemotherapy that last for many months.
5. Exclusion of patients receiving VEGF and EGRF inhibitors is not based on any clinical evidence and would preclude treatment with ESA's for dyspneic lung cancer patients on chemotherapy, adjuvant breast cancer patients receiving dose dense therapy, and other critical patient subgroups. For example, no patient on Avastin would be eligible for ESA's, regardless of the other chemotherapy being administered concurrently.
6. Non-coverage of MDS and multiple myeloma patients is not based on clinical data. Multiple randomized trials have shown evidence of efficacy of ESA's in both diseases without any adverse safety signals. Non-coverage would expose elderly patients to the avoidable complications of chronic transfusions and toxic chemotherapy.
7. In spite of in vitro evidence suggesting that certain cancer cell types express erythropoietin receptors, there is no clinical evidence that -- if those receptors actually exist -- they are functional. ESA use in patients receiving chemotherapy for such tumors has no clinical experience of tumor progression, or reduced efficacy of treatment. Restricting ESA use in patients with such cancers is theoretic and not evidence-based policy and therefore should be reconsidered.
8. One significant, unintended and unanalyzed effect of the draft ESA policy would be to place the national blood supply at significant risk due to the millions of avoidable transfusions that would be required under the proposed NCD.

The improvement in quality of life for hematology and oncology patients with ESA's rivals all the other medical accomplishments we have made over my entire career. Quality of life does matter!! Please, please, please do NOT let my patients suffer because of the misguided proposal CMS has produced. Do not turn your back on 15 years of clinical experience just to save money. The dollar saved will likely end up costing the government and society far more in the future anyway.

If you need any further information or if I can be of further assistance, please contact me at 901-683-0055.

Thank you for your consideration.

Benton M. Wheeler, M.D.

BERNARD BERNHARDT, M. D.  
ADVANCED ONCOLOGY ASSOCIATES  
50 GUION PLACE  
NEW ROCHELLE, NEW YORK 10801  
TELEPHONE 914 632-5397  
FAX 914 632-5450

June 11, 2007

Steve E. Phurrough, MD, MPA  
Director, Coverage and Analysis Group  
Centers for Medicare & Medicaid Services  
Mail Stop C1-09-06  
7500 Security Boulevard  
Baltimore, MD 21244

Re: Proposed Decision Memorandum CAG-00383N for the Use of Erythropoiesis Stimulating Agents (ESAs) for Non-Renal Disease Indications  
Dear Dr. Phurrough:

I am speaking for noone but myself and my patients. Your proposed regulation is irrational and damaging to my patients.

First, the news about strokes in patients receiving Epo with normal hemoglobins is very old news, and there are few if any hematologists/oncologists who are not aware of the data. I have capped the hemoglobin level at or below 12 for some time, as have my colleagues.

The data regarding failure of Epo to improve the hemoglobin level or reduce transfusion requirements was demonstrated in only one study. I have patients that I have treated with good responses even though they are getting chemo. It is also the case, I believe, that the hemoglobin levels would be even lower without Epo.

A 12 week cap makes no sense at all. If the drug is useful, then it should be given whenever medically indicated, not fixed at some arbitrary number.

The risk of Epo administration must be considered against the risk of

1. Not giving any blood product and allowing the hemoglobin to fall as low as it will
2. The risk of blood transfusion, which although small, is greater than the risk of Epo.

Please do not consider the nation's hematologists and oncologists stupid or unaware of the medical literature. I would strongly urge you to reconsider or modify your proposed regulation.

Sincerely,

Bernard Bernhardt, MD  
[Docb007@yahoo.com](mailto:Docb007@yahoo.com)



## Physicians

### Hematology & Oncology

Thomas A. Alberico, MD  
Bacon F. Alexander, III, MD  
Daniel M. Atienza, MD  
Bruce W. Booth, MD  
Robert L. Burger, MD, FACP  
Paul R. Conkling, MD  
Scott J. Cross, MD  
Mark T. Fleming, MD  
Edward A. George, MD, FACP  
Elizabeth A. Harden, MD, FACP  
John R. Howard, Jr., DO  
John F. Kessler, MD, FACP  
Scott Kruger, MD, FACP  
Michael E. Lee, MD  
John Q. A. Mattern, II, DO  
Dean S. McCaughey, III, MD  
John C. Paschold, MD, FACP  
David M. Powell, MD  
Christina W. Prillaman, MD, FACP  
John J. Regan, MD  
Ronald J. Ruskowski, MD  
S. George Saman, MD  
Joseph J. Schulz, MD  
Michael S. Steinberg, MD, FACP  
Alexander K. Su, MD  
Valiant D. Tan, MD

### Gynecological Oncology

Johnny Hyde, MD  
Munir F. Nasr, MD, FACOG  
Stacey J. Rogers, MD, FACOG  
Robert C. Squatrito, MD, FACOG

### Radiation Oncology

Michael L. Miller, DO

## Office Locations

### Southside

5900 Lake Wright Drive  
Norfolk, VA 23502  
(757) 466.8683  
FAX (757) 466.8892

1950 Glenn Mitchell, Ste. 102  
Virginia Beach, VA 23456  
(757) 368.0437  
FAX (757) 368.0492

5818 Harbour View Blvd, Suite 230  
Suffolk, VA 23435  
(757) 686.1042  
FAX (757) 686.1055

102 Fairview Dr, Suite E  
Franklin, VA 23851  
(757) 569.9709  
FAX (757) 569.6102

300 Medical Parkway, Suite 314  
Chesapeake, VA 23320  
(757) 549.4403  
FAX (757) 549.4332

150 Burnett's Way, Suite 310  
Suffolk, VA 23434  
(757) 539.0670  
FAX (757) 539.1062

### Peninsula

895 Middle Ground Blvd, Bldg 200  
Newport News, VA 23606  
(757) 873.9400  
FAX (757) 873.9420

3000 Coliseum Dr, Suite 104  
Hampton, VA 23666  
(757) 827.9400  
FAX (757) 827.9320

3901 Treyburn Dr, Suite 2A  
Williamsburg, VA 23185  
(757) 229.2236  
FAX (757) 221.0409

6876 Main Street  
Gloucester, VA 23061  
(804) 693.3232  
FAX (804) 693.3342

### North Carolina

1503 B North Road St.  
Elizabeth City, NC 27909  
(252) 331.2044  
FAX (252) 331.1909

5565 Croatan Highway  
Kitty Hawk, NC 27949  
(252) 261.5800  
FAX (252) 261.5301

### Central Business Office

5900 Lake Wright Dr, Suite 300  
Norfolk, VA 23502  
(757) 213.5700  
FAX (757) 213.5701  
TOLL FREE (800) 998.3450

## Web Address

www.virginiacancer.com

June 12, 2007

Stephen Phurrough, M.D. MPA  
Elizabeth Koller, M.D., F.A.C.E.  
Marsha Ciccanti, RN  
Coverage Analysis Group/Office of Clinical Standards  
Quality Center for Medicare and Medicaid Services  
Mail Stop C1-12-28 7500  
Baltimore, Maryland 21244-1849

Re: ESA guidelines

Dear Committee Members:

I have been a practicing medical oncologist since 1974. During this time I have seen remarkable improvements in the care of cancer patients. Not only are more lives being saved but quality of life issues have been addressed and have been markedly improved. One of the major improvements in quality of life has been secondary to erythropoietin and its derivatives. So many of our patients have been extremely exhausted and have required multiple transfusions that have had side effects (both reactions and iron overload). Erythropoietin has made a dramatic improvement in these problems. I have had multiple patients that no longer require transfusions, have excellent quality of life and are able to live productive lives. These drugs are extremely useful in both cancer patients, patients receiving chemotherapy as well as many of the hematologic disorders such as the myelodysplastic syndromes.

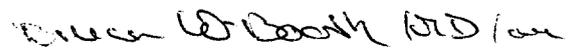
Although I agree that guidelines should be made for the use of erythropoietin and its derivatives, I think if there is a dramatic reduction in their use we will have a significant and major problem with decreased quality of life. Having done this type of therapy for many years, I don't want to go back to the 1970s, 80s and early 90s.

Page 2

Our clinic has made an effort from the very beginning to be very judicious in the use and if anything we underuse the medications. I do not feel there should be further restriction in a blanket like approach to the use of these drugs. I do feel that if the patient is asymptomatic and the hemoglobin is high, the drugs should not be used.

I request that your committee be reasonable in looking for a rational use of these drugs and not significantly adjust the current guidelines or recommendations. Having fought for so long for our patients and having helped advance medical oncology in the care of these patients over all these years, I just don't want to return to the years in which quality of life for cancer patients was so miserable.

Sincerely,

  
BRUCE W. BOOTH, M.D.

BWB/mm

**Ciccanti, Maria L. (CMS/OCSQ)**

---

**From:** Holden, Cathy [CHolden1@Reshealthcare.org]

**Sent:** Tuesday, May 22, 2007 2:57 PM

**To:** Ciccanti, Maria L. (CMS/OCSQ)

**Subject:** Erythropoietin usage

The FDA is considering some significant changes to the labeling of Erythropoietin as a result of several trials. All of the trials were off label use. The scariest outcome is CMS is considering limiting oncology patients to only 12 weeks of Erythropoietin treatment a year. This will be nothing less than catastrophic for patients. There is no distinction between the chemo naive patient who may only need a short term management and the person whose cancer is chronic and is on and off treatment, such as the lymphomas, for years. It will also impact the hospital, because we will see a increase in transfusion dependent patients. The cost of transfusion in the long run is probably higher than the cost of Procrit/Aranesp treatment. The consequences of chronic transfusion due to exposure, anti-body production and iron overload are also factors.

The consequences to the Quality of life to our patients must be considered before such a drastic measure is implemented.



## WEST PENN ALLEGHENY ONCOLOGY NETWORK

CHARLES H. SRODES, M.D., F.A.C.P.  
SIGURDUR R. PETURSSON, M.D., F.A.C.P.  
CYNTHIA K. EVANS, M.D.  
KATHY J. SELVAGGI, M.D., F.A.C.P.  
G. SCOTT LONG, M.D., PhD.  
MOSES S. RAJ, M.D.  
MOHAMMED F. ISLAM, M.D. M.S.  
GENE G. FINLEY, M.D.  
ALEX BARSOUK, M.D.  
HELEN ANALO, M.D.

MELISSA M. THIMONS, D.O.  
JOSE SILVA, M.D.  
JASON THOMAS, M.D.  
BEAULA KODURI, M.D.  
DIANE BUCHBARKER, M.D.  
HEATHER M. MISKE, D.O.  
DAVID G. MAYERNIK, M.D.  
ARUN BHANDARI, M.D.  
ARUNKUMAR SANJEEVI, M.D.  
AMJAD JALIL, M.D.  
JOHN A. LECH, D.O.

June 12, 2007

Steve E. Phurrough, MD, MPA  
Director, Coverage and Analysis Group  
Centers for Medicare & Medicaid Services  
7500 Security Boulevard  
Baltimore, MD 21244

RE: National Coverage Analysis for Erythropoiesis Stimulating Agents (ESAs) for Non-Renal Disease Indications (CAG-00383N)

Dear Sir or Madam:

We are writing to comment upon the proposed decision coverage memorandum regarding the use of erythropoiesis stimulating agents (ESAs) for cancer and related diseases. After review of the proposal, review of our prescribing practices, and discussion with physicians in our large group practice we have, as a group, concluded that the scope of the proposal is far too broad and the limits placed on ESA usage will have a profound negative impact on our patients with cancer and hematologic disease. We will address some of the most egregious aspects of the memorandum herein.

**1. The conclusion that ESA use is not necessary and reasonable for patients with myelodysplasia (MDS) or myeloid cancer.**

Although use of ESAs in this setting is considered off label by the FDA, we and many other practicing hematologists and oncologists have used these agents for more than a decade to great advantage in these diseases, resulting in fewer transfusions and improved quality of life. MDS patients often require multiple transfusions over a period of years resulting in iron overload, a clinical situation that can be delayed or avoided entirely through judicious use of ESAs. We have not seen patterns of excessive thrombosis, nor have we observed progression to myeloid

---

ADMINISTRATIVE OFFICE  
247 MOREWOOD AVENUE – PITTSBURGH, PA 15213  
PHONE: 412-622-0290 --- FAX: 412-681-7605

leukemia in this setting. Many of our patients appreciate the convenience of a single weekly injection as opposed to several hours in a chair or hospital bed receiving a blood transfusion. We cannot find within the CMS memorandum any specific justification for this proposed change.

**2. The conclusion that ESA use is not necessary and reasonable for patients with anemia receiving radiotherapy.**

The basis of this appears to be the Danish Head and Neck Cancer Group Study in which patients received darbepoetin alfa in order to achieve extremely high hemoglobin levels, improve oxygen delivery to the cancer and thereby reduce tumor hypoxia. Unfortunately, there appeared to be an adverse effect of the darbepoetin alfa on outcome with an increase in cancer-specific deaths in the treated group. No one in our practice and no oncologist known to our group would initiate therapy at the hemoglobin level specified in the trial, nor would any of us attempt to achieve such a high hemoglobin level. We have not experienced the kind of rapid progression in our patients noted in this Danish trial.

**3. The conclusion that ESA use is not necessary and reasonable for patients receiving monoclonal antibodies such as bevacizumab or anti-EGFR antibodies.**

Most of these biologics are given in conjunction with chemotherapy, and the chemotherapy-induced anemia is treated with ESAs to great advantage in our and many other oncology practices. For example, bevacizumab is often administered in conjunction with and enhances the efficacy of chemotherapy in a wide variety of human tumors. It is common for patients to become anemic when receiving such combination therapies, and ESAs are often used in this setting. Although one publication found adverse outcomes with panitumumab when administered in conjunction with darbepoetin alfa in advanced colorectal cancer patients, this hardly justifies painting all of these biologics with a broad brush and limiting access to ESAs for a large subgroup of our patients who benefit from these agents.

**4. The conclusion that ESA use is not necessary and reasonable for patients with thrombotic episodes related to malignancy.**

Cancer is a thrombogenic state, as all of us are aware. Many patients may develop thrombotic episodes either from their underlying malignancy or from chemotherapy. Standard anticoagulant strategies are employed and usually prevent recurrent episodes. Once patients are adequately anticoagulated, it is hard for us to understand why ESAs should be withheld in this population.

Next, the CMS memorandum recommends specific limitations on ESA use. Many of these are unreasonable and are not supported by the available data. Specifically:

**1. Initiation at a hemoglobin of less than 9 grams or less than 10 grams for patients with known symptomatic cardiovascular disease that cannot be treated with blood transfusion.**

We find this recommendation ill conceived. Many cancer patients have fatigue, shortness of breath and other adverse symptoms affecting their day-to-day lives with hemoglobin values higher than those levels. Early therapy with ESAs has been demonstrated to significantly improve quality of life for chemotherapy patients suffering chemotherapy-induced anemia. Our current practice, based upon the recent FDA recommendations, calls for initiation of therapy at a hemoglobin of less than 11 grams targeting a hemoglobin not to exceed 12 grams. It appears to

us that this is a reasonable practice guideline and provides a good balance among patient convenience, quality of life and patient safety.

**2. A maximum duration of therapy of 12 weeks per year.**

Therapy for many individuals lasts much longer than 12 weeks and their chemotherapy induced anemia does not promptly resolve with cessation of chemotherapy. A reasonable percentage of patients, especially older patients, take longer for their bone marrow to recover from the effects of chemotherapy. Limiting ESA use to 12 weeks per year is unreasonable based upon available evidence and will result in reduced quality of life for our patients.

**3. The maximum covered treatment dose is 126,000 units in a four-week period**

The standard dosage of epoetin alfa is 40,000 units weekly or 160,000 units in a four-week period. The darbepoetin alfa dosage recommended in the CMS memorandum approximates our clinical practice but does not account for patients who are larger than 70 kg who may be under dosed at those levels.

**4. Cessation of therapy if there is poor drug response after 4 weeks of treatment.**

The median time to response is 4 weeks but many patients require longer administration to see results. Moreover, poor response as measured by hemoglobin rise is not a reasonable endpoint in MDS patients. Many of these patients are treated with the goal of hemoglobin maintenance and reduction in transfusion requirement.

**Conclusion:**

The proposed CMS decision memorandum will place an undue burden on our cancer patients, and is in direct opposition to our practice of putting the patient's interest first. The current CMS proposal has serious deficiencies that will severely hinder our ability to provide the best care possible while minimizing the negative aspects of treatment. Increased transfusion and related risks (disease transmission, allergic reactions, etc.) will be the result with a concomitant decrement in quality of life for this most vulnerable patient population. The increase in blood product usage will strain an already taxed blood banking system and result in unnecessary hospital admissions for blood transfusion.

CMS should carefully consider the adverse effects of this proposal before implementing such sweeping changes. We remind CMS that the Food and Drug Administration (FDA) is the agency responsible for pharmaceutical approval and monitoring of drug safety and we urge CMS to be guided by FDA recommendations.

Respectfully submitted by the physicians of the West Penn Allegheny Oncology Network,  
Pittsburgh, Pennsylvania.

## Ciccanti, Maria L. (CMS/OCSQ)

---

**From:** CMS CAGInquiries  
**Sent:** Tuesday, June 05, 2007 7:34 AM  
**To:** Ciccanti, Maria L. (CMS/OCSQ)  
**Subject:** FW: Growth Factors for Hematology/Oncology patients.

>-----Original Message-----

>From: Charlotte Artigues [mailto:cartigues@utahcancer.com]

>Sent: Monday, June 04, 2007 3:22 PM

>To: CMS CAGInquiries

>Subject: Growth Factors for Hematology/Oncology patients.

>  
>Public Comment re: Erythropoiesis Stimulating Agents (ESAs) guidelines  
>Title of NCA/CAL: Erythropoiesis Stimulating Agents (ESAs) for non-renal  
>disease indications

>  
>  
>As an employee of Utah Cancer Specialists, and patient care advocate, I  
>am concerned about the proposed erythropoietic stimulating agent (ESA)  
>guidelines under consideration. While I understand the need for proper  
>use of these medications, the proposal falls short of providing the  
>best standard of care recommended by oncology organizations such as  
>NCCN, ASCO and ASH. The current proposals will result in a compromised  
>quality of life for our patients, increased blood transfusion  
>requirements with the associated co-morbidity and risk and, ultimately,  
>prove more costly to society than judicious use of ESAs. Please  
>reconsider these guidelines encouraging physicians to carefully weigh  
>the risk/benefit with patients and allow providers to treat this  
>growing population with the best and most compassionate standard of care.

>  
>Chemotherapy-induced anemia is a well-known side effect of  
>myelosuppressive therapy. Furthermore it is quite responsive to ESAs  
>when iron stores, vitamin B12 and folate deficiencies and other  
>underlying processes have been corrected. Holding initiation of ESA  
>until the hemoglobin drops to <9mg/dl will delay response and most  
>likely result in transfusion for a greater number of our chemotherapy  
>patients. Most chemotherapy regimens last a minimum of 16 weeks (and  
>many are much longer). Therefore, limiting the covered treatment  
>duration to 12 weeks annually will be inadequate treatment for many of our patients on continued  
>myelosuppressive therapy.

>  
>According to the proposed guidelines, the Myelodysplastic Syndrome  
>population will be denied access to any form of ESA under all  
>circumstances. While a portion of the MDS patients will not respond to  
>ESAs, a greater number benefit from these medications; reducing the  
>number of necessary blood transfusions, eliminating the complications  
>of iron overload that results from transfusion, enhanced productivity  
>by limiting time spent in a healthcare facility, and an overall  
>improved quality of life.

>  
>We do not dispute the recommendations to discontinue use of the ESAs if  
>the patient is non-responsive to treatment, however:  
>• The recommended four weeks is an inadequate timeframe in which to  
>evaluate patient responsiveness. Former guidelines allow 12 weeks to  
>determine response. Clearly, four weeks is an irresponsible timeframe.  
>• The proposed maximum treatment dose is insufficient to provide  
>standard doses within the recommended timeframes. The maximum covered

>four-week treatment dose is 126,000units of Procrit and 630mcg of Aranesp.

>At an average dose of 40,000 units of Procrit each week, we would need  
>160,000 units in four weeks. The average dose of Aranesp is 300mcg per  
>2 weeks – so the 630mcg would be sufficient.

>

>We encourage you to reconsider the list of specified conditions to  
>include other myeloid and erythroid cancers as well as anemia caused by  
>radiotherapy. Some patients will respond, therefore a trial of an ESA  
>medication seems prudent.

>

>Thank you for your consideration of this request. As a community  
>oncology practice we strive to provide the optimal care to our  
>patients. Please allow us the support we need to continue this practice.

>

>Respectfully,

>

>Charlotte Artigues RN, BSN, OCN

>Utah Cancer Specialists

>Lead RN Salt Lake Clinic

>(801) 933-6070

>



June 13, 2007

Steven Phurrough, M.D., MPH  
Coverage and Analysis Group  
Centers for Medicare and Medicaid Services  
Mail Stop: C1-13-18  
7500 Security Blvd  
Baltimore, MD 21224

RE: CAG-00383N:  
Proposed National Decision Memo for Erythropoiesis Stimulating  
Agents (ESA's) for Non-Renal Disease Indications

Dear Dr. Phurrough:

Thank you for the opportunity to comment on the proposed National Coverage Determination for Erythropoiesis Stimulating Agents ("ESAs") for non-renal disease indications. Although we are pleased that CMS has proposed to clarify the scope of Medicare coverage for ESAs, we are concerned that in the case of certain cancers and associated neoplastic conditions, the proposed National Coverage Determination may be too restrictive based on the available evidence.

As explained in more detail below, we are concerned that CMS's review of the existing scientific and medical literature did not address published studies that support wider use of ESAs, and did not review meta-analyses of the published research results. Moreover, we believe that the proposed limits in the NCD are inconsistent with our experience and data.

Second, we are concerned that if the proposed scope of coverage for ESAs were made final, many critically and chronically ill patients may not receive appropriate treatment, or may be subjected to unnecessary health risks presented by existing or alternative therapies. In sum, although we share CMS's concern that any clarity of coverage should take into account patient safety and the potential for adverse events, those risks are slight in comparison to the potential benefits to the individual beneficiary.

1. Background on Onmark

Onmark, Inc. is a Group Purchasing Organization whose primary focus is serving outpatient medical oncology and hematology-oncology practices nationwide. Onmark was formed in early 2005 and is an affiliate of Oncology

Therapeutics Network, J.V. (“OTN”). Founded in 1990, OTN is the 2<sup>nd</sup> largest specialty pharmaceutical distribution vendor and a leading specialty pharmacy vendor to office based oncologists and other outpatient practices.<sup>1</sup>

Onmark’s membership consists of over 1,500 physician practices comprising over 4,000 medical oncologists located in 50 states. Onmark and OTN have collectively developed a suite of clinical tools for use by the Onmark membership, including a host of tools designed for the treatment of patients with cancer.

OTN provides its customers with its Lynx<sup>®</sup> system, a best-in-class, web-enabled inventory control and charge capture system currently in use by over 1,000 medical oncologists in 50 states. The Lynx system captures robust patient data on the use of ESAs as well as other drugs used in the care of cancer patients.<sup>2</sup>

Onmark has licensed OTN’s de-identified Lynx data, which it uses as the backbone for Onmark’s numerous clinical initiatives. The Lynx data is the basis for much of the analysis and conclusions set forth in this comment letter.

In 2005, the Lynx System recorded over 199,000 patients and 3.89 million chemotherapy and supportive care drug administrations nation-wide. In 2006, the Lynx System recorded over 183,000 patients and 3.42 million chemotherapy and supportive care drug administrations. Additionally, our Lynx transaction records show that over 46,000 patients in 2005 and over 40,000 patients in 2006 received ESA therapy. Therefore, the Lynx System captures patient treatment information on a significant percentage of cancer patients treated in the community-based oncology setting.

## 2. Significant Evidence-Based Literature Supports The Use of ESAs for Anemia of Myelodysplasia (MDS).

There are many well-designed studies that support the use of ESA’s in MDS. Overall, ESA’s in these studies show an improvement in Hgb levels over baseline. Some studies report an enhanced effect with the addition of low dose WBC GF’s. The following studies all support use of ESA’s in MDS:

---

<sup>1</sup> OTN provides pharmaceutical distribution and related services to more than 3,500 community oncologists. OTN also distributes pharmaceutical and other supplies to more 1,400 urology and 400 rheumatology practices.

<sup>2</sup> OTN has recently added EMR features to the Lynx system that capture lab values including Hgb levels in advance of treatment. Once this feature becomes prevalent among our installed users, OTN will be uniquely able to develop a transparent, real-time solution to payors and physicians with regard to the appropriate ESA protocols. OTN and Onmark welcome the opportunity to demonstrate to CMS the Lynx solution.

- i. *A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes. Italian Cooperative Study Group for rHuEpo in Myelodysplastic Syndromes; Br J Haematol. 1998 Dec; 103(4):1070-4.*
- ii. *Maintenance treatment of the anemia of myelodysplastic syndromes with recombinant human granulocyte colony-stimulating factor and erythropoietin: evidence for in vivo synergy. Blood. 1996 May 15; 87(10):4076-81.*
- iii. *Response to recombinant human erythropoietin in patients with myelodysplastic syndromes. Clin Cancer Res. 1997 May;3(5):733-9.*
- iv. *The use of r-HuEpo in the treatment of anaemia related to myelodysplasia (MDS). Br J Haematol. 1995 Apr; 89(4):831-7.*
- v. *Serum erythropoietin level and marrow erythroid infiltration predict response to recombinant human erythropoietin in myelodysplastic syndromes. Haematologica. 1993 Mar-Apr; 78(2):118-22.*
- vi. *Efficacy of erythropoietin in the myelodysplastic syndromes: a meta-analysis of 205 patients from 17 studies. Br J Haematol. 1995 Jan; 89(1):67-71.*
- vii. *Health, economic, and quality-of-life effects of erythropoietin and granulocyte colony-stimulating factor for the treatment of myelodysplastic syndromes: a randomized, controlled trial. Blood. 2004 Jul 15; 104(2):321-7.*
- viii. *Treatment of anemia in myelodysplastic syndromes with granulocyte colony-stimulating factor plus erythropoietin: results from a randomized phase II study and long-term follow-up of 71 patients. Blood. 1998 Jul 1; 92(1):68-75.*
- ix. *Erythroid response to treatment with G-CSF plus erythropoietin for the anaemia of patients with myelodysplastic syndromes: proposal for a predictive model. Br J Haematol. 1997 Nov; 99(2):344-51.*
- x. *A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. Br J Haematol. 2003 Mar; 120(6):1037-46.*
- xi. *Impact of a new dosing regimen of epoetin alfa on quality of life and anemia in patients with low-risk myelodysplastic syndrome. Ann Hematol. 2005 Mar; 84(3):167-76.*

Moreover, the published research does not indicate that the use of ESAs in the treatment of MDS would compromise patient safety, or that there would be an unacceptable increase in the risk of adverse events directly related to the use of ESAs.

3. The Lynx Data and Other Factors Support Continued Use of ESAs for Patient Groups and Indications that the CMS Proposal Seeks to Exclude.

a. Anemia of Myelodysplasia.

In addition to the published research discussed above in Section 2, an analysis of the Lynx data from 213 patients treated for anemia related to MDS for the time period 5/1/2006-10/1/2006 shows an overall improvement in HCT levels from patient initiation to completion.

<u>ESA</u>	<u># of Pts Treated</u>	<u>Mean Hct at Initiation</u>	<u>Mean Hct at Discontinuation</u>	<u>Mean Initiation Dose</u>	<u>Mean Discontinuation Dose</u>
Epoetin alfa	116	30.17%	31.70%	40,754U	43,439U
Darbepoetin alfa	97	29.04%	32.19%	261mg	262mg
<b>Total</b>	<b>213</b>	<b>29.65%</b>	<b>31.92%</b>	<b>N/A</b>	<b>N/A</b>

The mean initiation HCT in the patients with reported HCT values was approximately 29.65% and the mean discontinuation HCT was 31.92%. With these mean HCT values, it is unlikely that these patients received blood transfusions. Additionally, the data establishes that ESA dosage was not appreciably increased over the course of treatment. The mean dose of Epoetin alfa at initiation was 40,754 Units and the mean dose of Epoetin alfa at last dose was 43,439. The mean dose of Darbepoetin alfa at initiation was 261mg and the mean dose of Darbepoetin alfa at last dose was 262mg.

On the basis of our experience, we recommend that CMS amend its coverage criteria for patients with MDS as follows:

- i. Allow patients with MDS to receive ESA's if they have a hemoglobin level of <1g/dl and a serum EPO level of ≤ 500 mU/ml.
- ii. Require reporting of Hgb/Hct levels before each subsequent dose of RBC GF to ensure that a rise in Hgb does not exceed the equivalent of 1g/dl per 2 week period.
- iii. Allow patients to continue ESA's as long as there is a 1 g/dL rise in hemoglobin after six weeks of therapy with darbepoetin or four weeks of therapy with epoetin.
- iv. Allow 1 dose escalation according to drug labeling for patients who do not respond to ESA's with a 1g/dl rise in Hgb.
- v. Require RBC GF discontinuation if there is less than a 1 g/dL rise in Hgb after 12 weeks of darbepoetin or eight

weeks of epoetin therapy, and a dose adjustment increase has already been made and/or IV Iron has been added.

- b. *Patients with Treatment Regimens including Anti-angiogenic drugs such as Bevacizumab.*

We are not aware of any clinical literature to support this exclusion, nor has CMS made reference to any such supporting literature in its proposed rule-making. There is no evidence that there is antagonism between drugs that prevent blood capillary formation (anti-angiogenesis agents) and interference by drugs that support Red Blood Cell formation. Moreover, there is no evidence that patient safety would be compromised.

**Recommendation:** CMS should remove this restriction in coverage policy.

- c. *Patients with treatment regimens including monoclonal/polyclonal antibodies directed against the epidermal growth factor (EGF) receptor.*

There is insufficient evidence in the clinical literature to support this exclusion.

**Recommendation:** CMS should remove this restriction in coverage policy.

- d. *Patients with certain cancer types in which the presence of erythropoietin receptors on either normal tissue/cell lines or malignant tissue/cell lines.*

We believe that CMS is taking a position based upon a hypothesis about the putative role of EPO receptors in tumor growth, and as a result, any action by CMS is premature.

**Recommendation:** CMS should study the purported role of EPO receptors and tumor growth to determine whether EPO receptors do promote tumor growth. Until there is conclusive evidence on this topic, CMS' coverage policy should change its coverage policy around this topic.

4. *The Lynx Data and Other Factors Support Continued or Unchanged Use of ESAs for Patient Groups and Indications that the CMS Proposal Seeks to Limit.*

- a. *Initiation at Hgb's of <9g/dl for patients without known cardiovascular disease and < 10g/dl in patients with documented symptomatic ischemic disease that cannot be treated with blood transfusions.*

ASCO and ASH jointly developed an evidence-based treatment guideline for the use of Erythropoietins in Anemia Associated with Cancer in 1997 that was recently updated in 2002.<sup>3</sup> These two organizations have conducted rigorous systematic reviews of the literature and have found ample evidence to support the initiation of ESA's for chemotherapy-induced anemia in patients with Hgb values of 10 or less.<sup>4</sup> Additionally, for patients with co-morbid conditions or symptoms of anemia, the joint committee found good literature to support the use of ESA's at initiation Hgb's of between 10g/dl and 12g/dl. Additionally, the NCCN has established guidelines for the use of ESA's in Anemia related to Cancer Treatment.<sup>5</sup> The NCCN guidelines are both evidence- and consensus based and recommend the initiation of ESA's for chemotherapy-induced anemia in patients with Hgb values of 11 or less.<sup>6</sup>

The rationale for CMS' proposal to begin ESA's at a Hgb of <9g/dl (in patients without known cardiovascular events) and <10g/dl in patients with documented symptomatic ischemic disease that cannot be treated with blood transfusions, appears to be arbitrary and unsupported by the literature.

**Recommendation:** CMS should use ASCO/ASH evidence-based guidelines or the NCCN's consensus-based guidelines for the initiation rules for ESA's and require that Hgb values be reported before ESA's can begin. CMS can require documentation of co-morbid conditions or symptoms of anemia in cases where a clinician believes that a patient requires the initiation of ESA's with Hgb's in the range of 11-12g/.

b. Setting a Maximum covered treatment duration of 12 weeks/year.

There is no evidence in the literature to support a maximum covered treatment duration/year of ESA's.

**Lynx Data and Community-based Treatment Patterns:**

In reviewing ESA usage patterns through the Lynx System over a 12 month period from November 1, 2004 through October 31, 2005, we found that over 36,000 patients were treated with ESA therapy due to Chemotherapy-induced anemia (CIA) for non-myeloid cancers. The mean duration of ESA regimens in weeks was 14.35 weeks for

---

<sup>3</sup> Rizzo JD, Lichtin AE, Woolf SH, et al. *Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology.* J Clin Oncol. 2002;20:4083-4107.

<sup>4</sup> *Id.*, at 4085

<sup>5</sup> The NCCN guideline for "Cancer and Treatment-Related Anemia" is available at [www.nccn.org](http://www.nccn.org).

<sup>6</sup> *Id.*

darbepoetin treated patients and 14.52 weeks for erythropoietin treated patients. Additionally, when evaluating ESA therapy due to CIA for a 2 year period ending April, 2007, the mean number of ESA regimens utilized with chemotherapy within a 12 month period was 1.3 for darbepoetin treated patients and 1.2 for erythropoietin-treated patients.

<u>ESA</u>	<u>Number of ESA Patient Regimens (Nov,2004-Oct,2005)</u>	<u>Mean ESA Therapy Duration, Weeks</u>	<u>Mean # of ESA Patient Regimens over 12 months (ending Apr,2007)</u>
Darbepoetin	23,160	14.52	1.3
Erythropoietin	13,248	14.35	1.2

Given that many cancer patients with metastatic disease require multiple courses of chemotherapy, and that multiple course chemotherapy is known to deplete bone marrow stores of erythropoietic progenitor cells, ESA support becomes even more critical. Limiting the covered treatment duration of ESA's to 12 weeks/year would deprive metastatic cancer patients from needed growth factor support to continue chemotherapy treatment, and potentially cause delays and dose reductions in chemotherapy treatment needed to improve survival.

**Recommendation:** CMS should remove this restriction in the draft coverage policy.

- c. Setting the Maximum covered 4 week treatment dose of erythropoietin alfa at 126,000 Units and 630mcg for darbepoetin alfa.

The recommended labeled dose of erythropoietin alfa is 150units/kg SC TIW or 40,000 units weekly. In practice, it is common for cancer centers to use the 40,000 units per week dose. Following the recommended dose restrictions over a 4 week period would place all patients treated with initial doses of epoetin alfa over the maximum treatment dose. This is an impractical recommendation. Additionally, the labeling for these agents includes a dose escalation for non-responders after specified time periods. This restriction would prevent the ability to dose escalate in non-responders. The table below summarizes OTN's Lynx data in relation to responses to ESA's after dose escalation from initiation ESA doses.

**Lynx Data and Community-based Treatment Patterns:** We have reviewed Lynx data of over 36,408 ESA patient-regimens utilized for chemotherapy-induced anemia over a 12 month period from November 1<sup>st</sup>, 2004 to October 31<sup>st</sup>, 2005. We found the following:

<u>ESA</u>	<u>Patient type</u>	<u>N PT regimens</u>	<u>Mean RBC-GF duration, weeks</u>	<u>Mean RBC-GF doses/ treatment regimen</u>	<u>Mean Total ESA Dose / 4 week treatment period*</u>
Darbe poetin alfa	Non-Myeloid Chemo	23,160	14.35	310.20	609.5mcg
Epoetin alfa	Non-Myeloid Chemo	13,248	14.52	44,249.08	120,203 Units

\* We have provided mean data for ease of comparison, but CMS should understand there is a range, and many otherwise eligible patients would fall outside of the proposed maximum allowable dose per four week interval. Mean Total ESA dose/4 week treatment period was calculated by taking the mean total dose over the mean duration of RBC-GF therapy to get the mean dose/week and then multiplying by 4.

We looked at dose-escalated patients over the time period of May, 2005-April, 2007 to determine the mean total ESA dose/4 week treatment period in these patients. Of 53,285 patients treated with darbepoetin, 11,577 patients (21.7%) required a dose escalation. Of 28,043 patients treated with epoetin alfa, 6,888 (24.5%) required a dose escalation. The average total dose of darbepoetin alfa and epoetin alfa per 4-week treatment period was 714.44mcg and 188,335 Units respectively.

<u>Drug</u>	<u>N Pts</u>	<u>N Pts (%) Requiring ESA Dose Escalation</u>	<u>Avg Total ESA Dose Per 4-Week Treatment Period</u>	<u>Avg ESA Dose/administration Per 4-Week Treatment Period</u>
Total	81,328	18,465 (22.7%)	--	--
Darbepoetin alfa	53,285	11,577 (21.7%)	714.44 mcg	307.70 mcg
Epoetin alfa	28,043	6,888 (24.5%)	188,335.43 Units	57803.35 Units

ESA dosing requirements and dosing escalation determinations must be left in the hands of experienced clinicians who treat cancer patients on a day in and day out basis, and should not be regulated by CMS.

**Recommendation:** CMS should remove this restriction in coverage policy, but require that Hgb values be reported with each dose of ESA. Require discontinuation if there is no effect as measured by at least a 1g/dl rise in Hgb values over a 12 week period for darbepoetin alfa and an 8 week period for epoetin alfa after appropriate dose escalation practices in non-responding patients.

- d. Continued use of drug is not reasonable and necessary if there is evidence of poor drug response (hgb rise <1g/dl) after 4 weeks of treatment.

The ASCO/ASH guidelines recommend that a dose escalation of ESA's be tried in non-responders after 4 weeks of Epoetin alfa treatment. This data is based on evidence from 4 trials in which non-responders were dose escalated after 4 weeks of initial treatment.<sup>7</sup>

**Community-based Treatment Patterns:**

We evaluated dose escalation effects on hemoglobin values in initial non-responders to ESA treatment in CIA patients over the time period of May, 2005-April, 2007. This is a subset inclusive of 6,208 patients with reported Hgb values over the 2 year time period. Of the 6,208 patients with initiation hemoglobins, defined as a Hgb value recorded within 7 days of the first ESA in the ESA regimen, 2,346 did not have at least a 1g/dl rise from their initiation hemoglobin. Of those non-responders, 885 patients received a dose escalation of their ESA. 104 out of 885 patients had a >1g/dl rise in hemoglobin values over the subsequent 4 week time period and the average hemoglobin rise, 4 weeks after dose escalation was 1.9g/dl.

<u>Drug</u>	<u>N Pts</u>	<u>Avg Initiation Hgb</u>	<u>N Pts With No Hgb Response After 4 Weeks of Erythropoietin Treatment</u>	<u>N Pts With ESA Dose Escalation (Out of Those with No Hgb Response)</u>	<u>N Pts With Hgb Response &gt; 1 g/dl in subsequent 4-Week Period</u>	<u>Avg Hgb Rise 4 Weeks After Dose Escalation</u>
Total	6208	10.41	2346	885	104	1.90
Darbepoetin alfa	4302	10.43	1689	599	60	1.86
Epoetin alfa	1906	10.36	657	286	44	1.97

A subset of non-responding ESA patients, will respond to ESA therapy after dose escalation. Based upon recommendations by ASCO/ASH and NCCN guidelines and data from community-based practices, it is reasonable to dose escalate initial non-responders to ESA Therapy after 4 weeks of therapy.

**Recommendation:** CMS should remove this restriction in coverage policy.

<sup>7</sup> See Rizzo, et. al, at 4085.

Letter to CMS  
June 13, 2007  
Page 10 of 10

Onmark appreciates the opportunity to provide comments to CMS' proposed rule-making re ESA utilization. Please do not hesitate to contact us should you wish to discuss any of the matters set forth above.

ONMARK, INC.

A handwritten signature in black ink, appearing to read "Clark Avery". The signature is written in a cursive style with a large initial "C".

Clark Avery  
President & General Manager

WASHINGTON LEGAL FOUNDATION

2009 MASSACHUSETTS AVENUE, N.W.  
WASHINGTON, D. C. 20036  
202 588-0302  
www.wlf.org

June 13, 2007

Steve Phurrough, MD, MPA  
Director, Coverage and Analysis Group  
Centers for Medicare and Medicaid Services  
Department of Health and Human Services  
Mail Stop: C1-09-06  
7500 Security Blvd.  
Baltimore, Maryland 21244

**Re: Proposed Decision Memorandum for Erythropoiesis Stimulating Agents (ESAs) for Non-Renal Disease Indications (CAG-00383N)**

Dear Dr. Phurrough:

The Washington Legal Foundation (WLF) appreciates the opportunity to submit comments to the Centers for Medicare and Medicaid Services (CMS) on the above-referenced proposed decision memorandum for Erythropoiesis Stimulating Agents (ESAs) for Non-Renal Disease Indications (hereafter NCD). WLF is a non-profit public interest law and policy center based in Washington, D.C., with supporters nationwide. WLF promotes free market policies through litigation, administrative proceedings, publications and advocacy before state and federal government agencies, including CMS and the Food and Drug Administration (FDA).

As set forth below, WLF urges CMS to withdraw its proposed national coverage determination for ESAs for the following reasons:

(1) CMS does not have authority under the Social Security Act to limit or eliminate coverage for FDA-approved uses of ESAs in cancer treatment regimens. The statute requires CMS to provide coverage for such products when used for "medically accepted indications." A medically accepted indication includes any use approved by FDA.

(2) The CMS determination would constitute arbitrary and capricious decision-making in violation of the Administrative Procedure Act. That is because the Secretary of Health and Human Services (HHS) is ultimately responsible for decisions by CMS and FDA, and here each agency has reached different and irreconcilable conclusions on the same set of facts about the benefit-risk profile of ESAs.

(3) Beyond being unlawful, CMS's intrusion into FDA's area of expertise will adversely affect the delivery of patient care and development of new medications. The proposal could lead to malpractice allegations against physicians who use an ESA contrary to Medicare coverage criteria. The CMS decision also unsettles legal doctrines critical to a manufacturer's decisions regarding drug development.

**I. Background: The CMS's Proposed National Coverage Determination for ESAs**

In its decision memorandum for ESAs, CMS proposes no longer to cover ESA treatment for the following conditions:

- Any anemia in cancer or cancer treatment patients due to foliate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis.
- The anemia of myelodysplasia.
- The anemia of myeloid cancers.
- The anemia associated with the treatment of myeloid cancers or erythroid cancers.
- The anemia of cancer not related to cancer treatment.
- Any anemia associated with radiotherapy.
- Prophylactic use to prevent chemotherapy-induced anemia.
- Prophylactic use to reduce tumor hypoxia.
- Patients with erythropoietin-type resistance due to neutralizing antibodies.
- Patients with treatment regimens including anti-angiogenic drugs such as bevacizumab (Avastin).
- Patients with treatment regimens including monoclonal/polyclonal antibodies directed against the epidermal growth factor receptor (EGFR).
- Anemia due to cancer treatment if patients have uncontrolled hypertension.
- Patients with thrombotic episodes related to malignancy.

Moreover, while CMS indicated that it would continue to cover the use of ESAs for certain types of cancer, it proposes to do so only under the following additional conditions relating to dosing and duration of therapy:

- The hemoglobin/hematocrit levels immediately prior to initiation of dosing for the month should be less than 9 g/dl/27% in patients without known cardiovascular disease and less than 10 g/dl/30% in patients with documented symptomatic ischemic disease that cannot be treated with blood transfusion. The latter patients should be alerted to the increased potential for thrombosis and sequelae.
- The maximum covered treatment duration is 12 weeks per year.
- The maximum covered four-week treatment dose is 126,000 units for erythropoietin and 630 µg for darbepoietin.

In support of these proposed determinations, CMS cites “emerging safety concerns” about ESAs, and it declares that it is responding to FDA’s decision to add black box warnings to the labels of all ESAs. CMS has, however, gone well beyond FDA’s determination for ESAs by, in effect, concluding that the benefit-risk balance of ESAs requires their use in narrower circumstances than those approved by FDA. Indeed, while FDA would allow for continued marketing of ESAs under more stringent conditions, CMS would withhold coverage in certain situations because of what it perceives to be the deleterious effects of ESAs. As a result, the CMS proposal, if finalized, would override FDA’s determination of the benefit-risk balance for these products and have the effect of denying patients access to approved uses of ESAs.

## **II. Interests of the Washington Legal Foundation**

The Washington Legal Foundation is a public interest law and policy center with supporters in all 50 States. Since its founding in 1977, WLF has engaged in litigation and advocacy to defend and promote individual rights and a limited and accountable government, including in the area of patients’ rights. For example, WLF successfully challenged the constitutionality of FDA restrictions on the ability of doctors and patients to receive truthful information about off-label uses of FDA-approved medicines. *Washington Legal Found. v. Friedman*, 13 F. Sup. 2d 51 (D.D.C. 1998), *appeal dismissed*, 202 F.3d 331 (D.C. Cir. 2000). A panel of the federal appeals court in Washington recently ruled in WLF’s favor in its challenge to FDA restrictions on patient access to developmental drugs. *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 445 F.3d 470 (D.C. Cir.), *reh. en banc granted*, 2006 U.S. App. LEXIS 28974 (D.C. Cir. 2006). WLF is currently engaged in litigation with CMS regarding CMS’s restrictions on patient access to information about Medicare Part D prescription drug benefits. *Fox v. Leavitt*, No. 06-1490 (D.D.C.). WLF has previously submitted comments to CMS on February 10, 2004, and June 25, 2004, concerning Medicare coverage of off-label uses of FDA-approved cancer drugs under Part B, Part D, and the Section 641 demonstration program. WLF also submitted comments to CMS on June 6, 2005, concerning the agency’s draft

guidance entitled, “Factors CMS considers in Making a Determination of Coverage with Evidence Development.”

### **III. The CMS Is Not Authorized Under the Social Security Act to Deny or Limit Coverage for FDA-Approved Uses of ESAs in Cancer Treatment Regimes**

At the outset, WLF must emphasize that CMS does not have authority under the Social Security Act to limit or eliminate coverage for FDA-approved uses of ESAs by asserting that such therapy is not safe and, therefore, not necessary or reasonable. Under Section 1832 of the statute, a beneficiary of the Medicare program is entitled to payment made to him, or on his behalf, for “medical and other health services.” 42 U.S.C. § 1395k(a)(1). For the purposes of the statute, “medical and other health services” are defined to include, among other things, “services and supplies (including drugs and biologicals which are not usually self-administered by the patient) furnished as an incident to a physician’s professional service . . .” 42 U.S.C. § 1395x(s)(2)(A). The terms “drugs” and “biologicals” are defined to include those products that are “included . . . in the U.S. Pharmacopoeia, the National Formulary, or . . . in New Drugs or Accepted Dental Remedies.” 42 U.S.C. § 1395x(t)(1).

While the foregoing statutory provisions provide coverage for various types of pharmaceuticals, the Medicare statute also includes provisions that specifically mandate coverage of drugs and biologicals used in oncology settings. Section 1861(t)(2)(A) of the Social Security Act directs CMS to provide coverage for “drugs or biologicals used in an anticancer chemotherapeutic regimen for a medically accepted indication.” 42 U.S.C. § 1395x(t)(2)(A). The CMS has previously indicated that, for the purposes of this provision, a cancer treatment regimen includes a drug (such as an ESA) that is used to treat toxicities or side effects of the cancer treatment regimen when the drug is administered incident to a chemotherapy treatment.<sup>1</sup> A “medically accepted indication” includes any use which has been approved by FDA for the drug. 42 U.S.C. § 1395x(t)(2)(B).

In the instant case, CMS would deny coverage for approved uses of drugs and biologics utilized in anticancer chemotherapeutic regimens upon a finding that such coverage is not reasonable and necessary because it is not safe. To be sure, Section 1862(a)(1) of the Social Security Act authorizes CMS to deny coverage for items and services that are not determined to be “reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.” 42 U.S.C. § 1395y(1)(A). The statutory terms “reasonable” and “necessary” have, however, been consistently construed by CMS to mean that a product must be safe and effective, medically necessary, and not experimental. And, for the purposes of determining safety and efficacy, CMS has routinely relied on the findings of FDA that a drug or biologic is safe and effective for its approved uses.

---

<sup>1</sup> See Centers for Medicare & Medicaid Services, Medicare Benefit Policy Manual, CMS Pub. 100-02, § 50.4.5, *Unlabeled Use for Anti-Cancer Drugs* (Oct. 1, 2003).

The CMS may not now invoke the reasonable and necessary requirement in the Medicare statute to second-guess FDA's determinations about the safety and efficacy of approved ESAs. Indeed, while Congress expressly authorized the Secretary of HHS to limit coverage for medically inappropriate off-label uses of anticancer products, it chose not to establish the same exception for uses approved by FDA. Specifically, under Section 1861(t)(2)(B)(ii)(I) of the Act, the Secretary must generally provide coverage for an off-label use of an anticancer product if such use is supported by inclusion in certain authoritative compendia. That coverage, however, may be withheld where the Secretary has determined that the use is not "medically appropriate." 42 U.S.C. § 1395x(t)(2)(B). In contrast, by not authorizing the Secretary to make similar determinations for approved uses, Congress made clear that CMS may not base coverage decisions for approved anticancer products on its assessment of whether a particular use is "medically appropriate."<sup>2</sup>

#### **IV. The CMS Coverage Determination Would Constitute Arbitrary and Capricious Action Under the Administrative Procedure Act**

Even assuming *arguendo* that CMS's coverage determination for ESAs is somehow permissible under the Social Security Act, it would nonetheless constitute arbitrary and capricious decision-making on the part of the Secretary of Health and Human Services, in violation of the Administrative Procedure Act. 5 U.S.C. § 706(2)(A). The Secretary is, of course, ultimately responsible for determining what claims are covered for drugs and biologics under the Social Security Act. 42 U.S.C. § 1395x(t)(2)(A). Pursuant to the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 355(d), and Public Health Service Act (PHSA), 42 U.S.C. § 262, the Secretary is also responsible for authorizing approval and marketing of drugs and biological products.<sup>3</sup> In connection with issuance of the proposed coverage determination, and on the basis of the same facts, the Secretary has reached different and irreconcilable positions about the benefit-risk profile of ESAs under these separate federal statutes. That is arbitrary and capricious decision-making.

---

<sup>2</sup> See *e.g.*, *Russello v. United States*, 464 U.S. 16, 23 (1983) ("Where Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion."); *City of Chicago v. Environmental Defense Fund*, 511 U.S. 328, 338 (1994) ("[I]t is generally presumed that Congress acts intentionally and purposely when it includes particular language in one section of a statute but omits it in another."); *S. D. Warren Co. v. Me. Bd. of Env'tl. Prot.*, 126 S. Ct. 1843, 1852 (2006) ("[W]hen Congress fine-tunes its statutory definitions, it tends to do so with a purpose in mind."); *Sosa v. Alvarez-Machain*, 542 U.S. 692, 712 n.9 (2004) (observing that one party's request that the Court read a phrase into a statute, "when it is clear that Congress knew how to specify [that phrase] when it wanted to, runs afoul of the usual rule that when the legislature uses certain language in one part of the statute and different language in another, the court assumes different meanings were intended.") (internal quotation omitted).

<sup>3</sup> See Federal Food, Drug, and Cosmetic Act of 1938 §505(d), 21 U.S.C. § 355(d) (establishing a finding of safety and effectiveness as a precondition to approval of a new drug application); *see also* § 351 of the Public Health Service Act, 42 U.S.C. § 262 (providing that biologics license applications are to be approved "on the basis of a demonstration that the biologics product...is safe, pure, and potent...").

Although the Secretary has delegated his responsibilities under the SSA and the FDCA/PHSA to CMS and FDA, respectively, he is nonetheless the federal official charged by Congress with responsibility for administering these statutes. As described at the outset, the Secretary (acting through FDA) chose to address the safety concerns raised about ESAs by requiring black box warnings, updated warnings, and a change to the dosage and administration sections for all ESAs. With these changes, however, the Secretary decided to allow continued marketing of ESAs for use in all oncology settings.<sup>4</sup> On the other hand, the Secretary (acting through CMS) has reached a different conclusion about the benefit-risk balance of ESAs than FDA (the expert agency on such matters), and he proposes to withdraw coverage for approved uses of ESAs in certain anticancer chemotherapeutic regimens. This inconsistency in decision-making by the Secretary is improper under the APA.

Under the APA, a federal agency's actions, findings, and conclusions may not be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. 5 U.S.C. § 706(2)(A). In determining whether an agency acted in a manner consistent with this provision, the courts look to whether the decision-maker has "considered the relevant factors and articulated a 'rational connection between the facts found and the choice made.'" *Motor Vehicle Mfrs. Ass'n of the U.S. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). Applying that standard here, the Secretary cannot satisfy this test since, on the same set of facts, he has reached conflicting conclusions about the safety profile of ESAs. While CMS may assert that the Secretary's actions can be harmonized because its coverage decisions are different than FDA's determinations, that argument misses the point. Here, the Secretary has acted in an arbitrary and capricious manner because he has reached different conclusions about the underlying benefit-risk profile of ESAs.

#### **V. The CMS Determination Would Seriously Undermine the Existing Regulatory Framework Governing Patient Care and the Development of New Medicines**

By basing its proposed NCD on an analysis of the safety profile of ESAs, CMS has intruded into FDA's area of expertise and authority in a manner that will have serious adverse implications for the delivery of patient care and the development of new medications. CMS's prior determinations on Medicare coverage of drugs and devices have generally related to circumstances that FDA had not addressed. Typically, Medicare coverage determinations concern off-label uses of drugs<sup>5</sup> or the utility in specific clinical situations of diagnostic devices

---

<sup>4</sup> FDA may further revise the labeling for ESA products in light of the meeting of the Oncologic Drugs Advisory Committee (ODAC) on May 10, 2007. At this point, however, the risk profile upon which CMS based its decision and the determination itself are inconsistent with FDA's evaluation of the risk-benefit profile and decision to allow continued marketing.

<sup>5</sup>See, e.g., Centers for Medicare & Medicaid Services, CMS Pub. 100-03, Medicare National Coverage Determinations Manual § 200.1, *Nesiritide for Treatment of Heart Failure Patients* (Mar. 2, 2006) (denying coverage for Nesiritide when used off-label to treat congestive heart failure); *id.* § 110.17, *Anticancer Chemotherapy for Colorectal Cancer* (Jan. 28, 2005) (providing for coverage of the off-label use of oxaliplatin, irinotecan, cetuximab, and bevacizumab in specific clinical trials).

that have broad applications.<sup>6</sup> The CMS proposal on ESAs is the first time, to our knowledge, that CMS has second-guessed FDA's determination of a product's benefit-risk balance with respect to conditions of use that FDA has approved.

That intrusion into FDA's area of expertise would deny patients access to medicines that FDA has determined to be safe and effective. This denial would not be based on any issue within the expertise of CMS as administrator of a healthcare insurance program, but rather on CMS overriding FDA's determination of the benefit-risk balance. If CMS has authority to ignore FDA's conclusions, patient access to many approved therapies could be threatened. Moreover, while the ESA proposal involves restrictions on the use of drugs, if CMS can make its own determinations about benefit-risk balance, it also could expand Medicare coverage to uses considered *unsafe* by FDA. For example, CMS might conclude, contrary to FDA's determination, that a less expensive drug could safely be used in a particular situation instead of a more expensive alternative. If FDA's safety determination was correct, the result of CMS's policy would be harmful to patients.

In addition, CMS's coverage determination may decrease patient access to ESAs by opening the door to malpractice allegations against physicians who use a drug in accordance with its FDA-approved labeling but contrary to Medicare coverage criteria, even in the case of non-Medicare patients. Since CMS's proposal would effectively declare to be unsafe certain conditions of use that FDA has approved as safe, a patient injured by an FDA-approved use of the product could cite the Medicare coverage policy to support a malpractice action if that patient were prescribed the medication in a manner that was inconsistent with the NCD. Although the nuances of medical malpractice law vary from state to state, the basic malpractice analysis considers whether a practitioner has acted in a manner that a similarly situated "reasonable" practitioner would not have.<sup>7</sup> It is possible that a jury would give weight to CMS's conclusions about the benefit-risk balance of a product in assessing whether a practitioner acted reasonably, which could give rise to increased malpractice liability risk for those practitioners who prescribed medications for uses outside of the NCD. This heightened risk might discourage practitioners from prescribing the medication in a manner inconsistent with the NCD, which

---

<sup>6</sup>See, e.g., *id.* § 220.6, *Positron Emission Tomography (PET) Scans* (Apr. 4, 2005) (listing all Medicare-covered uses of positron emission tomography scans); *id.* § 220.5, *Ultrasonic Diagnostic Procedures* (Oct. 2, 2003) (setting forth procedures for which Medicare coverage is extended and identifying procedures that are considered experimental and should therefore not be covered).

<sup>7</sup>See, e.g., *Locke v. Pachtman*, 521 N.W.2d 786, 789 (Mich. 1994) ("Proof of a medical malpractice claim requires the demonstration of the following four factors: (1) the applicable standard of care, (2) breach of that standard of care by the defendant, (3) injury, and (4) proximate causation between the alleged breach and the injury.") (citing Mich. Comp. Laws § 600.2912a); *Rogers v. Meridian Park Hosp.*, 772 P.2d 929, 932 (Ore. 1989) ("Medical malpractice cases are nothing more than negligence actions against medical professionals. The fundamental issue in these cases, as in all negligence cases, is whether the defendant breached the standard of care and caused injury to the plaintiff."); *Hood v. Phillips*, 554 S.W.2d 160, 165 (Tex. 1977) ("The burden of proof is on the patient-plaintiff to establish that the physician-defendant has undertaken a mode or form of treatment which a reasonable and prudent member of the medical profession would not have undertaken under the same or similar circumstances."); *Duckworth v. Bennett*, 181 A. 558, 559 (Pa. 1935) ("A physician is required to exercise only such reasonable skill and diligence as is ordinarily exercised in his profession.").

could have the untoward effect of denying patients medication to which they otherwise would have had access.

CMS's proposal would also unsettle legal doctrines that are relevant to the risk-reward calculation that figures into pharmaceutical manufacturers' decision-making regarding drug discovery and development. Centralizing the review of drug safety and efficacy within one regulatory agency (i.e., FDA) enhances the efficiency of the drug development process, allowing manufacturers to gain experience with the agency and the regulatory framework in which it operates. FDA takes the position that it conducts a comprehensive evaluation of a product's benefits and risks under the conditions of use in the proposed labeling, and that States are therefore not permitted to upset FDA's judgment by imposing further requirements such as additional warnings.<sup>8</sup> FDA's position precludes courts from holding pharmaceutical manufacturers liable for injuries based on a theory that State law required the manufacturer to provide warnings that FDA did not require.

Although FDA's position has been accepted by some courts, it has been rejected by others<sup>9</sup> and the issue has not been finally resolved. *Compare Ehlis v. Shire Richwood, Inc.*, 233 F. Supp. 2d 1189, 1198 (D.N.D. 2002) with *Motus v. Pfizer*, 127 F. Supp. 2d 1085 (C.D. Cal. 2000). CMS's assertion of authority in the ESA case threatens to further undermine FDA's position and helps support an argument against FDA preemption of State law. For example, if a federal agency like CMS can recalculate FDA's benefit-risk balance for Medicare coverage purposes, it is difficult to see why a State should be prohibited from recalculating it for product liability purposes. CMS's action thus jeopardizes FDA's position on preemption and injects a level of regulatory unpredictability into the drug development process. WLF is concerned that CMS's position will discourage funding for research and development. In considering whether to expend the enormous sums required to obtain FDA approval of a new drug, companies will be reluctant to do so if the FDA-approved conditions for use can be ignored by Medicare or if FDA determinations regarding safety and efficacy could be disregarded by other federal or State agencies.

Finally, it is important to note that explicit regulation of drug labeling by States may become permissible if CMS's action is sustained. For example, the California Supreme Court invalidated an effort under that State's Proposition 65 to require a warning on nonprescription nicotine replacement therapy products. *Dowhal v. SmithKline Beecham Consumer Healthcare*, 32 Cal. 4th 910 (2004). In reaching that decision, the court deferred to FDA's judgment that the State warning on nicotine risks, although truthful, was preempted by FDA's expert determination that the State warning would create a greater risk by discouraging use of the products. *Id.* at 930-34. If CMS can override FDA's expert determinations on comparative benefits and risks, courts

---

<sup>8</sup> See 71 Fed. Reg. 3922, 3933-3936 (Jan. 24, 2006).

<sup>9</sup> See, e.g., *Motus v. Pfizer, Inc.*, 127 F. Supp. 2d 1085 (C.D. Cal. 2000), *summary judgment granted*, 196 F. Supp. 2d 984, 986 (C.D. Cal. 2001), *aff'd*, 358 F.3d 659 (9th Cir. 2004).

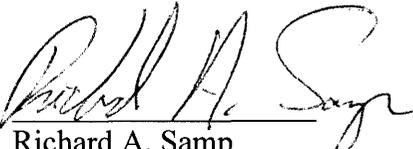
Steve Phurrough, MD, MPA  
Centers for Medicare and Medicaid Services  
June 13, 2007  
Page 9

may see little basis for preventing States from regulating products based on a risk assessment different from FDA's.

Accordingly, for the foregoing reasons, WLF urges CMS to withdraw its proposed NCD for ESAs. The proposal is clearly unlawful under the Social Security Act and the Administrative Procedure Act. It also would seriously undermine the regulatory framework governing the delivery of patient care and development of new medications. Thank you for your consideration of these comments.

Sincerely,

  
Daniel J. Popeo  
Chairman and General Counsel

  
Richard A. Samp  
Chief Counsel



## Oncology Nursing Society

125 Enterprise Drive • Pittsburgh, PA 15275-1214  
Toll Free: 866-257-4ONS • Phone: 412-859-6100 • Fax: 412-859-6165  
customer.service@ons.org • www.ons.org

May 21, 2007

Leslie V. Norwalk, Esq.  
Acting Administrator  
Centers for Medicare and Medicaid Services  
Department of Health and Human Services  
Room 445-G  
Hubert H. Humphrey Building  
200 Independence Avenue, S.W.  
Washington, D.C. 20201

Re: CAG#000383N, The Use of Erythropoiesis Stimulating Agents in Cancer and Related Neoplastic Conditions

Dear Acting Administrator Norwalk:

On behalf of the Oncology Nursing Society (ONS) – the largest professional oncology group in the United States, composed of more than 35,000 nurses and other health professionals dedicated to ensuring and advancing access to quality care for all individuals affected by cancer – we thank the agency for this opportunity to submit comments regarding “Use of Erythropoiesis Stimulating Agents in Cancer and Related Neoplastic Conditions.” As part of its mission, the Society works with policymakers to advance policies and programs that will reduce and prevent suffering from cancer, particularly among the Medicare population which is disproportionately affected by cancer.

As you know, oncology nurses play an integral role in administering and monitoring cancer treatment, as well as providing supportive care and managing patient treatment side-effects. Maximizing quality of life and minimizing side-effects, including anemia and related fatigue, are central goals and responsibilities of oncology nurses. To that end, ONS and its members are following closely the deliberations over the use of – and payment for – erythropoiesis stimulating agents (ESAs) to treat anemia in people with cancer.

ONS has long-standing positions that public and private payors should cover – and provide adequate reimbursement for – the benefits and services which health professionals, in consultation with their patients, believe are necessary and appropriate (Please see attached Position Statement). ONS maintains that such clinical decisions should be supported by guidelines, protocols, and the most up-to-date science to ensure that the care provided – and paid for – is evidence-based and the most appropriate for each individual patient's situation. As such, ONS believes that Medicare payment policy should be reflective of the full-range of

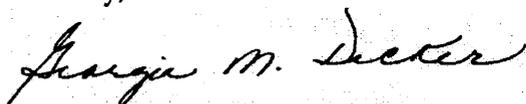
*Oncology Nursing Society  
Comments to the Centers for Medicare and Medicaid Services  
The Use of Erythropoiesis Stimulating Agents in Cancer and Related Neoplastic Conditions  
May 2007*

national practice guidelines, Food and Drug Administration (FDA) scientific determinations, and other valid and reliable evidence. ONS urges your agency to be deliberative in its review process and to take all the steps necessary to ensure that Medicare ESA coverage policy is evidence-based and aligned with expert opinion.

Given the unique role that oncology nurses play in monitoring and ameliorating anemia and other side-effects associated with cancer treatment, we would be happy to be a resource to you and your colleagues on this and other cancer care related matters. Again, we thank you for this opportunity to submit comments. If we can be of any assistance to you, please do not hesitate to contact us or our Washington, DC Health Policy Associate, Ilisa Halpern Paul (202/230-5145, [ilisa.paul@dbr.com](mailto:ilisa.paul@dbr.com)).

Respectfully submitted,

Sincerely,



Georgia M. Decker, MS, RN, CS-ANP, AOCN®  
President



Paula Rieger, RN, MSN, AOCN®, FAAN  
Chief Executive Officer



**FRED S. MARCUS, MD, AND ASSOCIATES**

A PROFESSIONAL CORPORATION

***Internal Medicine, Hematology, and Medical Oncology***

Fred S. Marcus, MD  
Shane P. Dormady, MD, PhD  
John A. Hayward, MD  
Debra D. St. Claire, MD  
Peggy Ross, RNP, MS

2940 Whipple Avenue, Suite B • Redwood City, California 94062  
(650) 216-8300 Telephone (650) 216-8401 Facsimile

Sherri Garoutte, RN, OCN  
Diana Goodenough, RN, OCN  
Theresa Koettters, RN, MS

June 5, 2007

Steve Phurrough, MD, MPA

Elizabeth Koller, MD, FACE

Maria Ciccanti, RN

Coverage Analysis Group

Office of Clinical Standards and Quality

Centers for Medicare and Medicaid Services

Mail Stop C1-12-28

7500 Baltimore, MD 21244-1849

Re: Comment Regarding Changes in Medicare Policy re: Erythropoiesis Stimulating Agents (ESAs) for  
Non-renal Disease Indications (CAG-00383N)

Thank you for inviting comment regarding your proposed changes in Medicare policy re: ESAs. I am an Oncology Certified Nurse, treating patients with a broad spectrum of malignancies and blood disorders in the Community setting for twenty years. I agree that growth factors have made a huge (positive) difference in our treatments and I agree that there is a need for national coverage standards as well as a rational, evidence-based response to FDA warnings about ESAs (and all drugs).

It is my experience that both darbepoetin alfa and epoetin alfa have equal efficacy in treating selected forms of anemia and I believe that CMS should therefore establish the same list of indications to support medical necessity for both. This list should include all indications where evidence shows that ESAs are safe and effective.

I believe that Quality of Life, reduced morbidity and side effects secondary to our antineoplastic therapies, and transfusion avoidance are relevant, important endpoints for patients living with cancer. Transfusions carry both expense (cost of blood, blood bank personnel time, nursing time, transfusion bed time, and the patient's time) and considerable risk (of reactions, HIV, and Hepatitis).

I disagree with discontinuing ESAs for failure to achieve a 1 g/dl Hemoglobin increase in four weeks; I do not believe that this is evidence-based. Clinical studies consistently show that the optimal response takes 2 – 12 weeks to occur.

Neither darbepoetin alfa nor epoetin alfa reliably achieves and increase of 1 g/dl in 4 weeks at standard doses. Standard doses usually require 5 – 7 weeks for 1 g/dl response.

I believe that there must be a provision for dose escalation in non-responders – it has been the standard of care of ten years to dose escalate in non-responders at 6 – 8 weeks. There has been no evidence showing a safety risk associated with dose escalation.

I agree with restricting the use of ESAs in most people who have a hemoglobin level of > 12 g/dl. Trials that pushed hemoglobin above the limit (in the hopes of improving patients' response rates to treatment) showed an increased risk of thrombotic events, clearly not in the patients' best interest. However, in patients who are currently undergoing chemotherapy, who have a hemoglobin level of 12.0 or 12.1 and who will be receiving myelosuppressive treatments within the next week, should receive ESAs with the goal of keeping the hemoglobin at the 12.0 g/dl level.

I disagree with your suggested change to not cover multiple myeloma, MDS, and chronic anemia of cancer. Transfusion avoidance is as important for people who are currently not receiving chemotherapy (such as people multiple myeloma, myelodysplastic syndromes, or metastatic cancers) as for those who are receiving chemotherapy. Studies that showed significant and life-threatening events in certain patients who have taken ESAs for non-renal diseases, do not appear to have included any patients with bone marrow failure (such as MDS). Most patients with MDS are elderly; many have comorbidities that make alternative treatments such as chronic transfusions and aggressive chemotherapy, very risky. ESAs have been found to be safe and beneficial (therapeutic as well as supportive) in all subtypes of MDS.

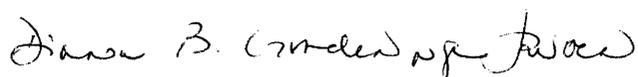
I disagree with a 12 week maximum allowance for ESA usage. When the original studies that formed the basis for FDA approval of ESAs in chemo-related anemia were done, they were done with a 12 week course of chemotherapy. In the last 20 years, the duration of antineoplastic therapies has increased due to the availability of supportive agents as well as the number of active agents available. For patients undergoing first, second, and third line regimens lasting even 6 -12 months in a given year, the 12 week maximum allowance is grossly inadequate. Also, there is no evidence suggesting that the use of ESAs for more than 12 weeks is associated with more safety issues (as there is with greatly elevated hemoglobin levels).

I disagree with your proposed non-coverage ESAs in patients receiving VEGF or EGFR inhibitors. These agents are known to induce anemia and are often given with other anemia-inducing regimens. There is no evidence that ESA usage antagonizes the therapeutic effect of VEGF/EGFR inhibitors.

In summary, I believe that the benefits of ESAs have been demonstrated in the literature in over 2000 patients, correcting anemia and reducing transfusion rates. While cancer patients' quality of life, functionality, and general well-being are greatly improved by maintaining hemoglobin concentrations near 12 g/dl, there is no evidence that transfusions are safer or more effective than ESA use in patients with Hemoglobin levels between 9 – 11. Your proposed changes could increase the blood demand by 20% and could risk depletion of the national blood supply.

**I strongly recommend that you approve use of ESAs:** 1) to be started at Hgb < 11 g/dl, 2) that dose escalation be allowed, 3) that treatment be held with Hgb > 12 and treatment be restarted as soon as Hgb subsequently drops below 12, 4) include coverage for MDS and Multiple Myeloma, 5) maintain coverage for patients receiving VEGF and EGFR inhibitors, and 6) coverage be continued for as long as chemo-induced anemia continues up to 12 weeks after chemotherapy is concluded. Thank you for inviting my comments.

Sincerely,



Diana Goodenough, RN, OCN

DBG:sdg

## Physicians

### *Hematology & Oncology*

Thomas A. Alberico, MD  
Burton F. Alexander, III, MD  
Daniel M. Atienza, MD  
Bruce W. Booth, MD  
Robert L. Burger, MD, FACP  
Paul R. Conkling, MD  
Scott J. Cross, MD  
Mark T. Fleming, MD  
Edward R. George, MD, FACP  
Elizabeth A. Harden, MD, FACP  
John R. Howard, Jr., DO  
John F. Kessler, MD, FACP  
Scott Kruger, MD, FACP  
Michael E. Lee, MD  
John Q. A. Mattern, II, DO  
Dean S. McCaughey, III, MD  
John C. Paschold, MD, FACP  
David M. Powell, MD  
Christina W. Prillaman, MD, FACP  
John J. Regan, MD  
Ronald J. Ruzkowski, MD  
S. George Saman, MD  
Joseph J. Schulz, MD  
Michael S. Steinberg, MD, FACP  
Alexander K. Su, MD  
Valiant D. Tan, MD

### *Gynecological Oncology*

Johnny Hyde, MD  
Munir F. Nasr, MD, FACOG  
Stacey J. Rogers, MD, FACOG  
Robert C. Squatrito, MD, FACOG

### *Radiation Oncology*

Michael L. Miller, DO

## Office Locations

### *Southside*

5900 Lake Wright Drive  
Norfolk, VA 23502  
(757) 466.8683  
FAX (757) 466.8892

1950 Glenn Mitchell, Ste. 102  
Virginia Beach, VA 23456  
(757) 368.0437  
FAX (757) 368.0492

5818 Harbour View Blvd, Suite 230  
Suffolk, VA 23435  
(757) 686.1042  
FAX (757) 686.1055

102 Fairview Dr, Suite E  
Franklin, VA 23851  
(757) 569.9709  
FAX (757) 569.6102

300 Medical Parkway, Suite 314  
Chesapeake, VA 23320  
(757) 549.4403  
FAX (757) 549.4332

150 Burnett's Way, Suite 310  
Suffolk, VA 23434  
(757) 539.0670  
FAX (757) 539.1062

### *Peninsula*

895 Middle Ground Blvd, Bldg 200  
Newport News, VA 23606  
(757) 873.9400  
FAX (757) 873.9420

3000 Coliseum Dr, Suite 104  
Hampton, VA 23666  
(757) 827.9400  
FAX (757) 827.9320

3901 Treyburn Dr, Suite 2A  
Williamsburg, VA 23185  
(757) 229.2236  
FAX (757) 221.0409

6876 Main Street  
Gloucester, VA 23061  
(804) 693.3232  
FAX (804) 693.3342

### *North Carolina*

1503 B North Road St.  
Elizabeth City, NC 27909  
(252) 331.2044  
FAX (252) 331.1909

5565 Croatan Highway  
Kitty Hawk, NC 27949  
(252) 261.5800  
FAX (252) 261.5301

### *Central Business Office*

5900 Lake Wright Dr, Suite 300  
Norfolk, VA 23502  
(757) 213.5700  
FAX (757) 213.5701  
TOLL FREE (800) 998.3450

## Web Address

[www.virginiacancer.com](http://www.virginiacancer.com)



Virginia  
Oncology Associates

June 8, 2207

Center of Medicare and  
Medicaid Services

To Whom It May Concern:

Re: Use of ESAs

I am currently in the practice of Hematology/Oncology in the Eastern Virginia area. I have been in practice since completion of my hematology/oncology fellowship in 1984. I am very concerned about CMS' recent limitations under consideration for the use of ESA. First of all, the use of ESA has dramatically improved the quality of life for many of my patients and has also dramatically reduced the need for transfusions. I think the avoidance of transfusions is always a good idea. I take particular exception to the idea presented by CMS that transfusions are safer than ESAs. Transfusions, while safer now than they were 10 or 15 years ago still pose considerable risks to our patients. There is the risk of alloimmunization. Despite careful testing, there continues to be risk for HIV and hepatitis exposure as well as the possibility of exposure to a number of other infectious agents, some that may not even have been detected yet. Independent of alloimmunization and infectious concerns, there are also the issues of chronic iron overload, volume overload and other reactions to red cell transfusions. It certainly does not provide a safer and more effective way of managing low hemoglobin.

Additionally, to wait until hemoglobin is less than 9 seems inadequate since improvement in well-being at a hemoglobin of 10-11 is remarkable and allows many of my patients to continue to be productive citizens. Also a maximum treatment of 12 weeks a year is inadequate for most patients.

Many patients with metastatic disease now will receive chemotherapy almost continuously during that period of time and need support to be able to tolerate those therapies.

Myelodysplastic syndrome should continue to be covered. These patients require lengthy support and are usually older where transfusions provide more serious side effects. It is also very useful to have ESAs in patients practicing Jehovah's Witnesses since their religious faith precludes the use of blood products.

I also agree with the concerns the Red Cross has in terms of the availability of blood supply if we should return to transfusions for all of these patients. Blood is a very valuable commodity and there is currently no substitute for patients who are bleeding due to trauma or surgery and there are already serious limitations on that supply. The reduction in the use of ESAs would further put a strain on that system.

I am also concerned about CMS' restriction based on the perceived erythropoietin receptors on certain tumor types. As yet, there is no convincing clinical data that those receptors are of any clinical significance.

I am very concerned about the future of my patients with these drastic cuts in the use of ESAs in their care and I respectfully request that you strongly reconsider these measures.

Sincerely,

  
ELIZABETH A. HARDEN, M.D.

EAH/mm



FRED S. MARCUS, MD, AND ASSOCIATES

A PROFESSIONAL CORPORATION

*Internal Medicine, Hematology, and Medical Oncology*

Fred S. Marcus, MD  
Shane P. Dormady, MD, PhD  
John A. Hayward, MD  
Debra D. St. Claire, MD  
Peggy Ross, RNP, MS

2940 Whipple Avenue, Suite B • Redwood City, California 94062  
(650) 216-8300 Telephone (650) 216-8401 Facsimile

Sherri Garoutte, RN, OCN  
Diana Goodenough, RN, OCN  
Theresa Koettters, RN, MS

June 5, 2007

Steve Phurrough, MD, MPA

Elizabeth Koller, MD, FACE

Maria Ciccanti, RN

Coverage Analysis Group  
Office of Clinical Standards and Quality  
Centers for Medicare and Medicaid Services  
Mail Stop C1-12-28  
7500 Baltimore, MD 21244-1849

Re: Comment Regarding Changes in Medicare Policy re: Erythropoiesis Stimulating Agents (ESAs) for  
Non-renal Disease Indications (CAG-00383N)

Thank you for inviting comment regarding your proposed changes in Medicare policy re: ESAs. I have been in the practice of Medical Oncology for over 25 years, treating patients with a broad spectrum of malignancies and blood disorders. I agree that growth factors have made a huge (positive) difference in our treatments and I agree that there is a need for national coverage standards as well as a rational, evidence-based response to FDA warnings about ESAs (and all drugs).

It is my experience that both darbepoetin alfa and epoetin alfa have equal efficacy in treating selected forms of anemia and I believe that CMS should therefore establish the same list of indications to support medical necessity. This list should include all indications where evidence shows that ESAs are safe and effective.

I believe that Quality of Life, reduced morbidity and side effects secondary to our antineoplastic therapies, and transfusion avoidance are relevant, important endpoints for patients living with cancer. Transfusions carry both expense (cost of blood, blood bank personnel time, nursing time, transfusion bed time, and the patient's time) and considerable risk (of reactions, HIV, and Hepatitis).

I disagree with discontinuing ESAs for failure to achieve a 1 g/dl Hemoglobin increase in four weeks; I do not believe that this is evidence-based. Clinical studies consistently show that the optimal response takes 8 – 12 weeks to occur.

Neither darbepoetin alfa nor epoetin alfa reliably achieves and increase of 1 g/dl in 4 weeks at standard doses. Standard doses usually require 5 – 7 weeks for 1 g/dl response.

I believe that there must be a provision for dose escalation in non-responders – it has been the standard of care of ten years to dose escalate in non-responders at 6 – 8 weeks. There has been no evidence showing a safety risk associated with dose escalation.

I agree with restricting the use of ESAs in most people who have a hemoglobin level of > 12 g/dl. Trials that pushed hemoglobin above the limit (in the hopes of improving patients' response rates to treatment) showed an increased risk of thrombotic events, clearly not in the patients' best interest. However, in patients who are currently undergoing chemotherapy, who have a hemoglobin level of 12.0 or 12.1 and who will be receiving myelosuppressive treatments within the next week, should receive ESAs with the goal of keeping the hemoglobin at the 12.0 g/dl level.

I disagree with your suggested change to not cover multiple myeloma, MDS, and chronic anemia of cancer. Transfusion avoidance is as important for people who are currently not receiving chemotherapy (such as people multiple myeloma, myelodysplastic syndromes, or metastatic cancers) as for those who are receiving chemotherapy. Studies that showed significant and life-threatening events in certain patients who have taken ESAs for non-renal diseases, do not appear to have included any patients with bone marrow failure (such as MDS). Most patients with MDS are elderly; many have comorbidities that make alternative treatments such as chronic transfusions and aggressive chemotherapy, very risky. ESAs have been found to be safe and beneficial (therapeutic as well as supportive) in all subtypes of MDS.

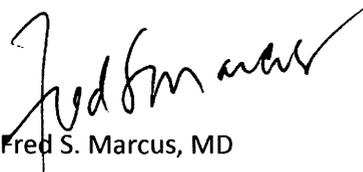
I disagree with a 12 week maximum allowance for ESA usage. When the original studies that formed the basis for FDA approval of ESAs in chemo-related anemia were done, they were done with a 12 week course of chemotherapy. In the last 20 years, the duration of antineoplastic therapies has increased due to the availability of supportive agents as well as the number of active agents available. For patients undergoing first, second, and third line regimens lasting even 6 -12 months in a given year, the 12 week maximum allowance is grossly inadequate. Also, there is no evidence suggesting that the use of ESAs for more than 12 weeks is associated with more safety issues (as there is with greatly elevated hemoglobin levels).

I disagree with your proposed non-coverage ESAs in patients receiving VEGF or EGFR inhibitors. These agents are known to induce anemia and are often given with other anemia-inducing regimens. There is no evidence that ESA usage antagonizes the therapeutic effect of VEGF/EGFR inhibitors.

In summary, I believe that the benefits of ESAs have been demonstrated in the literature in over 2000 patients, correcting anemia and reducing transfusion rates. While cancer patients' quality of life, functionality, and general well-being are greatly improved by maintaining hemoglobin concentrations near 12 g/dl, there is no evidence that transfusions are safer or more effective than ESA use in patients with Hemoglobin levels between 9 – 11. Your proposed changes could increase the blood demand by 20% and could risk depletion of the national blood supply.

**I strongly recommend that you approve use of ESAs:** 1) to be started at Hgb < 11 g/dl, 2) that dose escalation be allowed, 3) that treatment be held with Hgb > 12 and treatment be restarted as soon as Hgb subsequently drops below 12, 4) include coverage for MDS and Multiple Myeloma, 5) maintain coverage for patients receiving VEGF and EGFR inhibitors, and 6) coverage be continued for as long as chemo-induced anemia continues up to 12 weeks after chemotherapy is concluded. Thank you for inviting my comments.

Sincerely,



Fred S. Marcus, MD

FSM:sdg

Heme/Onc Phone: (724) 983-5900  
FAX: (724) 981-6205

Radiation Onc Phone: (724) 983-5905  
FAX: (724) 981-6206

**CANCER CARE CENTER**  
**Sharon Regional Health System**  
2320 Highland Road  
Hermitage, Pennsylvania 16148

**Hematology/Oncology**  
**Radiation Oncology**

06/04/2007

**COVERAGE ANALYSIS GROUP**  
**OFFICE OF CLINICAL STANDARDS AND QUALITY**  
**CENTERS FOR MEDICARE AND MEDICAID SERVICES**  
**Mailstop C1-12-28 7500 Baltimore, Maryland 21244-1849**

**ATTENTION: Steve Purrough, MD, MPH**  
**Elizabeth Koller, MD, FACE**  
**Maria Ciccanti, RN**

To Whom It May Concern:

I am writing to you on behalf of the Cancer Care Center of Sharon Regional Health System. I am writing in regards to the proposed national coverage determination for ESA coverage as released by CMS on May 14, 2007. While I am obviously very supportive of the concept of an NCD for these important agents, I share the concern of my colleagues across the country that the proposed NCD would reflect a significant coverage limitation that does not appear to be based on current scientific data. In addition, as supported by The American Society of Clinical Oncology, The American Society of Hematology, and the NCCN, several limitations seem to conflict with the current standard of care in this country.

Specifically, I believe that the criteria setting a hemoglobin of less than 9 grams as a treatment initiation point is inadequate. There is plenty of evidence to suggest that transfusion avoidance is better accomplished by an early intervention at a higher hemoglobin level, with a target of less than 11 grams superior to less than 10 grams by measures in at least six randomized clinical studies. Furthermore, I also believe that the "stopping rule" for a gram or less rise in hemoglobin at four weeks is not consistent with clinical trial data, which clearly demonstrates that a six to eight week interval may be required to achieve this one gram rise in hemoglobin. Furthermore, a maximum duration treatment of 12 weeks per year is inadequate for most of my patients. Please recognize that patients with metastatic cancer may be receiving multiple courses of chemotherapy and may last for many months longer than the 12 weeks. Finally, arbitrary exclusion of patients receiving VEGF, EGFR, and other critical patient subgroups does not appear to be supported by clinical evidence. In my personal experience, some of the most dramatic improvements both in hemoglobin responses and in quality of life were seen among patients with multiple myeloma and MDS.

Obviously, this issue is of significant relevance to practitioners in the field of medical oncology and hematology. I do appreciate your hard work at trying to come up with appropriate guidelines for the safe and appropriate use of this class of drugs. Nevertheless, I do hope that you will strongly reconsider the proposed NCD to accommodate the practical use of these drugs in clinical experience.



GEORGE C. GARROW, M.D.

GCG/mb D: 06/04/2007 3:00 P/T: 06/09/2007 11:53 A

cc: GEORGE C. GARROW, M.D.  
LINDA LOGUE  
JOHN ZIDANSEK

**ORIGINAL**

014

1 Orfordville Road  
Lyme, NH 03768  
gibb@dartmouth.edu

June 4, 2007

Maria Ciccanti, RN  
Lead Analyst  
Centers for Medicare and Medicaid Services  
7500 Security Boulevard  
Baltimore, MD 21244

RE: NCA Tracking Sheet for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N)

Dear Ms. Ciccanti:

I am writing in response to the decision of CMS to consider discontinuing financial support for patients receiving ESAs (erythropoietin and darbepoietin) for MDS. These patients experience gradually falling hemoglobin with or without a diminution of platelet count and WBC. ESAs are the first line of therapy for most patients with low-risk MDS, in terms of overall response rate and 2-year survival (1). About 40% of patients will respond to ESAs with a gradual rise in Hgb. Equally important, ESAs, such as Procrit, cause few side effects in MDS, as long as the Hgb is not raised above 12 g%. Under these circumstances, the risk of thrombosis is not increased. Many patients with MDS depend on ESAs to live a transfusion-free existence. Given the risks and time requirements inherent in regular transfusions, those of us who care for these patients strongly urge that ESAs not be removed from those drugs reimbursed by Medicare and Medicaid.

Sincerely yours,



Gibbons G. Cornwell III, MD  
Professor of Medicine Emeritus  
Section of Hematology and Oncology  
Dartmouth Medical School  
Lebanon, NH 03756

1. Br. J. Haematol 2007 Apr;137(2) : 125-32



● HEMATOLOGY & ONCOLOGY  
BOBBY L. GRAHAM, JR., M.D., FACP  
GERRY ANN HOUSTON, M.D., FACP  
VAN L. LACKEY, M.D., FACP  
MARTIN M. NEWCOMB, M.D.  
MANU S. PATEL, M.D.  
GUANGZHI QU, M.D., PhD.  
GRACE G. SHUMAKER, M.D.  
BOBBY S. WILKERSON, M.D.  
TAMMY H. YOUNG, M.D.

June 13, 2007

Coverage Analysis Group  
Office of Clinical Standards and Quality  
Centers for Medicare and Medicaid Services  
Mail Stop C1-12-28  
7500 Security Boulevard,  
Baltimore, MD 21244

**RE: Comments on Proposed National Coverage Determination for Erythropoietin Stimulating Agents (ESAs) CAG-00383N**

As a practicing medical oncologist and hematologist, I would like to comment on several points addressed in the proposed national coverage determination for erythropoietin stimulating agents (ESAs). In addition to the points addressed below, I am concerned about the blood supply in the state of Mississippi. We already have a shortage of blood products that affects the treatment of my patients. Restricting the use of ESA therapy for our MDS patients and waiting to start ESA therapy until the patient has a Hg below 9 will cause my patient population to need significantly more transfusions. With the blood supply already at a critical level, I am concerned that this NCD may endanger my other patients who already rely on this short supply.

Erythropoietin stimulating agents have been used to treat the anemia of myelodysplastic syndrome (MDS) for many years now. This is an accepted use and has been supported by our Local Medicare Coverage Determinations for many years. Scientific literature dating back to 1991 has shown ESAs to be safe, despite very high doses given to MDS patients (Stein, Abels, Krantz 1991). A special article summarizing the "evidence based clinical practice guidelines" of the American Society of Clinical Oncology and American Society of Hematology stated that the use of ESAs were supported for patients with myelodysplastic syndrome (Rizzo 2002). Denying coverage for ESA therapy for this patient population will be detrimental to the health of patient.

Both drugs have FDA approved dose schedules that exceed the limitation suggested in the coverage memo. Aranesp, for example, has a Q3 week dose schedule that would require a patient to receive 500 mcg every three weeks. In a month where a patient receives their Aranesp on week 1 and week 4 of the month the dose will be a total of 1000 mcg during the month. Procrit has a once weekly dose of between 40,000 and 60,000 units per week. A patient that receives 60,000 units per week will receive 300,000 units during a month that the patient happens to come in on 5 Mondays, for example. The FDA approved dose for both of these drugs exceeds the dose limitation suggested by CMS.

1227 NORTH STATE STREET • SUITE 101 • JACKSON, MS 39202 • 601.355.2485  
2969 CURRAN DRIVE NORTH • SUITE 200 • JACKSON, MS 39216 • 601.974.5600  
1860 CHADWICK DRIVE • SUITE 301 • JACKSON, MS 39204 • 601.373.4421  
2368 GROVE STREET • VICKSBURG, MS 39180 • 601.638.3447

108

As a board certified medical oncologist, I prescribe and oversee the administration of many drugs that require intense safety monitoring for drug toxicity and severe anaphylactic reactions. All of these drugs require informed consent and safety monitoring. All patients in our clinic receive informed consent before beginning treatment. It is also extreme to suggest that a patient being treated in a rural clinic be forced to travel hundreds of miles to the nearest facility participating in a clinical trial. Creating a policy that would require an anemic patient to travel to receive ESAs would be unfair to the patient.

Both FDA approved package inserts state that patients should be started on therapy when their Hg is at least 10. Most carriers now support the use of ESAs starting at a Hg of 11 so that therapy can be started to keep the patient from dropping to a Hg of 10 or 9. The objective is to remove the need for transfusion. It takes some time for my patients to respond to the ESA and waiting initiate treatment will result in clinical outcomes that are undesirable for the patient, including transfusions and clinical risks and symptoms associated with severe anemia. I have been able to start patients at a Hg of 11 for several years now and have noted that our patients require less medication to reach the target Hg of 12 (I hold ESA treatment at 12 per FDA guidelines and have for many years). Many studies regarding the use of ESA therapy have been published and very few even suggested waiting until the patient reached a Hg of 9. The National Comprehensive Cancer Network expert consensus panel cites multiple randomized studies that support the initiation of ESAs at hemoglobin levels less than 11g/dL.

A cancer patient receiving a long cycle of chemotherapy over 6 months or multiple cycles of chemotherapy could need ESA treatment for the entire cycle of chemotherapy. Patients treated for chemo induced anemia must also be treated long enough for the bone marrow to recover. It takes some older individuals longer to achieve this recovery of the bone marrow, so it is even more vital for these patients to receive their ESA treatment until it is no longer medically necessary.

If you need any additional information regarding these comments, please contact my office at 601-974-5600.

Sincerely,



Guangzhi Qu, MD, PhD

1. Rizzo JD, Lichtin AE, Woolf SH, et al. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology (ASH). *Blood* 2002; 100(7):2303-20.
2. Stein RS, Abels RI, Krantz SB. Pharmacologic doses of recombinant human erythropoietin in the treatment of myelodysplastic syndromes. *Blood* 1991; 78(7): 1658-63.
3. Thompson JA, Gilliland DG, Prchal JT, et al. Effect of recombinant human erythropoietin combined with granulocyte/macrophage colony-stimulating factor in the treatment of patients with myelodysplastic syndrome. *Blood* 2000;87(10): 4067-81.

Health Net, Inc. applauds CMS on their reassessment of erythropoiesis stimulating agents (ESAs) in the treatment of anemia in cancer patients who are undergoing chemotherapy, as well as other non-cancerous conditions. ESAs have for a long time been touted as effective at increasing hemoglobin concentrations, reducing the need for transfusion, and improving quality of life, tumor progression, and survival. Yet, studies of ESA use in patients with cancer in the last five years have shown that these outcomes do not improve in all patients, and in some they worsen. Notwithstanding the fact that these research studies titrated ESAs at a higher than recommended dose (e.g., 40,000 IU every week) to overcorrect anemia to normal hemoglobin levels (e.g., 12 to 14 g/dL), all of these trials were terminated once it was realized that subjects treated with ESAs were having poorer clinical outcomes than placebo. Moreover, there is no way of predicting how individual patients will be affected, who should and should not use the drug, or even what dose to prescribe. Such fundamental issues need to be resolved, and urgently. Despite the addition of new black box warnings were added to the labeling, we are pleased that CMS has taken action to consider the totality of the evidence to date and consider what's best for patients by issuing this Proposed Decision Memo to seek public comment regarding the exact settings for future use of ESAs. It is fitting at this time for CMS to state publically their revised guidelines and seek feedback from Managed Care Organizations and Health Plans.

## **Health Net's Current Indications And Usage Guidelines**

### **EPOGEN**

Patient is diagnosed with ONE of the following:

- Anemia of chronic renal failure (CRF) (both dialysis and non-dialysis patients)
- Zidovudine (AZT) therapy induced anemia
- Chemotherapy-induced anemia
- Surgery patients at high risk for perioperative allogeneic blood transfusions with significant, anticipated blood loss during elective, noncardiac, nonvascular surgery (typically pre-operative use for hip or knee surgery), and patient is not a candidate for autologous blood donation
- Patient is on combination therapy (pegylated interferon and ribavirin) for treatment of hepatitis C to maintain the recommended ribavirin dose through the first 20 weeks
- Myelodysplastic syndrome with erythropoietin < 500 mU/ml

AND

Hematocrit (Hct) and hemoglobin (Hgb) values prior to initiation of therapy are:

- Cancer, myelodysplastic syndrome, anemia of CRF, or zidovudine-treated patients: hematocrit (Hct) < 33% or hemoglobin (Hgb) < 11 gm/dL
- Patients undergoing surgery: Hct range 30%-39% or Hgb range 10 gm/dL-13 gm/dL
- Hepatitis C patients on combination therapy: Hct < 30% or Hgb < 10 gm/dL

AND

155

Documentation of adequate iron stores drawn within 60 days of the request must be submitted prior to initiation of therapy and when Aranesp dose is increased (Transferrin saturation should be greater than or equal to 20% and Ferritin greater than or equal to 100 ng/ml).

AND

Documentation of iron supplementation

**Further information:**

Epoetin is contraindicated in patients with uncontrolled hypertension.

The following new boxed warning was added to Erythropoietin Stimulating Agents (ESAs) prescribing information, when administered to target a hemoglobin of greater than 12 g/dL:

- Increased the risk for death and for serious cardiovascular events;
- Shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy; and
- Shortened overall survival and increased deaths attributed to disease progression at four months in patients with metastatic breast cancer receiving chemotherapy.
- The new boxed warning also states that ESAs increased the risk of death when administered to target a hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for this population. In addition, for patients receiving ESAs pre-operatively for reduction of allogeneic blood transfusions, a higher incidence of deep venous thrombosis was documented in patients receiving Epoetin alfa who were not receiving prophylactic anticoagulation. Aranesp is not approved for this indication.

### **Dosing Regimen**

**Anemia in Chronic Renal Failure:**

- Dosage should be adjusted to maintain a target hemoglobin not to exceed 12 gm/dL.
- If the Hgb increases by more than 1.0 gm/dl in a 2-week period, the dose should be decreased by approximately 25%.
- If the increase hemoglobin is less than 1 gm/dL over 4 weeks and iron stores are adequate, the dose of Aranesp may be increased by approximately 25% of the previous dose. Further increases may be made at 4-week intervals until the specified hemoglobin is obtained.

**Anemia in Chemotherapy-induced Anemia:**

- If Hgb increase is < 1 gm/dL after 6 weeks of therapy, the dose should be increased up to 4.5 mcg/kg.
- If the Hgb increases by more than 1.0 gm/dL in a 2-week period, the dose should be decreased by approximately 25%.

- If the Hgb exceeds 13 g/dL, doses should be temporarily withheld until Hgb falls to 12 g/dL. Therapy should be reinitiated at a dose approximately 25% below the previous dose.

## **ARANESP**

Patient is diagnosed with **one** of the FDA-approved indications:

- Treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis; or
- Treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy

AND

Hematocrit (Hct) and hemoglobin (Hgb) values prior to initiation of therapy: Hct < 33% or Hgb < 11 gm/dL

AND

Documentation of adequate iron stores drawn within 60 days of the request must be submitted prior to initiation of therapy and when Aranesp dose is increased (Transferrin saturation should be greater than or equal to 20% and Ferritin greater than or equal to 100 ng/ml).

AND

Documentation of iron supplementation

AND

Failure or clinically significant adverse effects to Procrit

### **Further Information:**

The following new boxed warning was added to Erythropoietin Stimulating Agents (ESAs) prescribing information, when administered to target a hemoglobin of greater than 12 g/dL:

- Increased the risk for death and for serious cardiovascular events; and
- Shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy; and
- Shortened overall survival and increased deaths attributed to disease progression at four months in patients with metastatic breast cancer receiving chemotherapy; and
- The new boxed warning also states that ESAs increased the risk of death when administered to target a hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for this population. In addition, for patients receiving ESAs pre-operatively for reduction of allogeneic blood transfusions, a higher incidence of deep venous

thrombosis was documented in patients receiving Epoetin alfa who were not receiving prophylactic anticoagulation. Aranesp is not approved for this indication.

## **Dosing Regimen**

### **Anemia in Chronic Renal Failure:**

- Dosage should be adjusted to maintain a target hemoglobin not to exceed 12 gm/dl.
- If the Hgb increases by more than 1.0 gm/dl in a 2-week period, the dose should be decreased by approximately 25%.
- If the increase hemoglobin is less than 1 gm/dl over 4 weeks and iron stores are adequate, the dose of Aranesp may be increased by approximately 25% of the previous dose. Further increases may be made at 4-week intervals until the specified hemoglobin is obtained.

### **Anemia in Chemotherapy-induced Anemia:**

- If Hgb increase is < 1 gm/dL after 6 weeks of therapy, the dose should be increased up to 4.5 mcg/kg.
- If the Hgb increases by more than 1.0 gm/dl in a 2-week period, the dose should be decreased by approximately 40%.
- If the Hgb exceeds 13 gm/dl, doses should be temporarily withheld until Hgb falls to 12 gm/dl. Therapy should be reinitiated at a dose approximately 40% below the previous dose

# SOUTH CAROLINA ONCOLOGY SOCIETY

June 11, 2007

**President:**

James D. Bearden, III, M.D.  
(Spartanburg)

**President-Elect:**

Elizabeth Christian, M.D.  
(Charleston)

**Secretary/Treasurer:**

Eric Nelson, M.D.  
(Spartanburg)

**Immediate Past-President:**

Darren E. Mullins, M.D.  
(Georgetown)

**Members at Large:**

Neal Christiansen, M.D.  
(Columbia)

Drew Monitto, M.D.  
(Spartanburg)

Steve Phurrough, MD, MPA  
Coverage Analysis Group  
Centers for Medicare & Medicaid Services  
Department of Health and Human Services  
7500 Security Blvd., Mailstop: C1-13-18  
Baltimore, MD 21244

Dear Dr. Phurrough:

RE: Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for Non-Renal Disease Indications (CAG-00383N).

On behalf of over 300 members of the South Carolina Oncology Society, I am writing to convey our comments and concerns regarding the Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for Non-Renal Disease Indications (CAG-00383N).

Our society realizes there are safety concerns regarding the use of ESAs. However, the proposed coverage decision inappropriately restricts the use of ESAs because a number of the proposals are not supported by scientific evidence based data. The proposals rely on poor quality data, or are in conflict with expert scientific analysis or recommendations from the American Society of Hematology and the American Society of Clinical Oncology. There is also no clinical evidence of EPO receptor involvement in tumor progression. Linking ESA use in patients with certain types of cancer is not evidence based. Finally, the proposed policy does not take into consideration recommendations by the FDA's Oncology Drug Advisory Committee during a May 10<sup>th</sup> meeting.

The South Carolina Oncology Society is especially concerned about the exclusion of use of ESAs with treatment of anemia due to myelodysplasia (MDS). There is evidence to support the use of ESAs in a significant number of patients with anemia associated with MDS to decrease the need for blood transfusions. Unfortunately, there are few effective treatment options for MDS. Denial for coverage for ESAs will deprive patients with MDS of an effective therapy for their illness, one on which many of them already depend.

All of us are dismayed by other aspects of the coverage decision which are arbitrary, premature, and not based on evidence based medicine or scientific data. These include the maximum coverage duration of 12 weeks per year, which is not adequate either for patients who are undergoing chemotherapy or for those with anemia due to MDS. The proposal of not starting ESA therapy when hemoglobin is less than 9 grams per deciliter in the absence of cardiovascular disease will greatly enhance the risks of blood transfusion and decrease the quality of life.

The maximum four week dosage limits are inadequate, as is the limit of four weeks of treatment while awaiting response. Most national studies have demonstrated that it takes at least eight weeks. In addition, as a result of this NCD, an additional strain will be placed on the Nation's blood supply.

The State of South Carolina has a very large population of Medicare beneficiaries. Coverage decisions which resemble the above decision affect a very significant portion of our patients. Our State Society is committed to ensuring that cancer patients have access to the entire continuum of quality cancer care, including access to the most appropriate cancer therapies in the most appropriate settings. It is our thought that the under use of appropriate therapies is as detrimental as over use. Coverage decisions should be guided by the best available scientific evidence and should adhere to guidelines created through sound quality based clinical trials. The recommendations of the American Society of Hematology and the American Society of Clinical Oncology provide these guidelines. Therapy should be based on the highest degree of patient access, safety and efficacy and not based solely on economic considerations.

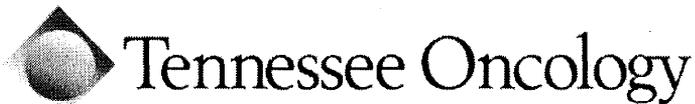
Your consideration in this matter and reversal of this decision or creation of a more appropriate proposal is desperately needed.

Sincerely,



James D. Bearden, III, MD  
President

Jdb/kst



Stuart C. Spigel, M.D.  
Charles E. McKay, M.D.  
Eric L. Raefsky, M.D.  
E. Anthony Greco, M.D.  
John D. Hainsworth, M.D.  
Anthony A. Meluch, M.D.  
Dana S. Thompson, M.D.  
Michel E. Kuzur, M.D.  
Fernando T. Miranda, M.D.  
Nancy W. Peacock, M.D.  
Jeffrey F. Patton, M.D.  
Howard A. Burris III, M.D.  
John H. Barton Jr., M.D.  
Mainuddin Ahmed, M.D.  
Mitchell A. Toomey, M.D.  
Victor G. Gian, M.D.  
Adil I. Mohyuddin, M.D.  
Dianna L. Shipley, M.D.  
William H. Liggett Jr., M.D.  
Rohit R. Patel, M.D.  
Lester L. Porter III, M.D.  
Natalie R. Dickson, M.D.  
Denise A. Yardley, M.D.  
Mark G. Mainwaring, M.D.  
Kirk Barnes, M.D.  
Habib Doss, M.D.  
David R. Spigel, M.D.  
James D. Peyton, M.D.  
John D. Zubkus, M.D.  
Laura F. McClure-Barnes, M.D.  
R. Seth Cooper, M.D.  
Alan G. Cohen, M.D.  
W. Charles Penley, M.D.  
Patrick B. Murphy, M.D.  
Ruth E. Tamar, M.D.  
Jia Bi, M.D.  
Jamie K. Waselenko, M.D.  
Ian W. Flinn, M.D.  
Kent C. Shih, M.D.  
Jeffrey R. Infante, M.D.

Health Psychologists  
Amy Johnson, Ph.D.  
Sherian Anderson, Ph.D.

**Southern Hills Medical Center**  
397 Wallace Road, Suite C-201  
Nashville, Tennessee 37211  
(615) 333-2481  
Fax (615) 781-3923

Baptist Medical Building  
Nashville, TN • (615) 329-0570

Centennial Medical Center  
Nashville, TN • (615) 320-5090

Gateway Medical Center  
Clarksville, TN • (931) 906-2004

Lebanon, TN • (615) 453-5623

Middle Tennessee Medical Center  
Murfreesboro, TN • (615) 848-0488

Skyline Medical Center  
Nashville, TN • (615) 860-1556

St. Thomas Hospital  
Nashville, TN • Ste. 707 (615) 385-3751

Summit Medical Center  
Hermitage, TN • (615) 871-9996

Sumner Regional Medical Center  
Gallatin, TN • (615) 451-5481

TN Oncology P.E.T. Services  
Nashville, TN • (615) 320-7387

Tennessee P.E.T. Scan  
Murfreesboro, TN • (615) 890-5858

Tullahoma, TN • (931) 393-3143

May 24, 2007

Steve Phurrough, MD, MPA  
Director, Coverage and Analysis Group  
Centers for Medicare and Medicaid Services

Re: Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for Non-Renal Disease Indications (CAG-00383N).

I am writing on behalf of the 40 medical oncologist group Tennessee Oncology, but more importantly on behalf of the patients for whom we care regarding the Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for the Non-Renal Disease Indications (CAG-00383N).

We have followed with great interest the recent publications suggesting a possible safety signal for the ESA class. Our evaluation shows that of the 7 publications (5 in oncology patients) in every publication with a safety concern, ESAs were used in a method that is outside the norm for how these agents are used in the community oncology setting. These studies either investigated the use of ESAs with a high hemoglobin target or investigated the use in patients with cancer not undergoing chemotherapy and near the end of life, neither of which is a standard practice in community oncology. The standard of care in the community is to follow accepted national clinical guidelines such as those published by ASCO and NCCN.

Upon review of the significant literature, we are unable to find any suggestion of a safety signal when these agents are used while following these accepted clinical guidelines. There is actually a large literature, including pooled analysis that would strongly suggest that these agents are indeed safe when used according to widely accepted guidelines. In view of these data, it seems less than reasonable to extrapolate a safety signal seen in an experimental setting that does not apply to current clinical practice. Our assessment shows that the limitations listed in the proposed NCD are not supported by the available science.

In addition, there are aspects of the proposed NCD that appear completely arbitrary. There is no literature to support limiting initiation of ESA to hemoglobin of 9 but there is literature that shows the risk of requiring a transfusion goes up the lower the initiation hemoglobin, with an initiation level of 11 appearing to be optimal. Likewise, there is no data to support an arbitrary 12 week limit to therapy. Review of the 7 publications showing a safety signal does not reveal a relationship between length of exposure to ESA and safety, so we are unable to find a scientific explanation for these recommendations. ESA therapy has been recognized as a standard of care for myelodysplasia (MDS) by national guidelines (ASCO, ASH, and NCCN) for years. We were unable to identify any safety concerns in any of the MDS literature. It is not clear to us what justification one would propose to change the standard of care for this disease.

As practicing oncologists, we have all experienced a significant improvement in the quality of life for our cancer patients since the advent of ESAs. Anyone who would deny that there is significant improvement in the quality of life of a patient who has an improvement in their baseline hemoglobin from 10 or 11 to 12 has certainly not cared for patients in the oncology setting. These agents make a significant impact on our patient's lives and we feel that limiting our patient's access to these life improving agents would be tragic. As oncologists, we spend our entire careers making risk benefit decisions. Based upon our review of the literature and our greater than 10 years of experience, we feel the benefits greatly outweigh the risks to ESA use to the majority of our patients with anemia. To suggest that CMS is better positioned to judge this risk benefit decision is objectionable to our medical professionals.

We ask that your final NCD be based upon the available scientific evidence and allow us to continue to follow our evidence based national treatment guidelines.

Sincerely,

Jeff Patton, MD  
Chief Medical Officer  
Tennessee Oncology

**Other Clinics:** Ashland City, TN • Carthage, TN • Dickson, TN • Fayetteville, TN • Franklin, TN  
Hendersonville, TN • Lawrenceburg, TN • Manchester, TN • McMinnville, TN

Pulaski, TN • Shelbyville, TN • Smithville, TN • Smyrna, TN • Springfield, TN • Waverly, TN • Winchester, TN

156

# NEW ENGLAND HEMATOLOGY/ONCOLOGY ASSOCIATES, P.C.

*Timothy P. O'Connor, M.D. Jeffrey S. Wisch, M.D.  
Caroline C. Block, M.D. Marcia J. Browne, M.D. Brenda E. Haynes, M.D.*

---

May 25, 2007

Steve Phurrough, MD, MPA  
Director, Coverage and Analysis Group  
Centers for Medicare and Medicaid Services  
7500 Security Boulevard  
Baltimore, MD 21244

Re: Proposed Decisions Memo for Erythropoiesis Stimulating Agents for Nonrenal Disease Indications (CAG-00383N)

Dear Dr. Phurrough:

This letter is being written on behalf of the members of the Massachusetts Society of Clinical Oncologists to convey our concerns regarding the proposed decision memo for erythropoiesis stimulating agents (ESAs) for nonrenal disease indications (CAG-00383N).

As medical oncologists we are acutely aware that patient safety must be foremost in the treatment of disease. We also believe that in as much as possible, scientific data is required to support safety and efficacy of drugs which are used in the market place. When evaluating drugs, there is always a risk/benefit profile, which needs to be studied prior to the use of a drug. With regards to the use of ESAs, however, we feel that the proposed restrictions of their use has not been based upon quality data and in many cases is in conflict with scientific data supporting the use of ESAs in patients with hematological or oncological illnesses. We are concerned that the proposed decision memo for ESAs is too harsh in restricting ESAs as proposed. This, we believe, will have a pejorative effect on a very large number of patients whose quality of life will be severely altered.

Limiting the use of ESAs in patients with underlying myelodysplastic syndromes (MDS) and restrictions in the treatment of anemia secondary to neoplasia or chemotherapy will place a huge burden on our blood banks, and they are already overburdened. There is significant data, particularly in the case of MDS that has demonstrated ESAs as an effective therapy for the illness, wherein many cases no other therapy is available. In addition, restricting the use of ESAs for patients undergoing chemotherapy will also have a detrimental effect in that quality of life is often the key issue in treating patients with underlying cancer.

We feel that the decisions which you have proposed are arbitrary and are not based on scientific data. Although we agree it is vitally important to make sure treatments are safe, it is equally as important to make certain that patients are not deprived of treatments which have been proven to be effective and safe when used appropriately.

May 25, 2007

Re: Proposed Decisions Memo for Erythropoiesis Stimulating Agents for Nonrenal Disease Indications  
(CAG-00383N)

Page 2

Like many states, Massachusetts has a very large population of Medicare beneficiaries, and we are concerned that your coverage decision has not been well studied, given the huge impact it will have if the policy is changed. We ask that you reconsider the importance of the use of ESAs in patients with underlying hematological and oncological diseases and not develop a policy until this situation has been well studied and commented upon by experts in the hematology and oncology community.

Sincerely,

Jeffrey S. Wisch, MD  
Member Board of Directors  
Massachusetts Society of Clinical Oncology

JSW/gm

**Ciccanti, Maria L. (CMS/OCSQ)**

**From:** CMS CAGInquiries  
**Sent:** Tuesday, June 05, 2007 7:30 AM  
**To:** Ciccanti, Maria L. (CMS/OCSQ)  
**Subject:** FW: Public comment on ESA's

**From:** Jenny Jones [mailto:jjones@utahcancer.com]  
**Sent:** Monday, June 04, 2007 2:51 PM  
**To:** CMS CAGInquiries  
**Cc:** Marsha Fetzer  
**Subject:** Public comment on ESA's

Title of NCA/CAL:

Erythropoiesis Stimulating Agents  
 (ESAs) for non-renal disease  
 indications

Public Comment re: Erythropoiesis Stimulating Agents (ESAs) guidelines

As an employee of Utah Cancer Specialists, and patient care advocate, I am concerned about the proposed erythropoietic stimulating agent (ESA) guidelines under consideration. While I understand the need for proper use of these medications, the proposal falls short of providing the best standard of care recommended by oncology organizations such as NCCN, ASCO and ASH. The current proposals will result in a compromised quality of life for our patients, increased blood transfusion requirements with the associated co-morbidity and risk and, ultimately, prove more costly to society than judicious use of ESAs. Please reconsider these guidelines encouraging physicians to carefully weigh the risk/benefit with patients and allow providers to treat this growing population with the best and most compassionate standard of care.

Chemotherapy-induced anemia is a well-known side effect of myelosuppressive therapy. Furthermore it is quite responsive to ESAs when iron stores, vitamin B12 and folate deficiencies and other underlying processes have been corrected. Holding initiation of ESA until the hemoglobin drops to <9mg/dl will delay response and most likely result in transfusion for a greater number of our chemotherapy patients. Most chemotherapy regimens last a minimum of 16 weeks (and many are much longer). Therefore, limiting the covered treatment duration to 12 weeks annually will be inadequate treatment for many of our patients on continued myelosuppressive therapy.

According to the proposed guidelines, the Myelodysplastic Syndrome population will be denied access to any form of ESA under all circumstances. While a portion of the MDS patients will not respond to ESAs, a greater number benefit from these medications; reducing the number of necessary blood transfusions, eliminating the complications of iron overload that results from transfusion, enhanced productivity by limiting time spent in a healthcare facility, and an overall improved quality of life.

We do not dispute the recommendations to discontinue use of the ESAs if the patient is non-responsive to treatment, however:

- The recommended four weeks is an inadequate timeframe in which to evaluate patient responsiveness. Former guidelines allow 12 weeks to determine response. Clearly, four weeks is an irresponsible timeframe.
- The proposed maximum treatment dose is insufficient to provide standard doses within the recommended timeframes. The maximum covered four-week treatment dose is 126,000units of Procrit and 630mcg of Aranesp. At an average dose of 40,000 units of Procrit each week, we would need 160,000 units in four weeks. The average dose of Aranesp is 300mcg per 2 weeks – so the 630mcg would be sufficient.

We encourage you to reconsider the list of specified conditions to include other myeloid and erythroid cancers as well as anemia caused by radiotherapy. Some patients will respond, therefore a trial of an ESA medication seems prudent.

Thank you for your consideration of this request. As a community oncology practice we strive to provide the optimal care to our patients. Please allow us the support we need to continue this practice.

Respectfully,

06/11/2007

168



---

3 Bethesda Metro Center, Suite 508, Bethesda, MD 20814 (301) 656-8877 (800) 327-5183 Fax (301) 656-7133  
www.acoi.org

June 8, 2007

Leslie V. Norwalk, Esq.  
Acting Administrator  
Centers for Medicare and Medicaid Services  
7500 Security Boulevard  
Baltimore, MD 21244-1850

Subject: Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-Renal Disease Indications (CAG-00383N)

Dear Administrator Norwalk:

The ACOI appreciates the opportunity to comment on the Centers for Medicare and Medicaid Services' (CMS) Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-Renal Disease Indications.

The American College of Osteopathic Internists (ACOI), which represents the nation's osteopathic internists and medical subspecialists including oncologists, is dedicated to the advancement of osteopathic internal medicine through excellence in education, advocacy, research and the opportunity for service. To this end, the ACOI strives to advance federal rules and regulations which provide osteopathic internists and medical subspecialists the ability to provide the highest level of quality care to their patients. The Proposed Decision Memo under consideration will impede this ability and negatively effect the quality of cancer care available to Medicare beneficiaries.

The administration of ESAs serves an important role in the treatment of patients with cancer and related conditions. CMS' effort to determine whether there is sufficient evidence to conclude that ESA treatment is not reasonable and necessary for certain clinical conditions is too broad and fails to consider all applicable data. This is evidenced by the fact that the Proposed Decision Memo leaves open the ability of local contractors to make reasonable and necessary determinations for conditions not addressed in the memo. This would set the stage for broad discrepancies in the quality of care available to Medicare beneficiaries across the country. As a result, prior to implementing guidelines that will have negative implications for patient care, CMS should engage in additional reviews of existing studies and of the numerous studies still under way.

A one-size-fits-all approach to cancer treatment, as set forth in the Proposed Decision Memo, does not work and does not necessarily result in better quality care. The provisions set forth in the memo, which would establish strict limits on timing and dosage, do not allow for the necessary flexibility to treat a patient's unique conditions. In fact, some of the guidelines



Leslie V. Norwalk

June 8, 2007

Page 2 of 2

provided for in the memo are counter to readily available clinical trial data. For instance, a 12 week per-year maximum can be inadequate for many conditions and courses of treatment that may be necessary to treat and promote recovery from cancer. To this end, careful consideration must be given to the realities of providing cancer treatment to Medicare beneficiaries.

Implementation of the Proposed Decision Memo will act as a setback to the advancement of cancer care and the care made available to Medicare beneficiaries. ESA treatment allows a physician to effectively manage and treat a cancer patient without a strong reliance on blood transfusions. The reductions in coverage for ESAs will create an increased need for blood transfusions and will subject cancer patients, many of whom already have suppressed immune systems, to a much greater risk of infection and other serious side-effects caused by continual transfusions. ESAs allow cancer patients to live the highest quality of life possible without resorting to antiquated and less effective protocols.

CMS is also seeking public comment on whether coverage for ESA therapy for Medicare beneficiaries with cancer should occur only within appropriately designated clinical research studies where informed consent and safety monitoring can be assured. The ACOI does not support this requirement for Medicare beneficiaries to have access to ESAs. This provision would simply create barriers to care for those who are not able to access "appropriately designated clinical research studies" under the guise of promoting safety monitoring and the attainment of informed consent. There are other ways to accomplish these goals without greatly curtailing the utilization of appropriate ESAs, as determined by the patient and physician.

The ACOI appreciates the opportunity to provide these comments. We look forward to working with CMS in the future on these and other issues of importance impacting the nation's health care delivery system.

Sincerely,

A handwritten signature in black ink, appearing to read "Joanna R. Pease". The signature is fluid and cursive, written over a white background.

Joanna R. Pease, DO, FACOI  
President

C: ACOI Board of Directors  
ACOI Clinical Practice Committee  
ACOI Government Affairs Committee



**Joaquin Duato**  
President

---

Ortho Biotech Products, L.P.  
430 Route 22 East  
Bridgewater, NJ 08807-0914  
(908) 541-4822 Phone

June 13, 2007

Steve Phurrough, MD, MPA  
Director, Coverage and Analysis Group  
Office of Clinical Standards and Quality  
Mail stop C1-09-06  
Centers for Medicare and Medicaid Services (CMS)  
7500 Security Boulevard  
Baltimore, MD 21244

Re: Proposed Coverage Decision Memorandum for the Use of Erythropoiesis  
Stimulating Agents in Cancer and Related Neoplastic Conditions (CAG-00383N)

Dear Dr. Phurrough:

On behalf of Ortho Biotech Products, L.P., I am pleased to submit comments on the Proposed Coverage Decision Memorandum for the Use of Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions (CAG-00383N). Ortho Biotech Products, L.P. markets PROCRI<sup>®</sup> (Epoetin alfa), a manufactured form of a naturally occurring hormone (erythropoietin) administered by subcutaneous injection to stimulate the bone marrow's production of red blood cells. Clinical studies and approximately 20 years of clinical experience have demonstrated Epoetin alfa effectively treats chemotherapy-induced anemia by increasing hemoglobin, reducing red blood cell transfusion utilization, and reducing anemia-related symptoms, particularly fatigue.

We strongly support CMS's goal of ensuring that its coverage policies encourage appropriate and safe use of ESAs, and discourage uses that are known to be inappropriate. However, we are concerned that the proposed National Coverage Determination (NCD) would restrict coverage of ESAs for certain conditions that are medically reasonable and necessary, and would impose dosing and administration requirements that are incompatible with recently revised product labeling. In particular, the full use described in the labeling for ESAs and other prescription drugs should be covered whenever those uses are the subject of a NCD. The U.S. Food and Drug Administration (FDA) approves the product labeling for prescription drugs only after careful consideration of all available evidence, and a thoughtful determination that the uses described therein are safe and effective as supported by substantial evidence.

Uses that have been determined by the Secretary of Health and Human Services (HHS) to be safe and effective on the basis of substantial evidence should not be declared by CMS to lack necessity or reasonableness.

Section 1861(t)(2) of the Social Security Act defines the drugs covered by Medicare Part B as including all drugs and biologics that are: "used in an anticancer chemotherapeutic regimen for a medically accepted indication." That provision further defines a medically accepted indication as including: "any use which has been approved by the Food and Drug Administration for the drug. . .", as well as uses listed in certain compendia, unless the Secretary of HHS has determined that "the use is not medically appropriate or the use is identified as not indicated in one or more such compendia."

The standard for FDA's approval of an oncology drug product includes a finding by the Secretary of HHS that the drug is safe and effective for its labeled use, based upon substantial evidence consisting of adequate and well-controlled clinical trials. This standard is clearly higher than, and includes the determination of "medically appropriate", the Secretary makes in determining coverage of a drug product.

With respect to the compendia indications for PROCRIT, such as myelodysplastic syndrome there are robust clinical data, as evidenced in our accompanying Clinical White Paper, by which the Secretary could determine that the compendia listed uses are medically appropriate. Equally, these data refute any determination that the compendia listed uses of PROCRIT are not medically appropriate. As such, those uses should not be the subject of a National Coverage Determination, but should be left to case-by-case assessments of medical necessity or Local Coverage Determinations (LCD).

The NCD in its draft form may lead to unintended consequences that raise serious public health and safety concerns. We are particularly concerned that the determination will increase red blood cell transfusion rates, and result in increased and known transfusion risks as well as those presently unknown, but likely to emerge. In addition, the impact of these proposed restrictions on the available blood supply, both nationally and locally, as well as on transfusion services, should be carefully considered by CMS. Moreover, the draft determination does not acknowledge the improved patient reported outcomes associated with the use of ESAs. The implementation of the draft determination would likely result in a decreased quality of life for Medicare beneficiaries with conditions where the safety and effectiveness of ESAs have been demonstrated.

#### **Summary of Ortho Biotech's Recommendations on the Proposed NCD**

- The results of clinical studies, outlined in the attached Clinical White Paper, demonstrate that PROCRIT is safe and effective when used for FDA-approved indications, and for other medically-accepted uses listed in the DrugPoints<sup>®</sup> Compendium (which, in July, 2007, will succeed USP DI<sup>®</sup>). The final NCD should allow for the appropriate use of ESAs for these indications.
- We do not object, in principle, to a determination that ESAs are not reasonable and necessary for the following nine conditions:
  - any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis;
  - anemia of myeloid cancers;
  - anemia associated with the treatment of myeloid cancers or erythroid cancers;
  - anemia of cancer not related to cancer treatment;

- any anemia associated with radiotherapy;
- prophylactic use to prevent chemotherapy-induced anemia;
- prophylactic use to reduce tumor hypoxia;
- patients with erythropoietin-type resistance due to neutralizing antibodies; and,
- anemia due to cancer treatment if patients have uncontrolled hypertension.

However, the final determination should clarify that “myeloid cancers” refers to acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) but not to myelodysplasia or multiple myeloma. Additionally, coverage for the use of ESAs in several of these conditions may be reasonable and necessary when such use is part of an evidence development program.

- CMS should specifically allow coverage of ESA use for these conditions:
  - anemia of myelodysplasia or myelodysplastic syndrome (MDS);
  - anemia in patients with treatment regimens including anti-angiogenic drugs;
  - anemia in patients with treatment regimens including monoclonal/polyclonal antibodies directed against the epidermal growth factor (EGF) receptor; and,
  - patients with thrombotic episodes related to malignancy.
- The presence of functional EPO receptors on tumors and tumor proliferation in response to exogenous EPO has not been demonstrated, and thus should not form a basis for determining medical necessity or appropriateness for the described tumor types. Coverage determinations should not be premised on highly theoretical models. In particular, we believe Medicare should not ignore proven clinical benefits of ESA treatment while giving greater weight to theoretical risks.
- The final coverage determination should cover ESA use in patients with chemotherapy-induced anemia if they have a hemoglobin concentration below 11 g/dL, and suspend coverage in patients who reach a Hb concentration over 12 g/dL during a course of treatment, which is consistent with ESA prescribing information.
- ESAs may be necessary for a duration longer than 12 weeks annually, particularly for patients who receive more than one course of chemotherapy in a year. The final coverage determination should restrict the duration of coverage for ESAs to periods of ongoing chemotherapy, and for up to a 3 month period following chemotherapy completion. In most individual cases, ESA treatment duration will be shortened if the final determination prevents coverage for patients with a hemoglobin concentration above 12 g/dL, but ESA coverage should be permitted for a full course of chemotherapy where medically appropriate and necessary.
- Coverage for ESAs should not be subject to an arbitrary dosing cap during a treatment period. The efficacy and safety of ESAs, as demonstrated in controlled clinical trials, are incumbent upon the dose titration described in approved product labeling. The final coverage determination should support the use of ESAs starting with the lowest dose needed to avoid a transfusion, as described in approved labeling, and increasing the dose as needed and as described in the labeling information, to obtain a therapeutic effect. The arbitrary dose limits described in the draft NCD interfere with physicians’ ability to appropriately individualize patient care. In practice, if CMS limits ESA use with a Hb limit (i.e., suspending coverage for Hb > 12 g/dL), an appropriate patient-specific dose limit will in fact be in place. Moreover, any arbitrary dose limit will create unintended reimbursement incentives.

- The proposed determination to discontinue coverage if there is evidence of poor drug response after 4 weeks is inconsistent with FDA approved labeling, clinical trial evidence, and anemia treatment guidelines. A determination to discontinue coverage if there is evidence of poor drug response (i.e. hemoglobin/hematocrit rise <1 g/dl/<3%) at week 8 of treatment (after appropriate dose titration) would be more consistent with clinical trial evidence and established anemia treatment guidelines.
- The final determination should eliminate the following proposals due to lack of supporting scientific evidence:
  - Non-coverage of continued administration if there is an increase in fluid retention or weight (5 kg) after 2 weeks of treatment; and,
  - Non-coverage if there is a rapid rise in hemoglobin/hematocrit >1 g/dL >3% after 2 weeks of treatment.
- Ortho Biotech (OBI) is interested in discussing further Coverage with Evidence Development (CED) approaches for patients with anemia of cancer not related to chemotherapy treatment. We do not believe CED is an appropriate coverage approach for patients with chemotherapy-induced anemia, given the body of evidence demonstrating that ESAs are reasonable and necessary for the treatment of these patients.
- In recognition of our shared interest in developing additional evidence on ESA use, OBI recommends that CMS consider a Pharmacovigilance and Evidence Development Program for ESAs that will include periodic reports from manufacturers, consideration of the pharmacovigilance plans developed with the FDA, and other important elements described in our detailed comments below.

### **Detailed Comments**

Our comments are organized into four sections as outlined below:

#### **A. Background**

1. Safety record and benefits of PROCRIT when used for labeled indications and for indications listed in the DrugPoints Compendium (formerly USP DI).
2. Safety signals that have emerged from recent ESA clinical trials, particularly those targeting Hb levels > 12 g/dL
3. Potential risks to the country's blood supply associated with decreased ESA use

#### **B. Response to CMS Proposed Decision Memorandum**

1. Clinical conditions for which proposed non-coverage is appropriate
2. Clinical conditions for which proposed non-coverage is not appropriate
3. Coverage restrictions based on the presence of EPO receptors
4. Hemoglobin/hematocrit levels for initiation of ESA treatment
5. Maximum covered treatment duration of 12 weeks per year
6. Maximum covered 4 week treatment dose of 126,000 units for erythropoietin and 630 µg for darbepoetin
7. Non-coverage for poor drug response (hemoglobin/hematocrit rise <1 g/dl/<3%) after 4 weeks of treatment
8. Non-coverage for increase in fluid retention or weight (5 kg) after 2 weeks of treatment
9. Non-coverage for rapid rise in hemoglobin/hematocrit >1 g/dl/>3% after 2 weeks of treatment
10. Coverage with Evidence Development (CED)

- C. OBI's recommended coverage policies for PROCRIT coverage and administration
- D. Pharmacovigilance and Evidence Development Program
- E. Conclusion

As noted throughout this comment letter, additional details and documentation to support our position are included in the attached Clinical White Paper.

## **A. Background**

### **1. Safety Record and Benefits of ESAs**

Medicare has provided coverage for patients receiving Epoetin alfa since 1989, when it was first approved to avoid transfusions in end-stage renal disease patients treated with dialysis. Epoetin alfa was subsequently approved by FDA for use in chronic renal failure patients (pre-dialysis) and zidovudine-treated HIV-infected patients (1990), as well as for cancer patients receiving chemotherapy (1993), and for patients scheduled for elective, noncardiac, nonvascular surgery (1996) who are not able or willing to donate autologous blood despite significant anticipated blood loss. Since 1989, the DrugPoints Compendium (formerly USP DI) has reviewed evidence in the peer-reviewed literature and, in addition to the FDA-approved indications, currently lists PROCRIT as beneficial for use in anemia related to treatment of hepatitis C, critical illness, MDS, chronic/ neoplastic disease, and blood unit collection for autotransfusion.

ESAs are an important beneficial therapeutic option for anemia treatment in patients who might otherwise require transfusions. Multiple randomized and non-randomized clinical trials involving approximately 15,000 patients treated with ESAs for chemotherapy-induced anemia have been performed over the past 20 years. ESAs have been demonstrated to reduce transfusion risks by approximately 50% and have an acceptable safety profile when used according to label.

It is estimated that over four million patients worldwide have been treated with epoetin alfa. While transfusions are certainly necessary and beneficial in acute situations, many risks associated with transfusion have been well documented, including allergic reactions, transmission of infectious agents, and immunomodulation effects such as TRALI (transfusion-related acute lung injury), especially in patients who are already compromised. Despite high safety standards for the blood supply, many patients still view transfusions with distress and anxiety and clearly want to avoid them.

We share CMS' concerns for safety, but urge CMS to give appropriate consideration to the benefits of ESAs, particularly the widely studied benefits of patient-reported outcomes. According to the General Methodological Principles that are described in numerous national coverage decision memos:

*CMS determines whether an intervention is reasonable and necessary by evaluating its risks and benefits. For all determinations, CMS evaluates whether reported benefits translate into improved net health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses.*

In the case of ESAs, patients have benefited from the reduction in fatigue that is associated with anemia treatment, in addition to transfusion avoidance. While the FDA has not accepted patient-reported outcomes as labeling claims for ESAs in the United States, its thinking on such claims has been, and is constantly, evolving. The FDA issued draft guidance on patient reported outcomes (PROs) for purposes of labeling claims in March 2006, but has since stated publicly its intent to make significant revisions to the guidance when finalized ([http://www.fda.gov/cder/present/DIA2006/Burke\\_Rock.pdf](http://www.fda.gov/cder/present/DIA2006/Burke_Rock.pdf)). Other regulatory bodies have a higher level of acceptance of the outcomes data generated from randomized controlled trials. The EMEA and Health Canada have included symptom-based, patient reported outcomes data in the product labeling for ESAs. CMS should carefully consider the large body of evidence of improved PROs that have been reported with ESA use in patients with chemotherapy-related anemia when finalizing its coverage determination. This type of anemia is a common complication of myelosuppressive chemotherapy, with the frequency of occurrence dependent on the underlying malignancy and the regimen and intensity of chemotherapy utilized.

Anemia is highly associated with fatigue and diminished patient-reported health status in patients with cancer who are receiving chemotherapy. The impact of fatigue on the lives of patients with cancer is significant, with the vast majority reporting that it prevented them from leading a "normal" life, required alterations in their activities of daily living, and was more significant than cancer-related pain. Cancer-associated fatigue also has economic repercussions for both employed patients with cancer, who miss an average of 4.2 workdays per month, and their caregivers, who take time off from work to assist them.

The causes of fatigue are multifactorial and the relationship between hemoglobin concentration and intensity of fatigue is not well understood. However, since patient-reported levels of fatigue in patients who had cancer have been shown to correlate directly with the degree of anemia, anemia is often treated for palliation of symptoms as per guidelines established by the National Comprehensive Cancer Network (NCCN).

## 2. Safety Signals from Investigational Studies

Recent safety signals, including an increased risk of thromboembolic events (TVE), reduced survival, and possible tumor growth, have emerged from investigational cancer studies, particularly when ESAs were used **beyond** the correction of anemia (target Hb > 12g/dL).

The risks of ESAs in cancer patients are described in product labeling. An increased incidence of thrombotic events has been observed when ESAs are used for the correction of chemotherapy-induced anemia. Adverse effects on survival and tumor progression are observed when ESAs are used off-label. With the exception of the Amgen Anemia of Cancer Trial (Glaspy 2007), all the studies below evaluated patients with higher Hb initiation levels (> 12 g/dL) and/or targeted higher Hb levels (> 12 g/dL) than currently recommended. The Amgen Anemia of Cancer Trial evaluated a patient population that is currently excluded in the FDA approved ESA labeling information. The table below summarizes these studies:

<b>Trial</b>	<b>N</b>	<b>Patient Population</b>	<b>Hb initiation (g/dL)</b>	<b>Hb target (g/dL)</b>	<b>FDA-approved use?</b>
<i>Potentiation of radiation therapy</i>					
ENHANCE (Henke 2003)	351	Head and neck cancer patients with radiation therapy	12/13	14/15	No
DAHANCA (Overgaard 2007)	522	Head and neck cancer patients with radiation therapy	14.5	15.5	No
<i>Potentiation of chemotherapy</i>					
BEST (Leyland-Jones 2005)	939	Breast cancer patients with chemotherapy	13	14	No
<i>Anemia of cancer</i>					
Amgen Anemia of cancer (Glaspy 2007)	985	Anemia of cancer	11	12	No
EPO CAN 20 (Wright 2007)	70	Anemia of cancer	12	14	No

More detailed summaries of these and other studies that investigated the use of ESAs outside the uses described in the current label are included in the recently revised prescribing information. In collaboration with the FDA, Ortho Biotech and Amgen Inc., another marketer of ESAs, updated the safety information in the product labeling for their ESAs to reflect these safety signals in March 2007. Additionally, it should be noted that an active epoetin alfa pharmacovigilance program is ongoing under the direction of Johnson and Johnson Pharmaceutical Research and Development. This program involves ongoing discussions, updates of clinical trial results, and post-marketing surveillance in collaboration with the FDA.

The extensive evidence base indicates that ESAs, when used according to product labeling (the treatment of anemia caused by concurrent chemotherapy, with a target hemoglobin concentration not to exceed 12g/dL), have no negative effect on survival or tumor growth. While there is an increased risk for TVEs, this risk is well described in product labeling, and is understood by health care providers.

As proposed, the NCD relies upon safety signals from the investigational studies to unduly limit uses of ESAs that have been shown to be reasonable and necessary. The final determination should cover all uses of ESAs described in approved product labeling, for which there necessarily exists substantial evidence of the safety and effectiveness of those uses, and any other use for which safety signals have not been observed and there is a body of evidence supporting the use, such as there is for MDS. Any other approach threatens patient access and health outcomes.

### 3. Potential Risks to the Nation's Blood Supply Associated with Decreased ESA Use

The nation's blood supply is a limited resource that could be further strained by the increased demand for transfusions that would likely result from an overly restrictive coverage policy on the use of ESAs. From 1987 to 1997, the collection of allogeneic blood declined from a high of 13.6 million to 11.9 million units. Although supply of blood

has increased since then, so has demand, and the current margin between supply and demand has shrunk.

Additionally, processes used for qualifying fully screened units further exacerbate this situation. In 2004, 240,000 units were rejected after screening, leaving a margin of only 648,000 units or 4.5% of the available supply. Based on the 2005 Nationwide Blood Collection and Utilization Survey Report, 8.5% of surveyed hospitals reported postponement of elective surgeries on 1 or more days in 2004 because of blood inventory shortages (range: 1 to 39 days a year). Sixteen percent of hospitals reported they were not able to meet their non-surgical blood needs on at least one day. Although demand is fairly constant, the blood supply is actually highly variable throughout the year. This has led to transient shortages during holiday periods typically associated with low donation.

Ortho Biotech performed a modeling simulation to estimate the impact that limiting the use of ESAs in chemotherapy-induced anemia would have on the U.S. blood supply (data on file). The excess number of units that would be required if patients were not treated with ESAs, was contrasted with the 2004 marginal blood supply data (most recent data available). Model inputs were drawn from the published literature or expert opinion where literature was lacking. Estimates were developed for a range of scenarios and incorporated into appropriate sensitivity analyses.

The model predicts that up to a third of the marginal U.S. blood supply would be required to cover the incremental demand for blood that would arise from a 25% decrease in the use of ESAs (see attached model). Nearly two-thirds of the marginal blood supply could be compromised with a 50% reduction of ESA use in patients with chemotherapy-induced anemia. Recently, Wall Street analysts reported their estimates that implementation of the draft NCD may decrease ESA utilization from 25% to 70% (Porges 2007, Werber 2007, Ende 2007, Hopkins 2007). Such changes in ESA utilization would be associated with an incremental demand of 118,000-237,000 units of blood. This added pressure on the blood supply could be even larger due to regional variations in the number of available units, and the variable frequency of donation.

We urge CMS to consider the potential negative consequences on the nation's blood supply by restricting the use of ESAs.

## **B. Response to CMS Proposed Decision Memo**

### **1. Clinical Conditions for which Proposed Non-Coverage Is Appropriate**

CMS proposes thirteen clinical conditions for which ESA treatment would not be reasonable and necessary.

We agree, in principle, and do not object to a determination that ESAs are not reasonable and necessary for the following nine uses:

1. the treatment of any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis;
2. the treatment of anemia of myeloid cancers;
3. the treatment of anemia associated with the treatment of myeloid cancers or erythroid cancers;

4. the treatment of anemia of cancer not related to cancer treatment;
5. the treatment any anemia associated with radiotherapy;
6. prophylactic use to prevent chemotherapy-induced anemia;
7. prophylactic use to reduce tumor hypoxia;
8. use in patients with erythropoietin-type resistance due to neutralizing antibodies; and,
9. treatment of anemia due to cancer treatment if patients have uncontrolled hypertension.

The determination should clarify that the term “myeloid cancers” refers to acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), and not to myelodysplasia or multiple myeloma. Additionally, coverage for the use of ESAs in several of these conditions may be reasonable and necessary when such use is part of an evidence development program.

## 2. Clinical Conditions for which ESAs are reasonable and necessary

CMS should allow coverage for the following four conditions based on the body of evidence demonstrating ESAs are reasonable and necessary:

- The anemia of myelodysplasia or myelodysplastic syndrome (MDS)

MDS is not considered a myeloid cancer but rather a disorder of ineffective hematopoiesis. Anemia is the most frequent complication of this irreversible chronic bone marrow disorder that requires long-term transfusions, and is commonly treated with ESAs. Transfusion dependency has been associated with reduced survival and morbidity, including iron overload. ESA benefits include reduced dependency on transfusions, especially in MDS patients presenting with serum erythropoietin levels < 500 mUnits/mL. In addition, studies of EPO use in low risk MDS patients have suggested that survival is improved compared to historical controls. The natural history of MDS is associated with a proportion of patients transforming to acute leukemia, although there is no evidence that use of EPO accelerates this transformation.

No safety signal has emerged regarding ESAs use in anemia of MDS. Currently, the anemia of MDS is covered by virtually every carrier under LCDs that were recently revised to withdraw coverage for the anemia of cancer. Carriers should continue to exercise discretion when covering the use of ESAs to treat the anemia of MDS based on the existing body of clinical trial evidence, and the fact that no safety signal has emerged. Treatment guidelines, e.g., ASH/ASCO, NCCN, British and Italian national guidelines, and major compendia (DrugPoints (formerly USP DI) and AHFS), have endorsed the use of EPO for MDS. Additionally, CMS appears to have recognized the value of ESA treatment by incorporating evaluation of iron stores for MDS patients undergoing ESA treatment as a physician quality measure under the Physician Voluntary Reporting Program (PVRP).

- Anemia in patients with treatment regimens including anti-angiogenic drugs such as bevacizumab and monoclonal/polyclonal antibodies directed against the epidermal growth factor (EGF) receptor e.g., cetuximab (Erbix<sup>®</sup>) and panitumumab (Vectibix<sup>™</sup>)

The proposal to restrict coverage for patients whose chemotherapy regimens include an anti-angiogenic or anti-epidermal growth factor receptor agent lacks a sufficient scientific foundation. No safety signals have been identified with the concomitant use of ESAs in the clinical settings where these approved regimens are widely utilized, e.g., colorectal and lung cancer. Furthermore, ESAs for the treatment of anemia are allowed in the ongoing clinical trials evaluating potential new indications for these agents in combination with chemotherapy. This policy would adversely affect many patients for whom anti-angiogenic agents are administered in combination with myelosuppressive chemotherapy regimens that commonly cause anemia.

The final coverage determination should be based upon scientific evidence and not on theoretical concerns of overlapping toxicity, which, based on the data from the large registration trials and pharmacovigilance program, remain unsubstantiated. Because there is no basis to conclude that the use of ESAs is not reasonable and necessary in every patient receiving anti-angiogenic drugs, the final national coverage determination should rely on local carrier discretion to determine coverage. We believe CMS would set a new precedent in its coverage of treatments by ignoring the proven benefits of anemia treatment in these patients while giving greater weight to theoretical risks. We recommend that this proposal be withdrawn.

- Patients with thrombotic episodes related to malignancy

While ESAs are known to increase the risk of thromboembolic events, the determination of the acceptability of such risk should be made in the ordinary course of the practice of medicine, after discussion between healthcare practitioners, patients, and families about the known risks and benefits. Such informed decision-making should not be usurped through a national coverage determination.

### 3. Coverage restrictions based on the presence of EPO receptors (EPO-R)

There is inadequate scientific evidence upon which to base ESA coverage restrictions concerning selected tumor types that may express EPO-R on the surface of their cells. While we recognize the theoretical concerns raised by the presence of such EPO-R on tumor cells, there is no evidence that these receptors are functional at pharmacologic ESA doses, nor have they been demonstrated to cause tumor growth in the presence of EPO in any *in vivo* model. We discuss the serious scientific limitations of this theoretical rationale underlying the proposed coverage restrictions in the attached Clinical White Paper.

Briefly stated, the scientific data supporting the presence of functional EPO-R on the surface of tumor cells has significant limitations and are thus unreliable as a basis for selecting specific tumor types for coverage restrictions. The biologic relevance of detecting EPO-R in tumor cells is uncertain, given the lack of antibody specificity for cell surface expression of the EPO-R on tumor cells. The antibody utilized in cited assays recognizes multiple proteins and is unable to differentiate between cytoplasmic and cell surface EPO-R expression. Furthermore even when such receptors are "present" in the tumor cells, there is no evidence of signaling from these receptors even in the presence of exogenous EPO at concentrations that are

nearly 2 logs greater than the maximal concentration achieved after labeled doses of EPO are administered. This, coupled with the fact that no studies have been able to derive a binding coefficient ( $K_d$ ) for the affinity of EPO to the receptors on tumor cells, suggests that, even if such receptors are present, they are irrelevant to the biology of the tumor. In fact, no studies, including those in the CMS proposed decision memorandum, have shown that exogenous EPO leads to increased tumor growth *in vivo*. Investigators reported less favorable tumor outcomes in EPO-treated head and neck cancer patients whose tumors "express" the EPO-R, have acknowledged such uncertainties.

*"... if we assume that SC695 (commercially available EPO-R antibody) lacks specificity & sensitivity, as claimed by a recent publication, interpretation of our data would become a real challenge..."* Henke (2006)

EPO effects on tumor oxygenation and microvasculature have been hypothesized as an alternative mechanism for explaining tumor progression in those studies designed to treat patients to high target Hb levels to potentiate a radiotherapy effect [e.g. 14-15 g/dL, Henke (2003), DAHANCA (Overgaard 2007)]. Specifically, maximal tumor oxygenation in squamous cell carcinoma of the head and neck has been observed at normal gender-specific Hb values. Above this optimal Hb range, studies have demonstrated that tumor oxygenation begins to worsen, potentially counteracting the anti-tumor effectiveness of localized radiotherapy delivered to the tumor (Vaulpel 2006).

FDA scientists have also reviewed this area and described the following:

- *"...a direct relationship between the presence of EPO receptors on tumors and tumor proliferation in response to exogenous EPO has not been established..."* (see, FDA briefing book, ODAC, May 2007).
- *"...In vitro and in vivo data do not provide convincing evidence that EPO promotes tumor growth and proliferation..."* (see, FDA briefing book, ODAC, May 2007)

An alternative explanation for the tumor progression observed when head and neck cancer patients receiving radiotherapy were treated to high Hb targets, based on ESAs detrimental effect on tumor oxygenation and viscosity at high Hb levels, is more strongly supported by the scientific evidence than the EPO-R mechanism. In summary, the use of an unreliable and unapproved immunoassay to detect the presence of non-functional EPO-R on tumors has significant limitations, and thus, should not form the basis of coverage restrictions for chemotherapy-induced anemia in selected tumor types.

#### 4. Coverage limitation to documented hemoglobin concentrations below 9 g/dL.

This limitation proposed in the draft NCD is inconsistent with the scientific evidence demonstrating the safety and efficacy of ESAs, the current standard of care, and established anemia treatment guidelines. None of the trials relied upon by FDA to establish the safety and efficacy of ESAs included entry criteria consistent with the draft NCD limitations. ESA pivotal trials, reviewed by the FDA, required initial hemoglobin concentrations to be below 10.5 -11.5 g/dL. We do not have a sufficient basis upon which to assess the utility of ESAs when treatment is limited to instances in which hemoglobin falls below 9 g/dL.

Indeed, peer-reviewed, published meta-analyses reported a lower risk of transfusions when ESA treatment is initiated at a baseline Hb level of 10-12 g/dL as compared with Hb < 10g/dL (see table below).

<b>Baseline Hb at ESA initiation</b>	<b>Relative risk for transfusion (95% CI)</b>
Hemoglobin < 10 g/dl	0.70 (0.65, 0.7)
Hemoglobin 10-12 g/dl	0.46 (0.40, 0.53)

Clinical trial and observational study evidence has demonstrated significantly lower transfusion frequency in patients with chemotherapy-induced anemia who are initiated at higher hemoglobin levels within anemia treatment guidelines recommending ESA initiation at Hb < 11 g/dL. These findings are consistent when patient groups are compared investigating those initiated with ESAs at Hb < 9 g/dL versus Hb 9-11 g/dL or Hb < 10 versus Hb 10-11 g/dL. Analyses from several studies show that ESA initiation closer to the Hb < 11 g/dL level is associated with lower transfusion frequency and are described more completely in the attached Clinical White Paper.

We recommend coverage for Hb < 11 g/dL at ESA initiation with target hemoglobin not to exceed 12 g/dL, which is consistent with labeling information and established anemia treatment guidelines. These suggested limitations are for the ESA treatment course rather than monthly initiation. Clinical trials have not investigated interrupted ESA treatment.

Coverage for ESAs should be suspended whenever hemoglobin concentrations exceed 12 g/dL in patients with chemotherapy-induced anemia. This is in contrast to the current CMS coverage policy on erythropoietin use in end-stage renal disease (ESRD) patients. For this very different patient population, Medicare's coverage policy is to maintain a target hematocrit level between 30% and 36%. However, because of variability in response to erythropoietin, CMS does not require monitoring by its contractors until the hematocrit level reaches 39.0 (or hemoglobin of 13.0). We recommend in the oncology population, which has a much shorter treatment duration and a differing physiologic state, that Hb level should not exceed 12 g/dL and coverage should be suspended whenever Hb exceeds 12 g/dL.

##### 5. Coverage limitations to a maximum treatment duration of 12 weeks/year

Many standard chemotherapy regimens that are associated with chemotherapy-induced anemia are administered for greater than 12 weeks. In addition, patients may receive more than one chemotherapy treatment regimen in a year, particularly those patients with metastatic or recurrent disease. Frequently, chemotherapy-induced anemia persists for 1-3 months following discontinuation of treatment.

The proposed coverage limitation by duration of treatment fails to account for the heterogeneity of chemotherapeutic regimens, co-morbid conditions, and patient responsiveness. Additionally, patients who require more than one course of chemotherapy in a year will be disadvantaged. A far better approach to limiting treatment duration is based upon individualized outcome measures, such as an upper hemoglobin concentration limit. A final coverage determination limiting coverage in instances where hemoglobin concentration exceeds 12 g/dL would have the practical effect of limiting treatment duration in most patients, but would permit longer uses of ESAs where medically reasonable and necessary. We recommend no annual restriction

on the number of weeks covered. CMS could, however, restrict ESA treatment to periods of ongoing chemotherapy plus three months following chemotherapy completion.

**6. The maximum covered 4 week treatment dose is 126,000 units for erythropoietin and 630 µg for darbepoetin**

Patient, tumor type, and treatment heterogeneity preclude definition of a maximum dosing limit that is premised on medical necessity and reasonableness. The proposed dosing limit is counter to the recommended epoetin alfa dosing in the prescribing information (e.g., a 100 kg patient would require 180,000 Units of EPO over 4 weeks based on 150 Units/kg TIW or 160,000 Units over 4 weeks based on 40,000 U QW). The prescribing information appropriately recommends dose escalation based on the initial response to the starting doses (e.g., a 100 kg patient may require 360,000 Units of EPO over 4 weeks based on 300 Units/kg TIW or 240,000 Units over 4 weeks based on 60,000 Units QW). Such escalations are based upon the adequate and well-controlled clinical trials demonstrating safety and effectiveness and supporting approval of ESAs. These escalations would be precluded under the proposed maximum limits in the proposed NCD. A far better approach to limiting dose is to use individualized outcome measures, such as an upper hemoglobin concentration limit. A final coverage determination limiting coverage in instances where hemoglobin concentration exceeds 12 g/dL would have the practical effect of limiting treatment dose in most patients, but would permit appropriate dose escalation of ESAs where medically reasonable and necessary.

We also note that the application of a dose cap could shift treatment selection to the agent with a maximum dose that accommodates the most patients, which could in turn be the higher priced ESA. As shown in the table below, the dose cap outlined in the proposed NCD (PROCRIT 126,000 Units and ARANESP 630 mcg) would result in a 66% higher payment when ARANESP is utilized compared to PROCRIT, without any additional clinical benefit (based on 2nd quarter 2007 Average Selling Price (ASP+ 6%)).

ESA	Dose	Payment Limit (ASP + 6%)	ARANESP Price Premium
PROCRIT	126,000 Units	\$1,190.95	66%
ARANESP	630 mcg	\$1,980.09	

NOTE: 2<sup>nd</sup> Qtr Payment Limit: PROCRIT -\$9.452/1,000 Units; ARANESP - \$3.143/mcg

This proposed NCD, if implemented, may have the unintended effect of establishing an arbitrary advantage for one product over another in a therapeutic category, limiting choice, costing more than it would otherwise, and increasing beneficiary co-pays. The only way to avoid providing an arbitrary advantage to one product is to not set maximum dose limits on either product. ESA dose can and will be appropriately and effectively constrained through implementation of an ESA initiation hemoglobin of < 11 g/dL and a hemoglobin level not to exceed 12 g/dL. This would obviate the need for separate maximum dose limits, which interfere with patient care.

Because ESAs should remain a covered treatment for beneficiaries with MDS, and because patients with MDS frequently require higher ESA doses than those needed by patients with chemotherapy-induced anemia, maximum doses for the latter would also impede effective doses for the former.

7. Limitations on use of ESA in patients with evidence of poor drug response (hemoglobin/hematocrit rise <1 g/dl/<3%) after 4 weeks of treatment

As described in the attached Clinical White Paper, Waltzman reported that 29% of patients without a 1 g/dL Hb rise at week 4 went on to have at least a 1 g/dL Hb rise by the end of the study. This demonstrates that a significant proportion of patients have continued improvements throughout ESA treatment. Dose escalations at 4 or 8 weeks based on lack of response are recommended as per the ESA prescribing information and national treatment guidelines. Placebo-controlled trials have indicated that poor drug response at week 4 is not predictive of hematologic response by the end of the trials. As currently proposed, this limitation would result in inadequate patient care.

We recommend the final coverage determination cover patients being treated with epoetin alfa in accordance with the dosing strategy described in approved product labeling and supported by substantial clinical evidence. In patients experiencing an initial poor response (hemoglobin improvement < 1 g/dL over baseline at four weeks), the dose should be escalated as described in approved product labeling. In those patients with continued poor response following an additional four weeks of treatment at the escalated weekly dose, (8 weeks of treatment), epoetin alfa should be discontinued. This allows an 8-week epoetin alfa treatment duration to assess individual patient response. Alternatively, patients treated with the epoetin alfa three times weekly are dose escalated for poor response after eight (8) weeks. In those patients with continued poor response following four weeks at the escalated dose, epoetin alfa should be discontinued. This allows a 12-week epoetin alfa treatment duration for the assessment of individual patient response.

We recognize that this clinically appropriate policy might be difficult to implement as a national coverage policy. Therefore, we believe that 8 weeks is an adequate and rational time period for treatment response assessment before coverage is withdrawn, given that the majority of epoetin alfa patients receive weekly dosing.

8. Limitations in the setting of an increase in fluid retention or weight gain (5 kg) after 2 weeks of treatment

There is no evidence upon which to conclude that use in the setting of an increase in fluid retention is not reasonable and necessary in at least some patients. The final determination should offer local carriers discretion to determine medical necessity and reasonableness on a case-by-case basis.

9. Limitations in instances where there is a rapid rise in hemoglobin/hematocrit >1 g/dl/>3% after 2 weeks of treatment

There is no evidence to support this proposal. We recommend that it be withdrawn. If there is a rapid rise in hemoglobin/hematocrit, the PROCRIT (epoetin alfa) dose should be reduced by 25%, not discontinued (as per prescribing information in the label).

## 10. Coverage with Evidence Development (CED)

The proposed NCD expressed interest in comments on whether coverage for ESAs for Medicare beneficiaries “with cancer” should occur only within appropriately designed clinical research studies where informed consent and safety monitoring can be assured.

Given that recent evidence from a clinical trial in patients with anemia of cancer (Glaspy 2007) showed excess mortality from ESA treatment, such treatment does not support coverage under section 1862(a)(1)(A). However, the impact of ESA treatment is unknown for anemia of cancer patients who have earlier stage disease or are in remission and not receiving concurrent chemotherapy, such as low grade lymphoma or multiple myeloma. We encourage CMS to explore coverage for treatment of anemia of cancer under CED.

We do not believe CED is an appropriate coverage approach for patients with chemotherapy-induced anemia, given the body of evidence demonstrating that ESAs are reasonable and necessary for the treatment of these patients. Applying Coverage with Study Participation to chemotherapy-induced anemia suggests that the current level of evidence is inadequate and, in the past, would have prompted a non-coverage decision. This is an extreme, overreaching and unprecedented interpretation of the current body of evidence, one that is simply without merit or support from a wide range of interested parties, including health care practitioners, patients and the organizations that represent them, manufacturers, researchers, and commercial insurers.

### **C. OBI's recommended coverage policies for PROCRIT coverage and administration**

Current Medicare drug coverage policies are appropriate and, in general, the safeguards inherent in the LCD process are working. Medicare drug coverage policy is described in Chapter 15, “Covered Medical and Other Health Services”, of the Medicare Benefit Policy Manual. As stated in section 50.4: “Drugs or biologicals approved for marketing by the Food and Drug Administration (FDA) are considered safe and effective for purposes of this requirement when used for indications specified on the labeling.”<sup>1</sup>

The coverage of an unlabeled use of a drug is described in section 50.4.2: “FDA approved drugs used for indications other than what is indicated on the official label may be covered under Medicare if the carrier determines the use to be medically accepted, taking into consideration the major drug compendia, authoritative medical literature and/or accepted standards of medical practice.”<sup>2</sup>

---

<sup>1</sup> The standard for FDA’s approval of an oncology drug product includes a finding by the Secretary of HHS that the drug is safe and effective for its labeled use, based upon substantial evidence consisting of adequate and well-controlled clinical trials. This standard is clearly higher than and includes the determination of “medically appropriate” the Secretary makes in determining coverage of a drug product.

<sup>2</sup> With respect to the compendia indications for PROCRIT, there is robust clinical data, as evidenced in our accompanying Clinical White Paper, by which the Secretary could determine that the compendia uses are medically appropriate. Equally, these data refute any determination that the compendium uses of PROCRIT are *not* medically appropriate. As such, those uses should not be the subject of a National Coverage Determination, but should be left to case-by-case assessments of medical necessity or local coverage determinations.

Finally, in the case of drugs used in an anti-cancer chemotherapeutic regimen, unlabeled uses are covered for a medically accepted indication as defined in section 50.5: "Effective January 1, 1994, unlabeled uses of FDA approved drugs and biologicals used in an anti-cancer chemotherapeutic regimen for a medically accepted indication are evaluated under the conditions described in this paragraph. A regimen is a combination of anti-cancer agents, which has been clinically recognized for the treatment of a specific type of cancer. For purposes of this provision, a cancer treatment regimen includes drugs used to treat toxicities or side effects of the cancer treatment regimen when the drug is administered incident to a chemotherapy treatment."<sup>3</sup>

These existing policies should remain the foundation on which any NCD is shaped. Thus, coverage for the anemia of MDS, which is listed in the USP and already covered under LCDs, should remain in place. Local discretion for coverage of conditions not listed in the label or in one of the recognized compendia, also would remain in place in the absence of exceptions specified in an NCD. In the case of ESAs, those exceptions would include non-coverage for the following conditions:

1. any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis;
2. the anemia of myeloid cancers;
3. the anemia associated with the treatment of myeloid cancers or erythroid cancers;
4. the anemia of cancer not related to cancer treatment;
5. any anemia associated with radiotherapy;
6. prophylactic use to prevent chemotherapy-induced anemia;
7. prophylactic use to reduce tumor hypoxia;
8. patients with erythropoietin-type resistance due to neutralizing antibodies; and,
9. anemia due to cancer treatment if patients have uncontrolled hypertension.

CMS should clarify that the term "myeloid cancers" refers to acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), and not to myelodysplasia or multiple myeloma.

In addition, guidance regarding dosing and administration could be included in an NCD but, as described above, that guidance should be limited to:

- 1) Specifying hemoglobin/hematocrit levels prior to initiation of dosing;
- 2) Specifying target hemoglobin/hematocrit levels;
- 3) Denying continued coverage after adequate treatment exposure and a poor response to therapy; and,
- 4) Restricting ESA treatment to periods of ongoing chemotherapy plus three months following chemotherapy completion.

These four items are sufficient to assure patient safety and obviate the need for guidance on the issues of treatment duration and treatment dose. To be consistent with

---

<sup>3</sup> Section 1861(t)(2) of the Social Security Act, 42 U.S.C. § 1395x(t)(2), defines the drugs covered by Medicare Part B as including all drugs and biologics that are "used in an anticancer chemotherapeutic regimen for a medically accepted indication." That provision further defines a medically accepted indication as including "any use which has been approved by the Food and Drug Administration for the drug. . . ." as well as uses listed in certain compendia unless the Secretary of HHS has determined that "the use is **not medically appropriate** or the use is identified as not indicated in one or more such compendia." *Id.*

labeling information, established anemia treatment guidelines, and ESA clinical trial designs, we recommend the following:

- The hemoglobin/hematocrit concentrations immediately prior to ESA initiation of therapy should be <11 g/dL/33%;
- The target hemoglobin/hematocrit concentrations for patients with chemotherapy-induced anemia should not exceed 12.0 g/dL/36%;
- Coverage should be denied for continued use of ESAs if there is evidence of poor drug response (hemoglobin/hematocrit rise <1 g/dl/<3%) after 8 weeks of treatment (including appropriate dose escalation); and,
- The treatment of cancer patients with ESAs for chemotherapy-induced anemia should be restricted to periods of ongoing chemotherapy and three months following chemotherapy completion.

The administration of ESAs in treatment of chemotherapy-induced anemia in patients who do not meet these requirements is not reasonable and necessary, and should not be covered.

#### **D. Pharmacovigilance and Evidence Development Program**

Both Amgen and Ortho Biotech take safety concerns seriously. Both companies are working closely with the FDA in the area of pharmacovigilance. Each company has pharmacovigilance programs underway to investigate ESA-related safety signals. The epoetin alfa pharmacovigilance program involves clinical trials updates, safety-related discussion and post-marketing surveillance that are accomplished in collaboration with the FDA. Our work with the FDA should reassure CMS that proper studies and safety monitoring of ESAs are underway.

We propose to CMS a Pharmacovigilance and Evidence Development Program, which would incorporate the following measures:

- Ongoing pharmacovigilance studies, with data on long-term safety of ESAs, which will be available over the next 12-18 months
- Additional pharmacovigilance studies resulting from discussions with FDA. We will ensure that CMS is aware of our plans for additional studies as these discussions proceed.
- Reports to CMS on the results of these studies, plans for additional studies, and our efforts to keep physicians and patients informed through ongoing communications.
- Coverage with evidence development in off-label uses. We aim to discuss the use of CED in developing better evidence for certain uses. Any development of a CED proposal will include a consultation process that includes physician and patient groups and other scientific stakeholders.

#### **E. Conclusion**

Ortho Biotech shares the concerns of CMS for the safety of Medicare beneficiaries and we support the development of policies regarding the appropriate use of ESAs. While we agree with several of the proposed coverage changes, we also believe that some of the proposed coverage changes:

- Are not supported by the available scientific and clinical evidence;
- Are inconsistent with section 1861(t)(2) of the Social Security Act, which defines the drugs covered by Medicare Part B as including all drugs and biologics that are: "used in an anticancer chemotherapeutic regimen for a medically accepted indication";

- Do not consider the substantial heterogeneity inherent in oncology patients and their treatments;
- Are contrary to current prescribing information in the FDA-approved label and independent, established national treatment guidelines;
- Expose beneficiaries to known and unknown risks of blood transfusions while putting significant pressure on the already constrained national blood supply and transfusion services; and,
- Unduly restrict coverage and access to ESAs, which will deny Medicare beneficiaries the benefits of ESA treatment, including improved quality of life.

We have identified the important benefits associated with ESA use, and highlighted the potential risks to the country's blood supply associated with decreased ESA use. Finally, we have recommended coverage policies for ESA treatment that build on existing Medicare drug coverage policy and are based on published medical literature demonstrating the safety, effectiveness and benefits of ESAs when used according to labeling, and as indicated in the most recent DrugPoints compendium (formerly USP DI).

Thank you for your consideration of our comments and recommendations. The references cited in the attached Clinical White Paper will be sent in three binders directly to you (hard copy due to size). If you have any questions, please contact Cathleen Dooley at 202-589-1008 ([cdooley@obius.inj.com](mailto:cdooley@obius.inj.com)).

Yours Sincerely,



Joaquin Duato  
President, Ortho Biotech Products, LP

Attachments: Clinical White Paper developed for CMS, June 2007  
Impact of transfusion model

cc: Maria Ciccanti, RN, Lead Analyst  
Shamiram Feinglass, MD MPH, Medical Officer  
Louis Jacques, MD, Division of Items and Devices  
Elizabeth Koller, MD, FACE, Medical Officer  
LCDR Tara Turner, PharmD



**FRED S. MARCUS, MD, AND ASSOCIATES**

A PROFESSIONAL CORPORATION

***Internal Medicine, Hematology, and Medical Oncology***

Fred S. Marcus, MD  
Shane P. Dormady, MD, PhD  
John A. Hayward, MD  
Debra D. St. Claire, MD  
Peggy Ross, RNP, MS

2940 Whipple Avenue, Suite B • Redwood City, California 94062  
(650) 216-8300 Telephone (650) 216-8401 Facsimile

Sherri Garoutte, RN, OCN  
Diana Goodenough, RN, OCN  
Theresa Koettters, RN, MS

June 5, 2007

Steve Phurrough, MD, MPA

Elizabeth Koller, MD, FACE

Maria Ciccanti, RN

Coverage Analysis Group

Office of Clinical Standards and Quality

Centers for Medicare and Medicaid Services

Mail Stop C1-12-28

7500 Baltimore, MD 21244-1849

Re: Comment Regarding Changes in Medicare Policy re: Erythropoiesis Stimulating Agents (ESAs) for  
Non-renal Disease Indications (CAG-00383N)

Thank you for inviting comment regarding your proposed changes in Medicare policy re: ESAs. I have been in the practice of Hematology and Medical Oncology in California and Hawaii for over 14 years, treating patients with a broad spectrum of malignancies and blood disorders. I agree that growth factors have made a huge (positive) difference in our treatments and I agree that there is a need for national coverage standards as well as a rational, evidence-based response to FDA warnings about ESAs (and all drugs).

It is my experience that both darbepoetin alfa and epoetin alfa have equal efficacy in treating selected forms of anemia and I believe that CMS should therefore establish the same list of indications to support medical necessity. This list should include all indications where evidence shows that ESAs are safe and effective.

I believe that Quality of Life, reduced morbidity and side effects secondary to our antineoplastic therapies, and transfusion avoidance are relevant, important endpoints for patients living with cancer. Transfusions carry both expense (cost of blood, blood bank personnel time, nursing time, transfusion bed time, and the patient's time) and considerable risk (of reactions, HIV, and Hepatitis).

I disagree with discontinuing ESAs for failure to achieve a 1 g/dl Hemoglobin increase in four weeks; I do not believe that this is evidence-based. Clinical studies consistently show that the optimal response takes 8 – 12 weeks to occur.

Neither darbepoetin alfa nor epoetin alfa reliably achieves and increase of 1 g/dl in 4 weeks at standard doses. Standard doses usually require 5 – 7 weeks for 1 g/dl response.

I believe that there must be a provision for dose escalation in non-responders – it has been the standard of care of ten years to dose escalate in non-responders at 6 – 8 weeks. There has been no evidence showing a safety risk associated with dose escalation.

I agree with restricting the use of ESAs in most people who have a hemoglobin level of > 12 g/dl. Trials that pushed hemoglobin above the limit (in the hopes of improving patients' response rates to treatment) showed an increased risk of thrombotic events, clearly not in the patients' best interest. However, in patients who are currently undergoing chemotherapy, who have a hemoglobin level of 12.0 or 12.1 and who will be receiving myelosuppressive treatments within the next week, should receive ESAs with the goal of keeping the hemoglobin at the 12.0 g/dl level.

I disagree with your suggested change to not cover multiple myeloma, MDS, and chronic anemia of cancer. Transfusion avoidance is as important for people who are currently not receiving chemotherapy (such as people multiple myeloma, myelodysplastic syndromes, or metastatic cancers) as for those who are receiving chemotherapy. Studies that showed significant and life-threatening events in certain patients who have taken ESAs for non-renal diseases, do not appear to have included any patients with bone marrow failure (such as MDS). Most patients with MDS are elderly; many have comorbidities that make alternative treatments such as chronic transfusions and aggressive chemotherapy, very risky. ESAs have been found to be safe and beneficial (therapeutic as well as supportive) in all subtypes of MDS.

I disagree with a 12 week maximum allowance for ESA usage. When the original studies that formed the basis for FDA approval of ESAs in chemo-related anemia were done, they were done with a 12 week course of chemotherapy. In the last 20 years, the duration of antineoplastic therapies has increased due to the availability of supportive agents as well as the number of active agents available. For patients undergoing first, second, and third line regimens lasting even 6 -12 months in a given year, the 12 week maximum allowance is grossly inadequate. Also, there is no evidence suggesting that the use of ESAs for more than 12 weeks is associated with more safety issues (as there is with greatly elevated hemoglobin levels).

I disagree with your proposed non-coverage ESAs in patients receiving VEGF or EGFR inhibitors. These agents are known to induce anemia and are often given with other anemia-inducing regimens. There is no evidence that ESA usage antagonizes the therapeutic effect of VEGF/EGFR inhibitors.

In summary, I believe that the benefits of ESAs have been demonstrated in the literature in over 2000 patients, correcting anemia and reducing transfusion rates. While cancer patients' quality of life, functionality, and general well-being are greatly improved by maintaining hemoglobin concentrations near 12 g/dl, there is no evidence that transfusions are safer or more effective than ESA use in patients with Hemoglobin levels between 9 – 11. Your proposed changes could increase the blood demand by 20% and could risk depletion of the national blood supply.

**I strongly recommend that you approve use of ESAs:** 1) to be started at Hgb < 11 g/dl, 2) that dose escalation be allowed, 3) that treatment be held with Hgb > 12 and treatment be restarted as soon as Hgb subsequently drops below 12, 4) include coverage for MDS and Multiple Myeloma, 5) maintain coverage for patients receiving VEGF and EGFR inhibitors, and 6) coverage be continued for as long as chemo-induced anemia continues up to 12 weeks after chemotherapy is concluded. Thank you for inviting my comments.

Sincerely,



John A. Hayward, MD

JAH:sdg

## Physicians

### *Hematology & Oncology*

Thomas A. Alberico, MD  
Burton F. Alexander, III, MD  
Daniel M. Atienza, MD  
Bruce W. Booth, MD  
Robert L. Burger, MD, FACP  
Paul R. Conkling, MD  
Scott J. Cross, MD  
Mark T. Fleming, MD  
Edward R. George, MD, FACP  
Elizabeth A. Harden, MD, FACP  
John R. Howard, Jr., DO  
John F. Kessler, MD, FACP  
Scott Kruger, MD, FACP  
Michael E. Lee, MD  
John Q. A. Mattern, II, DO  
Dean S. McGaughy, III, MD  
John C. Paschoid, MD, FACP  
David M. Powell, MD  
Christina W. Prillaman, MD, FACP  
John J. Regan, MD  
Ronald J. Ruszkowski, MD  
S. George Saman, MD  
Joseph J. Schulz, MD  
Michael S. Steinberg, MD, FACP  
Alexander K. Su, MD  
Valiant D. Tan, MD

### *Gynecological Oncology*

Johnny Hyde, MD  
Munir F. Nasr, MD, FACOG  
Stacey J. Rogers, MD, FACOG  
Robert C. Squatrito, MD, FACOG

### *Radiation Oncology*

Michael L. Miller, DO

### **Office Locations** *Southside*

5900 Lake Wright Drive  
Norfolk, VA 23502  
(757) 466.8683  
FAX (757) 466.8892

1950 Glenn Mitchell, Ste. 102  
Virginia Beach, VA 23456  
(757) 368.0437  
FAX (757) 368.0492

5818 Harbour View Blvd, Suite 230  
Suffolk, VA 23435  
(757) 686.1042  
FAX (757) 686.1055

102 Fairview Dr, Suite E  
Franklin, VA 23851  
(757) 569.9709  
FAX (757) 569.6102

300 Medical Parkway, Suite 314  
Chesapeake, VA 23320  
(757) 549.4403  
FAX (757) 549.4332

150 Burnett's Way, Suite 310  
Suffolk, VA 23434  
(757) 539.0670  
FAX (757) 539.1062

### *Peninsula*

895 Middle Ground Blvd, Bldg 200  
Newport News, VA 23606  
(757) 873.9400  
FAX (757) 873.9420

3000 Coliseum Dr, Suite 104  
Hampton, VA 23666  
(757) 827.9400  
FAX (757) 827.9320

3901 Treyburn Dr, Suite 2A  
Williamsburg, VA 23185  
(757) 229.2236  
FAX (757) 221.0409

6876 Main Street  
Gloucester, VA 23061  
(804) 693.3232  
FAX (804) 693.3342

### *North Carolina*

1503 B North Road St.  
Elizabeth City, NC 27909  
(252) 331.2044  
FAX (252) 331.1909

5565 Croatian Highway  
Kitty Hawk, NC 27949  
(252) 261.5800  
FAX (252) 261.5301

### *Central Business Office*

5900 Lake Wright Dr, Suite 300  
Norfolk, VA 23502  
(757) 213.5700  
FAX (757) 213.5701  
TOLL FREE (800) 998.3450

### **Web Address**

[www.virginiacancer.com](http://www.virginiacancer.com)



# Virginia Oncology Associates

June 5, 2007

Stephen Phurrough, MD, MPA  
Elizabeth Koller, MD, F.A.C.E.

Marsha Ciccanti, RN

Coverage Analysis Group/Office of Clinical Standards  
Quality Center for Medicare and Medicaid Services

Mail Stop C1-12-28 7500  
Baltimore, Maryland 21244-1849

Re: ESA Guidelines

Dear Committee:

I am writing to express my concerns regarding the proposed  
ESA regulations.

I am very much concerned about these proposals and feel  
that my group and I have done a good job in being careful  
and even conservative in the use of ESA's. I think they  
have been a blessing to cancer and hematologically  
disordered patients and have allowed us to minimize  
transfusions and the complications of transfusions  
(transfusion reactions and iron overload issues). I  
believe that we have tried to follow appropriate guidelines  
and pathways in the use of these agents and have not overly  
used same. I believe we have followed the guidelines for  
initiation of ESA's and also the discontinuation of ESA's  
and am concerned that if the thresholds for starting ESA's  
is lowered significantly more patients will be put in harms  
way from the standpoint of needing transfusions and the  
difficulties of same and will experience clinical symptoms  
that cancer patients or hematologic disorder patients do  
not need to experience. I believe there is ample medical  
evidence to support the continued use of ESA's and while  
some adjustment in the guidelines for the use of any drug  
needs to be looked at periodically, I believe that the  
current proposed regulations will take away from the  
quality of life for the cancer or blood disordered patient  
as well as significantly stress the quantity of blood  
products available for transfusion of our patients.

23

Re: ESA guidelines  
June 5, 2007  
Page 2

I respectfully request that your group continue to look at the rationale for use of these agents and not significantly adjust the current guidelines or recommendations, but continue to evaluate clinical data as it becomes available in peer review articles.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "J. Mattern", with a stylized flourish extending from the end.

John Q. A. Mattern, II, D.O.

JQAM/ch



## Dartmouth Medical School

---

Office of Student Affairs

Remsen 302  
Hanover, NH 03755-3833  
Tel: 603 650-1509  
Fax: 603 650-1169

June 1, 2007

Maria Ciccanti, RN  
Lead Analyst  
Centers for Medicare and Medicaid Services  
7500 Security Boulevard  
Baltimore, MD 21244

RE: NCA Tracking Sheet for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N)

Dear Ms. Ciccanti:

I am writing to give my opinion on restricting the use of erythropoietin in patients with myelodysplastic syndromes. I am strongly against this. I am a hematologist-oncologist practicing at Dartmouth and its affiliated VA Hospital. I have been in practice for 29 years after training at the NCI.

Although erythropoietin doesn't work for all patients with MDS, I have seen it have dramatic effects for some, improving their quality of life enormously. I believe it is both safer and less disruptive to patients' lives than frequent transfusions have been and would urge that it be approved for patients in whom it has demonstrated efficacy.

Thank you very much.

Sincerely yours,

Joseph O'Donnell, MD  
Professor of Medicine

JOD/lcm

**Ciccanti, Maria L. (CMS/OCSQ)**

**From:** CMS CAGInquiries  
**Sent:** Tuesday, June 05, 2007 11:25 AM  
**To:** Ciccanti, Maria L. (CMS/OCSQ)  
**Subject:** FW: COMMENT: Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications

**From:** Karen Kellogg [mailto:kkellogg@utahcancer.com]  
**Sent:** Tuesday, June 05, 2007 10:31 AM  
**To:** CMS CAGInquiries  
**Subject:** COMMENT: Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications

**Title of NCA/CAL:** **Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications**

Public Comment re: Erythropoiesis Stimulating Agents (ESAs) guidelines

As an employee of Utah Cancer Specialists, and patient care advocate, I am concerned about the proposed erythropoietic stimulating agent (ESA) guidelines under consideration. While I understand the need for proper use of these medications, the proposal falls short of providing the best standard of care recommended by oncology organizations such as NCCN, ASCO and ASH. The current proposals will result in a compromised quality of life for our patients, increased blood transfusion requirements with the associated co-morbidity and risk and, ultimately, prove more costly to society than judicious use of ESAs. Please reconsider these guidelines encouraging physicians to carefully weigh the risk/benefit with patients and allow providers to treat this growing population with the best and most compassionate standard of care.

Chemotherapy-induced anemia is a well-known side effect of myelosuppressive therapy. Furthermore it is quite responsive to ESAs when iron stores, vitamin B12 and folate deficiencies and other underlying processes have been corrected. Holding initiation of ESA until the hemoglobin drops to  $<9$ mg/dl will delay response and most likely result in transfusion for a greater number of our chemotherapy patients. Most chemotherapy regimens last a minimum of 16 weeks (and many are much longer). Therefore, limiting the covered treatment duration to 12 weeks annually will be inadequate treatment for many of our patients on continued myelosuppressive therapy.

According to the proposed guidelines, the Myelodysplastic Syndrome population will be denied access to any form of ESA under all circumstances. While a portion of the MDS patients will not respond to ESAs, a greater number benefit from these medications; reducing the number of necessary blood transfusions, eliminating the complications of iron overload that results from transfusion, enhanced productivity by limiting time spent in a healthcare facility, and an overall improved quality of life.

We do not dispute the recommendations to discontinue use of the ESAs if the patient is non-responsive to treatment, however:

- The recommended four weeks is an inadequate timeframe in which to evaluate patient responsiveness. Former guidelines allow 12 weeks to determine response. Clearly, four weeks is an irresponsible timeframe.
- The proposed maximum treatment dose is insufficient to provide standard doses within the recommended timeframes. The maximum covered four-week treatment dose is 126,000units of Procrit and 630mcg of Aranesp. At an average dose of 40,000 units of Procrit each week, we would need 160,000 units in four weeks. The average dose of Aranesp is 300mcg per 2 weeks – so the 630mcg would be sufficient.

We encourage you to reconsider the list of specified conditions to include other myeloid and erythroid cancers as well as anemia caused by radiotherapy. Some patients will respond, therefore a trial of an ESA medication seems prudent.

Thank you for your consideration of this request. As a community oncology practice we strive to provide the optimal care to our patients. Please allow us the support we need to continue this practice.

Respectfully,

Karen Kellogg BS Pharm RPh  
 Director of Pharmaceutical Services

06/11/2007

175

**Ciccanti, Maria L. (CMS/OCSQ)**

**From:** CMS CAGInquiries  
**Sent:** Tuesday, June 05, 2007 7:30 AM  
**To:** Ciccanti, Maria L. (CMS/OCSQ)  
**Subject:** FW: COMMENT ON PROPOSED ESA GUIDELINES

**From:** Kendell Brinkmann [mailto:kbrinkmann@utahcancer.com]  
**Sent:** Monday, June 04, 2007 4:16 PM  
**To:** CMS CAGInquiries  
**Subject:** COMMENT ON PROPOSED ESA GUIDELINES

Title of NCA/CAL: Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications

Public Comment re: Erythropoiesis Stimulating Agents (ESAs) guidelines

As an employee of Utah Cancer Specialists, and patient care advocate, I am concerned about the proposed erythropoietic stimulating agent (ESA) guidelines under consideration. While I understand the need for proper use of these medications, the proposal falls short of providing the best standard of care recommended by oncology organizations such as NCCN, ASCO and ASH. The current proposals will result in a compromised quality of life for our patients, increased blood transfusion requirements with the associated co-morbidity and risk and, ultimately, prove more costly to society than judicious use of ESAs. Please reconsider these guidelines encouraging physicians to carefully weigh the risk/benefit with patients and allow providers to treat this growing population with the best and most compassionate standard of care.

Chemotherapy-induced anemia is a well-known side effect of myelosuppressive therapy. Furthermore it is quite responsive to ESAs when iron stores, vitamin B12 and folate deficiencies and other underlying processes have been corrected. Holding initiation of ESA until the hemoglobin drops to  $<9\text{mg/dl}$  will delay response and most likely result in transfusion for a greater number of our chemotherapy patients. Most chemotherapy regimens last a minimum of 16 weeks (and many are much longer). Therefore, limiting the covered treatment duration to 12 weeks annually will be inadequate treatment for many of our patients on continued myelosuppressive therapy.

According to the proposed guidelines, the Myelodysplastic Syndrome population will be denied access to any form of ESA under all circumstances. While a portion of the MDS patients will not respond to ESAs, a greater number benefit from these medications; reducing the number of necessary blood transfusions, eliminating the complications of iron overload that results from transfusion, enhanced productivity by limiting time spent in a healthcare facility, and an overall improved quality of life.

We do not dispute the recommendations to discontinue use of the ESAs if the patient is non-responsive to treatment, however:

- The recommended four weeks is an inadequate timeframe in which to evaluate patient responsiveness. Former guidelines allow 12 weeks to determine response. Clearly, four weeks is an irresponsible timeframe.
- The proposed maximum treatment dose is insufficient to provide standard doses within the recommended timeframes. The maximum covered four-week treatment dose is 126,000units of Procrit and 630mcg of Aranesp. At an average dose of 40,000 units of Procrit each week, we would need 160,000 units in four weeks. The average dose of Aranesp is 300mcg per 2 weeks – so the 630mcg would be sufficient.

We encourage you to reconsider the list of specified conditions to include other myeloid and erythroid cancers as well as anemia caused by radiotherapy. Some patients will respond, therefore a trial of an ESA medication seems prudent.

Thank you for your consideration of this request. As a community oncology practice we strive to provide the optimal care to our patients. Please allow us the support we need to continue this practice.

Respectfully,

*Kendell L. Brinkmann, RN, BC, CCN*  
 Director of Clinical Services

06/11/2007

189



Barry Boston, M.D.  
Reed Baskin, M.D.  
Kathleen Spiers, M.D.  
Furhan Yunus, M.D.  
Thomas Ratliff, M.D.  
Sohail Minhas, M.D.  
Mohammad Jahanzeb, M.D.  
Donna Przepiorka, M.D., Ph.D.  
Omar El-Ghandour, M.D.  
Francis Buadi, M.D.  
Raymond Osaroglagbon, M.D.  
Rajneesh Nath, M.D.  
Andrew Liman, M.D.

**Fellows**

Naveed Aslam, MD  
Brian McClune, DO  
Sal Vasireddy, MD  
Sarah Waheed, MD  
Jasjit C. Sachdev, MD  
Jeffrey Allen, MD  
Gregory Franz, MD  
Arshad Husain, MD  
Salil Goorha, MD

**Nurse Practitioners**

Fran Alford-West, DNSc, FNP  
Mary Nell Phillips, MSN, FNP  
Jené Smith, ACNP, MSN

**Medical Center**

1331 Union Avenue, Suite 800  
Memphis, TN 38104  
901.725.1785 866.448.2224

**East**

6005 Park Avenue, Suite 225B  
Memphis, TN 38119  
901.684.2400 800.494.9856

**Bartlett, TN**

901.383.5570 800.494.9856

**Somerville, TN**

901.516.4099 800.494.9856

**Grenada, MS**

662.294.9101 866.448.2224

**Southaven, MS**

662.349.2442 866.448.2224

**Forrest City, AR**

870.630.1700 866.448.2224

[www.utcancer.com](http://www.utcancer.com)

1331 Union Ave, Suite 800  
Memphis, TN 38104

June 11, 2007

TO: Centers for Medicare and Medicaid Services (CMS)

SUBJECT: CMS proposal for Erythropoiesis Stimulating Agents (ESA)

The University of Tennessee Cancer Institute supports the scientific medical evidence, clinical studies, and comments from the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the American Society of Hematology (ASH) concerning the upcoming CMS decision on ESA treatment guidelines for patients with cancer and other life-threatening illnesses.

Major questionable points for consideration:

1. Discontinuing treatment if no change in hemoglobin levels after four weeks is not sufficient time to allow production of red blood cells, the body takes four to six weeks, or to increase the ESA dosage per manufacturer prescribing guidelines.
2. Waiting for the hemoglobin level to be below 9g/dL Hgb to start ESA treatment is not recommended and studies have shown to reduce the occurrence of blood transfusions is to start treatment at < 11b/dL Hgb.
3. The limitation of ESA treatments to twelve weeks per year is not acceptable due to the variable regimen treatments, change in regimen therapy due to progression of disease, or the overall length of treatment time.

Our Oncologists and Hematologists must be able to use their knowledge, training, and judgment in order to give our patients the best treatments and possible outcomes. ESA treatments for our patients are an extremely important part of their success to fight these diseases, reduce the number of blood transfusions, and improve their quality of life.

Sincerely,

A handwritten signature in black ink, appearing to read 'Kevin Kramer', is written over a white background.

Kevin Kramer

Pharmaceutical Utilization Manager

For the Physicians of the University of Tennessee Cancer Institute

An artificial limitation  
that is without scientific  
basis. I am also concerned  
about the potential  
restrictions on treatment  
duration.

Thank you for your  
consideration

Sincerely,  
Lela Chellan

June 15, 2007

Dear Mr. Phurrough,  
As a member of the Medicare  
system, I am dismayed to  
learn that the Centers for  
Medicare and Medicaid  
are preparing to deny the  
use of ESA's to a significant  
portion of our country's senior  
citizens specifically, those  
suffering from Myelodysplasia  
(MDS) a bone marrow  
failure syndrome that can  
lead to Leukemia. For  
many suffering from MDS is a  
chronic disease which could  
require up to 52 weeks per yr  
treatment a limit of 12  
weeks ~~per year~~ is clearly



# Texas Society of Medical Oncology

June 13, 2007

**President**

Christopher Ruud, M.D.  
Temple

**President Elect**

Luis Campos, M.D.  
Houston

**Secretary**

Jerry D. Fain, Jr., M.D.  
Austin

**Treasurer**

William Jordan, D.O.  
Forth Worth

**Immediate Past-President**

Lewis J. Hellerstein, M.D., FACP  
Houston

**Director At Large:**

John Cox, D.O.  
Dallas

Timothy Dziuk, M.D.  
Austin

Billie Marek, M.D., FACP  
McAllen

Lon Smith, M.D.  
San Antonio

Vicente Valero, M.D.  
Houston

Steve Phurrough, MD, MPA  
Coverage Analysis Group  
Centers for Medicare & Medicaid Services  
Department of Health and Human Services  
7500 Security Blvd., Mailstop: C1-13-18  
Baltimore, MD 21244

Dear Dr. Phurrough:

Re: The Use of Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions (Administrative File: CAG #000383N)

The Texas Society of Medical Oncology (TSMO) represents over 330 practicing oncologists, many of whom engage in clinical research in or outside of academic institutions. The Centers for Medicare and Medicaid Services (CMS) has heard from some individuals as well as the organizations such as American Society of Clinical Oncology (ASCO), the American Society of Hematology (ASH), the Association of Community Cancer Centers (ACCC), various other state oncology organizations and US Oncology. These organizations gave appropriate documentation to show the following, and TSMO supports these points:

1. The use of Hgb. <9g is unreasonable and should be increased to 11g.
2. The "stopping rule" at 4 weeks is unreasonable and dose escalation should be indicated.
3. Maximum treatment duration of 12 weeks per year may be totally inadequate and might be considered, in practice, substandard care.
4. Exclusion of patients receiving VEGF and EGRF is not supported by evidence.
5. Non-coverage off Myelodysplastic Syndrome (MDS) and multiple myeloma contradicts adequate randomized studies.
6. There is no evidence that ESA use in patients with possible erythropoietin (EPO) receptors on tumors or neutralizing antibodies results in tumor progression. Evaluation of EPO receptors and antibodies are not standard and would escalate costs dramatically.

Not considered in the National Coverage Determination (NCD) is the morbidity and rare mortality from the increased use of blood transfusions and the cost involved, especially if hospital admission is required. Similarly, not studied is the adverse effect on the immune system and increased mortality as suggested by operative transfusion in patients with colon cancer.

The proposed changes may set cancer care back fifteen years, thus increasing the strain on the nation's blood supply. Blood banks and hospitals do not need the increased costs of administering lengthy blood transfusions when ESA treatment can accomplish the same goals in a manner easier for the patients.

In addition, CMS must remember that by taking ESAs, and increasing a patient's hemoglobin level, physicians are attempting to increase the quality of life of their patients that are undergoing very difficult treatments. To ask a patient to undergo a long blood transfusion, and one that can not be given in the same office that they are receiving their chemotherapy treatment, is a potential further detriment to their quality of life.

Increased tendency for Deep-Vein Thrombosis (DVT) is always a consideration in patients with malignancy and possible appropriate prophylactic measures vs. avoiding ESA's is a clinical decision not to be micromanaged by regulation. The problem is noted in the FDA insert as well as the medical literature.

One would hope that a physician would not inappropriately give any medications including ESAs. Guidelines are available through medical organizations, such as ASH and ASCO, which are more responsive to changing indications and contraindication than are federal regulations. In cases of apparent inappropriate use of current guidelines, Medicare (Trailblazer) has had a program of education, and, if indicated, suspension from the program.

Sincerely,

A handwritten signature in black ink, appearing to read "Lewis Hellerstein". The signature is written in a cursive, flowing style with some loops and flourishes.

Lewis Hellerstein, MD, FACP  
Immediate Past President, and  
Oncology CAC Representative for Texas

## Ciccanti, Maria L. (CMS/OCSQ)

---

**From:** CMS CAGInquiries  
**Sent:** Tuesday, June 05, 2007 7:29 AM  
**To:** Ciccanti, Maria L. (CMS/OCSQ)  
**Subject:** FW: aranesp

>-----Original Message-----

>From: Lisa Anderson [mailto:landerson@utahcancer.com]  
>Sent: Monday, June 04, 2007 7:03 PM  
>To: CMS CAGInquiries  
>Cc: mfetzer@utahcancer.com  
>Subject: aranesp

>  
>Title of NCA/CAL: Erythropoiesis Stimulating Agents (ESAs) for non-renal  
>disease indications  
>  
>  
>Public Comment re: Erythropoiesis Stimulating Agents (ESAs) guidelines  
>  
>As an employee of Utah Cancer Specialists, and patient care advocate, I  
>am concerned about the proposed erythropoietic stimulating agent (ESA)  
>guidelines under consideration. While I understand the need for proper  
>use of these medications, the proposal falls short of providing the  
>best standard of care recommended by oncology organizations such as  
>NCCN, ASCO and ASH. The current proposals will result in a compromised  
>quality of life for our patients, increased blood transfusion  
>requirements with the associated co-morbidity and risk and, ultimately,  
>prove more costly to society than judicious use of ESAs. Please  
>reconsider these guidelines encouraging physicians to carefully weigh  
>the risk/benefit with patients and allow providers to treat this  
>growing population with the best and most compassionate standard of care.  
>  
>Chemotherapy-induced anemia is a well-known side effect of  
>myelosuppressive therapy. Furthermore it is quite responsive to ESAs  
>when iron stores, vitamin B12 and folate deficiencies and other  
>underlying processes have been corrected. Holding initiation of ESA  
>until the hemoglobin drops to <9mg/dl will delay response and most  
>likely result in transfusion for a greater number of our chemotherapy  
>patients. Most chemotherapy regimens last a minimum of 16 weeks (and  
>many are much longer). Therefore, limiting the covered treatment  
>duration to 12 weeks annually will be inadequate treatment for many of our patients on continued  
>myelosuppressive therapy.  
>  
>According to the proposed guidelines, the Myelodysplastic Syndrome  
>population will be denied access to any form of ESA under all  
>circumstances. While a portion of the MDS patients will not respond to  
>ESAs, a greater number benefit from these medications; reducing the  
>number of necessary blood transfusions, eliminating the complications  
>of iron overload that results from transfusion, enhanced productivity  
>by limiting time spent in a healthcare facility, and an overall  
>improved quality of life.  
>  
>We do not dispute the recommendations to discontinue use of the ESAs if  
>the patient is non-responsive to treatment, however:  
>• The recommended four weeks is an inadequate timeframe in which to  
>evaluate patient responsiveness. Former guidelines allow 12 weeks to  
>determine response. Clearly, four weeks is an irresponsible timeframe.

>• The proposed maximum treatment dose is insufficient to provide  
>standard doses within the recommended timeframes. The maximum covered  
>four-week treatment dose is 126,000units of Procrit and 630mcg of Aranesp.  
>At an average dose of 40,000 units of Procrit each week, we would need  
>160,000 units in four weeks. The average dose of Aranesp is 300mcg per  
>2 weeks – so the 630mcg would be sufficient.

>  
>We encourage you to reconsider the list of specified conditions to  
>include other myeloid and erythroid cancers as well as anemia caused by  
>radiotherapy. Some patients will respond, therefore a trial of an ESA  
>medication seems prudent.

>  
>Thank you for your consideration of this request. As a community  
>oncology practice we strive to provide the optimal care to our  
>patients. Please allow us the support we need to continue this practice.

>  
>Respectfully,

>  
>  
>  
>Lisa Anderson  
>Lead RN

>



www.oncologyconsultants.com

LUIS T. CAMPOS, M.D.
American Board of Internal Medicine
American Board of Medical Oncology

MIGUEL MIRO-GUESADA, M.D.
American Board of Internal Medicine
American Board of Medical Oncology
American Board of Hematology

CHARLES E. MANNER, M.D.
American Board of Internal Medicine
American Board of Hematology

PAUL Y. HOLOYE, M.D.
American Board of Internal Medicine
American Board of Medical Oncology

DAVID B. SANFORD, M.D.
American Board of Internal Medicine
American Board of Medical Oncology
American Board of Hematology

HARRY R. PRICE, M.D.
American Board of Internal Medicine
American Board of Medical Oncology

ASHA MURTHY, M.D.
American Board of Internal Medicine
American Board of Medical Oncology
American Board of Hematology

ANNA BELCHEVA, M.D.
American Board of Internal Medicine
American Board of Medical Oncology

ALEX P. NGUYEN, M.D.
American Board of Internal Medicine
American Board of Medical Oncology

WILLIAM S. VELASQUEZ, M.D.
American Board of Internal Medicine
American Board of Medical Oncology

June 11, 2007

Steve Phurrough, MD, MPA
Director, Coverage and Analysis Group
Centers for Medicare and Medicaid Services

This is Oncology Consultants, P.A. of Houston, Texas formal comment to the Centers for Medicare and Medicaid Services (CMS) Proposed National Coverage Decision (NCD) Memorandum (CAG 00383N) for the use of Erythropoietin Stimulating Agents (ESAs) in cancer and related neoplastic conditions.

We believe that CMS should not restrict access to ESAs for proven Food and Drug Administration (FDA) indications, compendia listings and NCCN guidelines. We also disagree with the decision to enforce clinical limitations on ESAs usage regarding dose and period of administration as such decision should be left to the practicing physicians following approved guidelines.

As a result of the above proposal by CMS, more patients with myelodysplastic syndrome (MDS) and chemotherapy induced anemia will require blood transfusions, producing an additional burden on the already strained blood banks, notwithstanding the inherited potential complications of blood transfusions.

The proposed NCD use of hemoglobin under 9 (Hb < 9/dl) as the treatment initiation point is inadequate. Current data shows that many patients who receive ESAs after Hb < 9/dl will require blood transfusions because ESAs usually work six to eight weeks after the initiation of therapy. Evidence suggests that transfusion avoidance is better accomplished by an earlier intervention at a higher hemoglobin level.

Furthermore, limiting the maximum treatment duration to twelve weeks per year is arbitrary and grossly inadequate for most patients and their care will be seriously impacted, especially for those being treated with chemotherapy for metastatic disease or those with anemia of MDS.

Exclusion of patients receiving VEGF and EGFR inhibitors regardless of administration of concurrent chemotherapy is also an erroneous decision.

Table with 8 columns: MEMORIAL CITY, ST. CATHERINE, PARK PLAZA, ST. LUKES, ST. JOSEPH, SUGAR LAND, WILLOWBROOK, SOUTHWEST. Each column lists address, phone, and fax numbers for various office locations.

Handwritten number 93

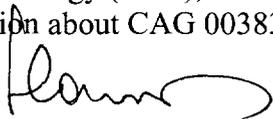
Non coverage of MDS and patients with multiple myeloma is not based on clinical data. Initial treatment for anemia of MDS with ESAs is recommended in most guidelines and it is an effective therapy in over 25% of patients. Multiple randomized trials have shown evidence of efficacy of ESAs in both diseases without any serious adverse events.

We recognize the presence of safety issues regarding the use of ESAs such as hypertension, fluid retention, thromboembolism and others that may occur in very few cases of rapid hemoglobin raise, all of which the clinician should be aware. However, the proposed restrictions are not strongly supported by scientific data and conflict with expert scientific analysis. Moreover, the proposed policy disregards recommendations made by the FDA's Oncology Drug Advisory Committee during the May 10<sup>th</sup>, 2007 meeting.

Present guidelines based on hemoglobin levels may not be perfect, but they are adequate and easy to implement. The proposed changes will place the practice of oncology where it was fifteen years ago when the supportive therapies were in their inception, forcing many patients to repetitive hospitalizations. The blood banks of the nation do not need this burden of increased transfusions that inexorably will be a product of this erroneously proposed policy.

It appears that the scientific motivation for this proposed policy is not strong enough at this time. Unfortunately, it will disrupt the care of the patients, reflecting in their wellbeing.

We support the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH), as well as other national organizations that have given their unfavorable opinion about CAG 00383N.



Oncology Consultants, P.A.  
Houston, Texas  
Luis T. Campos, MD  
Miguel V. Miro-Quesada, MD  
Charles E. Manner, MD  
Paul Y. Holoye, MD  
David R. Sanford, MD  
Harry R. Price, MD  
Asha Murthy, MD  
Anna Belcheva, MD  
William S. Velasquez, MD  
Alex P. Nguyen, MD

## Ciccanti, Maria L. (CMS/OCSQ)

---

**From:** CMS CAGInquiries  
**Sent:** Tuesday, June 05, 2007 7:30 AM  
**To:** Ciccanti, Maria L. (CMS/OCSQ)  
**Subject:** FW: Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications

>-----Original Message-----

>From: Dixie Lyons [mailto:dlyons@utahcancer.com]  
>Sent: Monday, June 04, 2007 2:43 PM  
>To: CMS CAGInquiries  
>Subject: Erythropoiesis Stimulating Agents (ESAs) for non-renal disease  
>indications  
>  
>Title of NCA/CAL: Erythropoiesis Stimulating Agents (ESAs) for non-renal  
>disease indications  
>  
>

>Public Comment re: Erythropoiesis Stimulating Agents (ESAs) guidelines  
>

>As an employee of Utah Cancer Specialists, and patient care advocate, I  
>am concerned about the proposed erythropoietic stimulating agent (ESA)  
>guidelines under consideration. While I understand the need for proper  
>use of these medications, the proposal falls short of providing the  
>best standard of care recommended by oncology organizations such as  
>NCCN, ASCO and ASH. The current proposals will result in a compromised  
>quality of life for our patients, increased blood transfusion  
>requirements with the associated co-morbidity and risk and, ultimately,  
>prove more costly to society than judicious use of ESAs. Please  
>reconsider these guidelines encouraging physicians to carefully weigh  
>the risk/benefit with patients and allow providers to treat this  
>growing population with the best and most compassionate standard of care.  
>

>Chemotherapy-induced anemia is a well-known side effect of  
>myelosuppressive therapy. Furthermore it is quite responsive to ESAs  
>when iron stores, vitamin B12 and folate deficiencies and other  
>underlying processes have been corrected. Holding initiation of ESA  
>until the hemoglobin drops to <9mg/dl will delay response and most  
>likely result in transfusion for a greater number of our chemotherapy  
>patients. Most chemotherapy regimens last a minimum of 16 weeks (and  
>many are much longer). Therefore, limiting the covered treatment  
>duration to 12 weeks annually will be inadequate treatment for many of our patients on continued  
>myelosuppressive therapy.  
>

>According to the proposed guidelines, the Myelodysplastic Syndrome  
>population will be denied access to any form of ESA under all  
>circumstances. While a portion of the MDS patients will not respond to  
>ESAs, a greater number benefit from these medications; reducing the  
>number of necessary blood transfusions, eliminating the complications  
>of iron overload that results from transfusion, enhanced productivity  
>by limiting time spent in a healthcare facility, and an overall  
>improved quality of life.  
>

>We do not dispute the recommendations to discontinue use of the ESAs if  
>the patient is non-responsive to treatment, however:  
>• The recommended four weeks is an inadequate timeframe in which to  
>evaluate patient responsiveness. Former guidelines allow 12 weeks to  
>determine response. Clearly, four weeks is an irresponsible timeframe.

>• The proposed maximum treatment dose is insufficient to provide  
>standard doses within the recommended timeframes. The maximum covered  
>four-week treatment dose is 126,000units of Procrit and 630mcg of Aranesp.  
>At an average dose of 40,000 units of Procrit each week, we would need  
>160,000 units in four weeks. The average dose of Aranesp is 300mcg per  
>2 weeks – so the 630mcg would be sufficient.  
>  
>We encourage you to reconsider the list of specified conditions to  
>include other myeloid and erythroid cancers as well as anemia caused by  
>radiotherapy. Some patients will respond, therefore a trial of an ESA  
>medication seems prudent.  
>  
>Thank you for your consideration of this request. As a community  
>oncology practice we strive to provide the optimal care to our  
>patients. Please allow us the support we need to continue this practice.  
>  
>Respectfully,  
>  
>Dixie Lyons RN  
>

THE UNIVERSITY OF TEXAS  
MD ANDERSON  
CANCER CENTER

June 12, 2007

Steve Phurrough, MD, MPA  
Director  
Coverage and Analysis Group  
Centers for Medicare & Medicaid Services  
7500 Security Boulevard  
Baltimore, MD 21244

**By Electronic Delivery and Overnight Delivery**

**Re: Proposed Coverage Decision Memorandum for the Use of Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions (CAG-00383N)**

**Dear Dr. Phurrough, M.D., MPA:**

**Summary**

The University of Texas M. D. Anderson Cancer Center is the largest center devoted exclusively to cancer prevention, research and treatment. In 2006, we served over 79,000 patients including 27,000 new patients. The use of the ESAs included approximately 4000 unique Medicare beneficiary patients for 2006 at the institution. Based on our concern that proposed rules may affect the quality of care and may compromise our patients, the institution is submitting the following comments for consideration.

While some of the proposals follow the FDA recommendations, others are not well thought out and do not appear to be supported by the evidence presented to the FDA. Standard of care for cancer patients include not only the FDA approved indication, but also, indications supported by references and in medical compendia. Many oncology groups across the nation have reviewed the literature and provide clinical guidance for the use of these drugs. We believe CMS should rely on best practices and evidence based guidelines to structure their payment program that includes but not limited to the following reviews by the Alliance for Dedicated Cancer Centers, National Comprehensive Cancer Network, American Society of Clinical Oncology, and US Oncology Physician Network

The following response provides an evidence-based response and adds clinical experience information to your proposal. Please be advised that comments reflect the need for continued coverage to provide the best and most appropriate care for our patients. Unsuitable limitations in coverage and reimbursement will affect our ability to care for our patients.

**Elements for comment**

**I. Insufficient evidence to support use of ESAs for below conditions:**

- 1. Any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis.**

**Comments:**

- Many other co-morbid conditions may co-exist with chemotherapy-induced anemia. That does not preclude a benefit from ESAs for these patients. This is an area that has not been studied sufficiently to rule out any benefit. In fact, many of the studies of ESAs in cancer patients did not routinely screen

patients for folate, B-12, or iron deficiency. As with many published guidelines, correction of concurrent deficiencies or factors should be included in the treatment plan.

## 2. The anemia of myelodysplasia.

Comments:

- This should continue to be an indication for coverage based on published evidence.
- There is sufficient evidence to support the use of ESAs as supportive therapy for patients with myelodysplastic syndrome, with or without myeloid growth factors.
- Use of ESAs is clearly supported in national guidelines, such as NCCN.

References to support MDS as an appropriate indication for ESAs:

Casadevall N, Durieux P, Dubois S, et al: Health, economic, and quality-of-life effects of erythropoietin and granulocyte colony-stimulating factor for the treatment of myelodysplastic syndromes: A randomized, controlled trial. *Blood* 104:321-327, 2004.

Stein RS, Abels RI, Krantz SB: Pharmacologic doses of recombinant human erythropoietin in the treatment of myelodysplastic syndromes. *Blood* 78:1658-1663, 1991.

Hellstrom-Lindberg E, Gulbrandsen N, Lindberg G, et al: A validated decision model for treating the anemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: Significant effects on quality of life. *Br J Haematol* 120:1037-1046, 2003.

Goy A, Belanger C, Casadevall N, et al: High doses of intravenous recombinant erythropoietin for the treatment of anaemia in myelodysplastic syndrome. *Br J Haematol* 84:232-237, 1993.

Mannone L, Gardin C, Quarre MC, et al: High-dose darbepoetin alpha in the treatment of anaemia of lower risk myelodysplastic syndrome results of a phase II study. *Br J Haematol* 133:513-519, 2006.

Stasi R, Abruzzese E, Lanzetta G, et al: Darbepoetin alfa for the treatment of anemic patients with low- and intermediate-1-risk myelodysplastic syndromes. *Ann Oncol* 16:1921-1927, 2005.

Musto P, Lanza F, Balleari E, et al: Darbepoetin alpha for the treatment of anaemia in low-intermediate risk myelodysplastic syndromes. *Br J Haematol* 128:204-209, 2005.

Clavio M, Balleari E, Garrone A, et al: Haemopoietic growth factors in myelodysplastic syndromes: Towards patient-oriented therapy? *J Exp Clin Cancer Res* 24:5-16, 2005.

Balleari E, Rossi E, Clavio M, et al: Erythropoietin plus granulocyte colony-stimulating factor is better than erythropoietin alone to treat anemia in low-risk myelodysplastic syndromes: Results from a randomized single-centre study. *Ann Hematol* 85:174-180, 2006.

Arshad M, Seiter K, Bilaniuk J, et al: Side effects related to cancer treatment: CASE 2. Splenic rupture following pegfilgrastim. *J Clin Oncol* 23:8533-8534, 2005.

Tsimberidou AM, Giles FJ, Khouri I, et al: Low-dose interleukin-11 in patients with bone marrow failure: Update of the M. D. Anderson Cancer Center experience. *Ann Oncol* 16:139-145, 2005.

Kaushansky K: Lineage-specific hematopoietic growth factors. *N Engl J Med* 354:2034-2045, 2006.

### **3. Anemia of myeloid cancers.**

Comments:

- There is literature to support the benefit of ESAs in CML.

Cortes J, O'Brien S et.al., Erythropoietin is Effective in Improving the Anemia Induced by Imatinib Mesylate Therapy in Patients with Chronic Myeloid Leukemia in Chronic Phase. *Cancer* 2004, 100:2396-2402.

- There is no literature to demonstrate a deleterious effect on AML patient
- Needs to be studied in clinical trials.

### **4. Anemia associated with the treatment of myeloid cancers or erythroid cancers.**

Comments:

- See comments for "Anemia of myeloid cancers."
- Needs to be studied in clinical trials.

### **5. The anemia of cancer not related to cancer treatment.**

Comments:

- More research required. This research should target lower hemoglobin levels (< 12 g/dL). Previous studies that demonstrate potential risk were for a higher targeted hemoglobin level.

### **6. Any anemia associated with radiotherapy.**

Comments:

- If the patient is concurrently receiving chemotherapy, then the patient should be a candidate for ESAs. i.e. chemoradiation treatment.
- Needs to be studied in clinical trials.

### **7. Prophylactic use to prevent chemotherapy-induced anemia.**

Comments:

- Needs to be studied in clinical trials.

### **8. Prophylactic use to reduce tumor hypoxia.**

Comments:

- Needs to be studied in clinical trials.

### **9. Patients with erythropoietin-type resistance due to neutralizing antibodies.**

Comments:

- We do not have a mechanism to test patients for neutralizing antibodies in the general population.
- There is no clinical situation in which this would be checked outside the context of a clinical trial.

**10. Patients with treatment regimens including anti-angiogenic drugs such as bevacizumab.**

Comments:

- There is no evidence that ESAs antagonize the therapeutic effect of anti-angiogenesis drugs, therefore there is no clinical rationale for non-coverage.
- Selected agents in this group are known to produce anemia and are often given with myelosuppressive chemotherapy.
- It should be noted that a consistent method of coding be utilized to differentiate between receiving chemotherapy and receiving anti-angiogenic drugs.

**11. Patients with treatment regimens including monoclonal/polyclonal antibodies directed against the epidermal growth factor (EGF) receptor.**

Comments:

- There is no evidence that ESAs antagonize the therapeutic effect of monoclonal/polyclonal antibodies therefore, there is no clinical rationale for non-coverage.
- Patients frequently receive these drugs concurrently with chemotherapy. These patients should be candidates for ESAs.

**12. Anemia due to cancer treatment if patients have uncontrolled hypertension.**

Comments:

- Uncontrolled hypertension needs to be defined.
- Any patient that is initiated on anti-hypertensive therapy and is subsequently controlled should be eligible for treatment with ESAs.

**13. Patients with thrombotic episodes related to malignancy.**

Comments:

- Patients treated with active or preventive anticoagulants are not at higher risk, therefore should be eligible for coverage.

**II. Proposed Reasonable and Necessary Indication for Anemia in cancers with the presence of erythropoietin receptors:**

Comments:

- Previous information released by the FDA does not support the conclusion to exclude these malignancies.
- The clinical relevance of receptors is unknown. Receptors exist in normal epithelial cells. No clinically meaningful level of over expression has been established.
- There are no available methods that establish sensitive and specificity for erythropoietic receptors.

**III. Proposed limitations:**

**1. Less than 9g/dl/27% in patients without known cardiovascular disease or less than 10g/dl/30% in patient with documented symptomatic ischemic disease.**

Comments:

- Most systematic reviews and international guidelines for the use of ESAs clearly state that an optimal hemoglobin level for initiating ESA therapy cannot be determined with the current evidence. Most of these publications also state a level of 9-11 g/dL as an appropriate starting point. Below 9 g/dL, most patients would be eligible for a red cell transfusion, if blood is available. However, with the shortage of

blood and blood products, it is prudent to try to begin therapy earlier to avoid the use of a scarce resource. Of course, preventing the hemoglobin level from rising above 12 g/dL.

- Blood product availability is of utmost importance. This is a finite commodity that is fraught with shortages and availability issues with relatively few eligible donors due to necessary, extensive screening. Blood transfusions also carry a risk of long term consequences including iron overload, infection and/or alloimmunization.
- In addition to a hemoglobin level as an initiation parameter, it is important that patient symptom also included the decision to initiate ESA therapy. Studies demonstrate quality of life indicators are associated with improved outcomes and minus any data to the contrary, existing guidelines should be accepted for coverage.

**2. Maximum covered treatment duration is 12 weeks/year.**

Comments:

- The maximum covered treatment needs to be for the duration of the chemotherapy; and 90 days post last dose of chemotherapy to allow for the bone marrow recovery.
- There is a potential for cyclic chemotherapy that may be months apart, with other modalities in between, so the 12 weeks/year is not reasonable.
- It is not possible to determine administratively how many weeks of therapy a patient have received across institutions and sometimes even across geographic regions.
- There is no mechanism in place to determine and monitor 12 weeks of therapy, on a rolling calendar basis.
- There is not data to support this restriction. Most chemotherapies are continued for many months and most patients with solid tumors receive first, second and third-line therapy or more with significant benefit. Therefore, this grossly underestimates the need for ESA therapy in chemotherapy-induced anemia.

**3. Maximum covered 4 week treatment dose is 126,000 units for erythropoietin and 630 mcg. for darbepoietin.**

Comments:

- Standard dosing for epoetin alpha is 40,000 units per week (approved dosing). The dosage of 126,000 units per 4 weeks is too low for this dosing schedule and needs to be increased. Maximum dosing based on an average i.e. 70 kg patient is not clinically applicable.
- For 10 years, clinical practice utilized a dose-escalation strategy in patients who did not have early response. Over the years, this practice has been questioned, but not clearly answered. Some meta-analyses have attempted to address the question of efficacy with this practice, but it is not clearly answered with the available data. Nonetheless, escalation has not been shown to be detrimental if the stopping point of 12 g/dL is followed. Only with targeting higher hemoglobin levels did they begin to see problems. So, this is not a dose-response phenomenon, it is a hemoglobin response phenomenon. Again, there is no data to refute to safety of dose escalation. There is equivocal evidence to support improved outcomes with this approach to dosing. Further research is needed.
- Additionally, darbepoetin dosing is not consistent. Generally patients will receive up to 600 mcg/week.

**4. Continued use of the drug is not reasonable and necessary if there is evidence of poor drug response after 4 weeks of treatment.**

Comments:

- Most responses to ESAs are seen at around 5-7 weeks. Therefore, a stopping point of 4 weeks without response seems more reasonable and evidence-based, since most of the clinical trials used this as a primary endpoint.
- Reported hemoglobin levels are not always reflective of drug activity Hemoglobin level can also be affected by fluid status and is not always accurate given a specific clinical situation.
- Previous studies show that ESAs have the majority of response after the fifth week of therapy. Discontinuation of treatment prior to the needed time to response will have negative patient consequences.

- The ability to measure and track levels will be difficult to operationalize.

5. **Continued administration of the drug is not reasonable and necessary if there is an increase in fluid retention or weight after 2 weeks of treatment.**

Comments:

- These are very nebulous and subjective criteria. These symptoms can be associated with many different clinical scenarios, including toxicity from chemotherapy (e.g., docetaxel fluid retention). It does not seem reasonable to discontinue therapy that has very little likelihood to cause these problems (the ESA). The incidence of these adverse effects related to ESAs is very low and is usually not clinically relevant.
- Administrative pitfalls exist in implementation: need to identify specific ICD-9 codes for this condition.

6. **Continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin/hematocrit after 2 weeks of treatment.**

Comments:

- It would be more prudent to state that, in the absence of a recent transfusion, perhaps the dose of ESA should be lowered by 50% and the patient monitored closely. If the hemoglobin level reaches 12 g/dL, the ESA should be stopped and reinitiated when it falls below 10g/dL.

IV. **Limiting coverage of ESAs to clinical studies:**

Comments:

- Clinical studies are not feasible for every situation. FDA is responsible for monitoring safety and efficacy of drug products. Existing methods to reach a clinical decision should continue through the existing methods.
- Clinical trials should not be used as a method to further restrict coverage for ESAs in cancer patients.

Conclusion

CMS's proposal to limit reimbursement for accepted standard of care is infringing on the clinical decision making process. Reimbursement policy should not be used to replace FDA's responsibility for appropriate review of drug indication, dosing, scheduling, monitoring and safety. The use of expert panels to determine appropriate use should be continued without interference from CMS. ESAs should be used judiciously with patient safety and benefit as the guiding principle. We recommend withdrawal of the proposal until further information and recommendations come from the FDA.

Sincerely,



M. Alma Rodriguez, M.D., F.A.C.P., Vice President of Medical Affairs, Professor of Medicine, Lymphoma/Myeloma



Tejpai Grover, M.D., MBA, Associate Professor, Chairman, Pharmacy Committee



Joel D. Lajeunesse, M.S., R.Ph., Vice President, Pharmacy



*American Association  
for Cancer Research*

615 Chestnut Street • 17th Floor • Philadelphia, PA 19106-4404  
Telephone: (215) 440-9300 • Fax: (215) 440-9313 • www.aacr.org

Margaret Foti, Ph.D., M.D. (h.c.)  
Chief Executive Officer

June 13, 2007

Steve Phurrough, MD, MPA, CPE  
Director, Coverage and Analysis Group  
Office of Clinical Standards and Quality  
Centers for Medicare and Medicaid Services  
Department of Health and Human Services  
Mail Stop: C1-09-06  
7500 Security Boulevard  
Baltimore, Maryland 21244

Dear Dr. Phurrough:

RE: National Coverage Analysis for Erythropoiesis Stimulating Agents (ESAs) for Non-Renal Disease Indications (CAG-00383N)

With a membership of over 26,000 basic, translational, and clinical researchers; healthcare professionals; cancer survivors; and patient advocates, the American Association of Cancer Research (AACR) is the oldest and largest professional organization dedicated to cancer research and the conquest of cancer. The AACR appreciates the opportunity to comment on the Proposed Decision Memorandum for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N).

The AACR recognizes the need to carefully consider the appropriate use of ESAs; however, we have significant concerns regarding the lack of sound scientific and clinical data to support certain conditions of the proposed decision memorandum. We have therefore prepared the accompanying commentary and analysis of existing data on this topic from our perspective as cancer researchers and clinical investigators in the academic setting, focused on the science of cancer biology. It is of paramount importance that all coverage decisions are guided by the best available scientific evidence such that treatments with optimum benefit and safety can be delivered to cancer patients.

### **Erythropoietin Receptors**

The AACR is particularly concerned with CMS' decision to base several provisions of the proposed coverage decision memorandum upon an evidence review that appeared to indicate that the presence of erythropoietin receptors (EPO-R) expressed by human tumor cells may predict increased risk for tumor progression and poorer overall survival in patients suffering from

cancer. The AACR strongly believes that the available evidence does not support a link between the expression of EPO-R by human tumor cells and poorer clinical outcomes.

It is apparent from the detailed background review included in the proposed decision memorandum that CMS quite appropriately hopes to ground the agency's updated ESA coverage recommendations upon the highest quality clinical evidence available. One commonly accepted definition of evidence-based medicine (EBM) is as follows: "Evidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision-making, and stresses the examination of evidence from clinical research."<sup>1</sup> Despite this definition, CMS' concerns about EPO-R in cancer appear to be based primarily on pathophysiologic rationale, and not on robust clinical evidence.<sup>2</sup> In addition, much of the existing body of literature regarding EPO-R expression in human cancer has recently been shown to be flawed, as several independent groups have now demonstrated that the reagents used to detect EPO-R in the majority of published studies actually have suboptimal staining properties, detecting cellular proteins other than EPO-R.<sup>3,4</sup> Therefore, coverage decisions based on theoretical concern about EPO-R expression in tumor cells cannot be considered to be EBM at present.

EPO-R mRNA has been reported in many normal tissues (e.g., brain<sup>5</sup>, muscle<sup>6</sup>, vascular endothelium<sup>7</sup>, endometrium<sup>8</sup>), albeit detected at levels much lower than those erythropoietic marrow cells that rely on endogenous or recombinant erythropoietin as a growth and survival factor. Studies of both primary cancer cells and immortalized cells in culture have not demonstrated higher levels of EPO-R mRNA when compared to these healthy tissues.

Additionally, the presence of EPO-R mRNA does not indicate the presence of functional cell surface EPO-R, as most EPO-R protein is not expressed on the cell surface, and that which is expressed on the cell surface can only be functional if it is present in the proper conformation and is associated with the intracellular Janus Kinase (JAK) tyrosine kinases. Although immunoblot analysis has detected moderate amounts of possible EPO-R in cancer cell lines, little or no receptor was detectable on the cell surface.<sup>9</sup> Consistent with that finding, in several studies, erythropoietin levels 10- to 1000-fold greater than the maximum plasma level observed in patients receiving doses of epoetin approved by the Food and Drug Administration (FDA) have been necessary in order for EPO-R stimulation to be observed in neoplastic cells *in vitro*.<sup>10</sup> In one such study, investigators had to culture cancer cells in a medium containing erythropoietin at an extraordinary high concentration – 250,000 U/L – before EPO-R-mediated tyrosine phosphorylation was observed.<sup>11</sup>

Currently, only polyclonal affinity-purified rabbit antibodies are commercially available for the putative detection of EPO-R on immunoblots and in immunochemical preparations. The three polyclonal antisera most widely used by investigators in the past 10 years include C-20 and M-20 (both marketed by Santa Cruz Biotechnology, Santa Cruz, California), and 07-311 (Upstate Biotechnology, Lake Placid, New York). When the sensitivity and specificity of the two Santa Cruz Biotechnology antibodies were recently analyzed in non-hematopoietic tissues, they performed quite poorly.<sup>3,4</sup> The C-20 antibody detected 3 proteins in tumor cell lines (35, 66 and 100 kDa); none of these proteins were within the predicted range for EPO-R (56-57 kDa).<sup>4</sup> The 66-kDa protein turned out to be a heat shock protein (HSP70) to which antibody binding was

abrogated in peptide competition experiments. Antibody M-20 identified a 59-KDa protein, potentially consistent with EPO-R, but neither M-20 nor C-20 proved suitable for detection of EPO-R using immunohistochemical methods: both demonstrated a positive signal in tissue sections taken from EPO-R knockout mice, where no EPO-R at all was present. With respect to the 07-311 antibody, Upstate Biotechnology recently withdrew this reagent from the market after its limitations were recognized by their scientists.

Of the 21 publications cited by CMS in the agency's evaluation of EPO-R expression in human tumor cells, 12 used the flawed Santa Cruz C-20 antibody, 3 used the withdrawn Upstate antibody or antisera similar to the Upstate reagent, 1 used an uncharacterized EPO-R antibody, 2 were reviews, and 3 publications dealt primarily with normal tissue or with erythroleukemia cells. Notably, the widely cited EPO-R analysis of the German Head & Neck Cancer study by Henke and colleagues, published in the *Journal of Clinical Oncology* in 2006, also used the flawed C-20 antibody.<sup>10, 12</sup> Therefore, these data have significant limitations, and the AACR believes that this body of evidence cannot be used to make a coverage determination about the use of ESAs in clinical practice.

### **Myelodysplastic Syndromes**

The AACR also has serious concerns about the decision by CMS to discontinue coverage of ESAs in conjunction with anemia of myelodysplastic syndrome (MDS). In MDS, erythroid progenitor cells are commonly part of the disease clone. Therefore, if any clinical disorder were to exhibit an undesired cell proliferative effect in the presence of ESAs, it might be expected to be MDS. However, this theoretical concern has not been borne out by clinical experience. Moreover, there exists abundant evidence of salutary clinical effect of ESAs in MDS. Indeed, ESA use in patients with MDS is part of a quality-of-care metric recently supported by CMS, and the use of ESA therapy in this setting is an integral part of expert guidelines and is uniformly supported by the clinical community. The AACR acknowledges and fully supports the efforts of CMS to limit the use of ESAs in clinical settings in which the potential for benefit is limited or does not outweigh the potential risks; however, select hematologic malignancies, such as MDS, represent a distinct exception.

Red blood cell (RBC) transfusion-dependence develops in the majority of MDS patients over time, and is recognized to adversely impact overall survival with a corresponding increased risk of leukemia progression that is incrementally proportionate to rises in RBC transfusion burden.<sup>13, 14</sup> Unlike non-hematologic malignancies, ESA treatment in MDS directly targets the malignant clone, and both prospective randomized phase III trial data and retrospective case control studies provide strong support for a significant survival benefit with reduction in leukemia potential in ESA responders. For patients with MDS, ESAs positively affect not only patient quality of life through reduction in transfusions and consequent organ complications related to overload, but also favorably impact overall survival and the risk for progression to acute myeloid leukemia (AML).

The only Phase III clinical trial evaluating hematologic response and the long-term benefit and safety of ESA treatment in MDS was performed by the Eastern Cooperative Oncology Group (ECOG). This study included 105 MDS patients randomized to treatment with either supportive

care alone or supportive care with recombinant human erythropoietin (rhuEPO) administered at a dose of 150  $\mu$ /kg/d. The dose of rhuEPO was increased to 300  $\mu$ /kg/d in the absence of hematologic response after four months of treatment. Patients randomized to supportive care alone could cross over to the rhuEPO arm after 4 months if they had a documented 50% or greater increase in transfusion requirement. Bone marrow aspirate and biopsy, as well as assessments of iron stores were evaluated before there was any change in treatment. Overall, 35% of patients treated with rhuEPO achieved an erythroid response compared to 9% in the supportive care arm ( $p=.002$ ). Of the patients who crossed over to rhuEPO treatment, 30% responded. Transformation to AML occurred in 3.6% of patients on supportive care and 0% of patients receiving rhuEPO with no difference in the frequency or distribution adverse events in either arm. Of particular importance, there was a significant survival advantage for erythroid responders who had a median survival of 53 months compared to 26 months for non-responders ( $p=.009$ ). Neither rhuEPO nor the addition of G-CSF was associated with an increase in the rate of transformation to acute leukemia.<sup>15</sup>

Jadersten et al. reported on the cumulative results from three Nordic MDS Group trials involving 129 MDS patients treated with ESAs that were followed for a minimum of 45 months after the last study entry. In this analysis, 129 patients treated with ESAs were followed for a minimum of 45 months after the last study entry. These trials evaluated treatment with rhuEPO at varied doses, with or without G-CSF. 39% of patients achieved a major erythroid response, characterized by an increase in hemoglobin  $>115$  g/L without need for RBC transfusion, and with a durable median duration of response of 23 months. 29% of the transfusion-dependent patients became transfusion independent during the study. Patients with a favorable response profile, as characterized by serum EPO concentration ( $<500$ mU/ml) and transfusion frequency ( $<2$  units/month), had a response rate of 60% and a median response duration of 24 months. Only 1 of 20 long-term responders developed AML. This study assessed the effect on long-term outcome by comparing treated patients with untreated patients selected from the IPSS database using multivariate Cox regression analysis, adjusting for major prognostic variables. There was no difference in survival (odds ratio [OR], 0.9; 95% confidence interval [CI], 0.7-1.2;  $P = .55$ ) or risk of AML evolution (OR, 1.3; 95% CI, 0.7-2.2;  $P = .40$ ) between treated and untreated patients.<sup>16</sup>

A second analysis performed by the Nordic Group compared treatment outcome with ESA to case matched, untreated controls from the University of Pavia database. All patients were anemic (Hgb  $<10$  g/dl) or transfusion dependent. Patients were matched for RBC transfusion burden, WHO category, and International Prognostic Scoring System (IPSS) risk score. Treatment with rhuEPO  $\pm$ G-CSF was associated with a significant improvement in survival in those MDS patients with low transfusion requirement compared to the untreated patients (HR 0.44,  $P < 0.001$ ). Moreover, ESA treatment response was associated with a lower risk of AML transformation compared to non-responders and untreated matched controls (HR 0.39,  $P = 0.001$ ). Although limited by its retrospective design, these data are consistent with the results of the ECOG prospective Phase III trial, and they support the notion that treatments such as ESA that effectively restore erythroid maturation potential in MDS are safe, and perhaps of greater importance may favorably impact the natural history of disease and lower the risk for AML progression.<sup>17</sup>

Similar findings were reported from an analysis of the Groupe Francophone des Myélodysplasies (GFM) experience involving 419 patients treated with ESAs in clinical trials performed between 1998 and 2005, which were compared to case matched MDS patients managed solely with supportive care in the IPSS/IMRAW database.<sup>18</sup> RhuEPO introduction was modeled as a time-dependent covariate. After 5 years follow-up, 8% of patients receiving rhuEPO and 16% of untreated patients in the IMRAW cohort progressed to AML ( $p=0.0002$ ). Multivariate analysis showed that EPO treatment ( $HR=0.2$ ,  $CI_{95\%} 0.1-0.3$ ) was independently associated with a lower risk for progression to AML in addition to favorable karyotype ( $HR=0.6$ ,  $CI_{95\%} 0.4-0.8$ ). Overall survival from diagnosis of MDS was significantly longer in the ESA-treated cohort with a 5-year overall survival of 82% vs. 47% for the IMRAW groups, respectively ( $p<0.0001$ ). These data further support the notion that response to ESA treatment is associated with a reduced risk of AML progression and improved survival in MDS patients.<sup>19</sup>

In addition to the positive impact on survival and transformation to AML, accumulating data in MDS indicate that debilitating fatigue and transfusion dependence significantly negatively impact patients' quality of life.<sup>20</sup> MDS primarily affects the elderly (median age: 65-70). Advanced age and conditions preclude the majority of MDS patients from receiving potentially curative treatment. Therefore, the AACR contends that symptomatic relief from anemia with ESAs should remain a therapeutic option for those MDS patients who have been shown to benefit from such treatment. The currently proposed policy of CMS would have significant adverse consequences for patients with MDS. We endorse the prior National Comprehensive Cancer Center Network (NCCN) recommendations for ESA use in the management of symptomatic anemia in MDS patients with low or intermediate-1 risk IPSS risk score (NCCN MDS Practice Guidelines v.1.2007) with a target hemoglobin of up to 12gm/dl.

### **Other Proposed Indications**

Moreover, the AACR also has serious reservations regarding the treatment restrictions outlined by CMS, including the guidelines for hemoglobin/hematocrit levels prior to initiation of therapy, the dosage and treatment duration recommendations, and indications for discontinuation of use following non-responsiveness at 4 weeks or in the case of fluid retention, as there is a profound lack of scientific data or clinical rationale to support these proposed restrictions.

### **In Conclusion**

The above analysis supports the view of the AACR that, to date, there is no credible scientific evidence to support the contention that human solid tumor cells express functional surface receptors for erythropoietin or that exposure to recombinant human erythropoietin promotes the survival or proliferation of human nonmyeloid malignancies, nor is there is any evidence that recombinant erythropoietin promotes leukemic progression in myelodysplastic states. Indeed, based on the available evidence, ESA therapy in MDS is clearly beneficial in terms of hemoglobin and transfusion endpoints. Furthermore, treatment of MDS patients with ESA may improve survival and the rate of progression to acute leukemia has been shown to be either unaltered or decreased. Therefore, the AACR supports the use of ESAs in these instances.

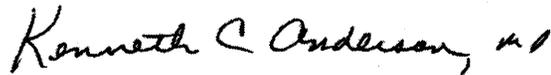
AACR  
June 13, 2007  
6

The AACR has serious concerns about CMS' proposed National Coverage Decision on the use of ESAs. Based on scientific evidence and the expert consensus of cancer researchers and physician-scientists, the AACR differs with the proposed restrictions and limitations on the use of ESAs. While current safety concerns suggest the need for CMS to review its policies concerning ESAs, the AACR believes that a number of the proposals in the NCA are not supported by scientific data in the literature and they are in conflict with expert scientific analysis.

The AACR respectfully asks that CMS take under consideration the scientific data cited above, as well as, the current and future deliberations of the FDA on this matter before finalizing its NCA for the use of ESAs. In addition, the AACR is partnering with the American Society of Hematology in a joint Task Force of experts to definitively clarify the risk-benefit of ESAs; this group of knowledgeable scientists is currently performing a rigorous analysis of the scientific and clinical issues surrounding their use for certain indications. Our scientific societies will be preparing these findings for submission to a peer-reviewed scientific publication in the near future.

We look forward to working with CMS as the agency examines the evidence for its proposed coverage policy and its implications for patients. Please do not hesitate to contact the AACR at [foti@aacr.org](mailto:foti@aacr.org) if we can answer any questions or provide assistance to CMS on this vitally important subject.

Sincerely yours,



Kenneth C. Anderson, MD  
Director, Jerome Lipper Multiple Myeloma Center,  
Dana-Farber Cancer Institute, Boston, MA



David P. Steensma, MD, FACP  
Associate Professor of Medicine  
Mayo Clinic, Rochester, MN



Alan F. List, MD  
Division Chief Malignant Hematology  
H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

AACR  
June 13, 2007  
7

Handwritten signature of Margaret Foti in cursive script.

Margaret Foti, PhD, MD (hc)  
Chief Executive Officer

Handwritten signature of Geoffrey M. Wahl in cursive script.

Geoffrey M. Wahl, PhD  
Past President

Handwritten signature of Raymond N. DuBois in cursive script.

Raymond N. DuBois, MD, PhD  
President-Elect

## Disclaimer

William N. Hait, MD, PhD, is President of the American Association for Cancer Research and a Senior Vice President with Johnson & Johnson Pharmaceuticals. Recognizing the possibility of a conflict of interest with respect to AACR's scientific analysis of data relating to the use of ESAs, Dr. Hait has recused himself from all discussion, deliberation, and actions taken by the AACR in this matter. Further, Dr. Hait has transferred all Presidential authorities relevant to this issue to AACR President-Elect, Raymond N. DuBois, MD, PhD, Professor, Vanderbilt-Ingram Cancer Center.

## REFERENCES

1. Evidence-based medicine. A new approach to teaching the practice of medicine. Evidence-Based Medicine Working Group. *Jama* 1992;268(17):2420-5.
2. Osterborg A, Aapro M, Cornes P, Haselbeck A, Hayward CR, Jelkmann W. Preclinical studies of erythropoietin receptor expression in tumour cells: impact on clinical use of erythropoietic proteins to correct cancer-related anaemia. *Eur J Cancer* 2007;43(3):510-9.
3. Brown WM, Maxwell P, Graham AN, Yakkundi A, Dunlop EA, Shi Z, et al. Erythropoietin receptor expression in non-small cell lung carcinoma: a question of antibody specificity. *Stem Cells* 2007;25(3):718-22.
4. Elliott S, Busse L, Bass MB, Lu H, Sarosi I, Sinclair AM, et al. Anti-Epo receptor antibodies do not predict Epo receptor expression. *Blood* 2006;107(5):1892-5.
5. Noguchi CT, Asavaritikrai P, Teng R, Jia Y. Role of erythropoietin in the brain. *Crit Rev Oncol Hematol* 2007.
6. Ogilvie M, Yu X, Nicolas-Metral V, Pulido SM, Liu C, Ruegg UT, et al. Erythropoietin stimulates proliferation and interferes with differentiation of myoblasts. *J Biol Chem* 2000;275(50):39754-61.
7. Fuste B, Serradell M, Escolar G, Cases A, Mazzara R, Castillo R, et al. Erythropoietin triggers a signaling pathway in endothelial cells and increases the thrombogenicity of their extracellular matrices in vitro. *Thromb Haemost* 2002;88(4):678-85.
8. Yasuda Y, Fujita Y, Musha T, Tanaka H, Shiokawa S, Nakamatsu K, et al. Expression of erythropoietin in human female reproductive organs. *Ital J Anat Embryol* 2001;106(2 Suppl 2):215-22.
9. Sinclair AM, Busse L, Rogers N, et al. EPO receptor transcription is not elevated nor predictive of surface expression in human tumor cells. (Abstract). *Proc Amer Assoc Cancer Res* 2005;46:5457.
10. Jelkmann W, Laugsch M. Problems in identifying functional erythropoietin receptors in cancer tissue. *J Clin Oncol* 2007;25(12):1627-8; author reply 1628.
11. Acs G, Acs P, Beckwith SM, Pitts RL, Clements E, Wong K, et al. Erythropoietin and erythropoietin receptor expression in human cancer. *Cancer Res* 2001;61(9):3561-5.
12. Henke M, Mattern D, Pepe M, Bezay C, Weissenberger C, Werner M, et al. Do erythropoietin receptors on cancer cells explain unexpected clinical findings? *J Clin Oncol* 2006;24(29):4708-13.



NORRIS COTTON  
CANCER CENTER

▲ DARTMOUTH-HITCHCOCK  
MEDICAL CENTER

One Medical Center Drive  
Lebanon, New Hampshire 03756  
www.cancer.dartmouth.edu  
(603) 653-3611  
fax (603) 653-9003

Office of the Director

June 11, 2007

Steve Phurrough, MD, MPA  
Coverage and Analysis Group  
Centers for Medicare and Medicaid Services  
Department of Health and Human Services  
Mailstop: C1-09-06  
7500 Security Boulevard  
Baltimore, MD 21244

**RE: Proposed Coverage Decision Memorandum for the Use of Erythropoiesis Stimulating Agents in Cancer and Related Neoplastic Conditions (CAG-00383N)**

Dear Dr. Phurrough,

I am writing as the Director of Norris Cotton Cancer Center at Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire to indicate my strong opposition of the proposition by CMS to discontinue re-imburement for erythropoietin stimulating agents used to treat patients with Myelodysplastic Syndrome (MDS). The proposed change by CMS strongly contradicts evidence-based research that demonstrates a clear improvement in hemoglobin levels, quality of life measures, and a decrease in the transfusion requirements for these patients.

If this proposal should be passed into law, a significant number of our MDS patients will need to receive pack red blood cell transfusions to remain alive. The impact of increased transfusion requirements for our numerous MDS patients, in a setting of red blood cell shortages, along with increased risk of infections to our patients (hepatitis virus, HIV), and a marked increased in costs required to provide transfusions, need to be seriously considered due to their impact on patient wellness and healthcare costs. The implementation of the proposed change will affect a large proportion of MDS patients and result in both increased suffering for these patients and for significant additional costs to our health care system.

Respectfully submitted,

Mark A. Israel, MD  
Professor of Pediatrics and Genetics  
Dartmouth Medical School  
Director, Norris Cotton Cancer Center



43



● HEMATOLOGY & ONCOLOGY  
BOBBY L. GRAHAM, JR., M.D., FACP  
GERRY ANN HOUSTON, M.D., FACP  
VAN L. LACKEY, M.D., FACP  
MARTIN M. NEWCOMB, M.D.  
MANU S. PATEL, M.D.  
GUANGZHI QU, M.D., PhD.  
GRACE G. SHUMAKER, M.D.  
BOBBY S. WILKERSON, M.D.  
TAMMY H. YOUNG, M.D.

June 13, 2007

Coverage Analysis Group  
Office of Clinical Standards and Quality  
Centers for Medicare and Medicaid Services  
Mail Stop C1-12-28  
7500 Security Boulevard,  
Baltimore, MD 21244

**RE: Comments on Proposed National Coverage Determination for Erythropoietin Stimulating Agents (ESAs) CAG-00383N**

Dear Coverage Analysis Group:

As a practicing medical oncologist in the state of Mississippi, I would like to submit the following comments regarding this coverage determination. In addition to the points addressed here, I am concerned about the blood supply in our state. We already have a shortage of blood products that affects the treatment of my patients. Restricting the use of ESA therapy for our MDS patients and waiting to start ESA therapy until the patient has a Hg below 9 will cause my patient population to need significantly more transfusions. With the blood supply already at a critical level, I am concerned that this coverage determination will have an adverse affect on the blood supply and endanger my other patients who already rely on this short supply.

Please note my additional comments regarding this National Proposed Coverage Determination:

1. "We are interested in public comment on whether coverage for ESA therapy for Medicare beneficiaries should only occur within appropriately designated clinical research studies where informed consent and safety monitoring can be assured."
  - a. I have some patients that are treated in a rural setting. These patients should not be forced to travel hundreds of miles to the nearest facility participating in a clinical trial. Patients requiring ESA therapy are anemic and many suffer from extreme fatigue. Asking these patients to travel even more to receive ESA therapy would be detrimental to their overall quality of life and wellbeing. CMS should not consider allowing ESA therapy to only be available within the clinical research community.
  - b. As a board certified medical oncologist, I prescribe and oversee the administration of many drugs that require intense safety monitoring for drug toxicity and severe anaphylactic reactions. All of these drugs require informed

1227 NORTH STATE STREET • SUITE 101 • JACKSON, MS 39202 • 601.355.2485  
2969 CURRAN DRIVE NORTH • SUITE 200 • JACKSON, MS 39216 • 601.974.5600  
1860 CHADWICK DRIVE • SUITE 301 • JACKSON, MS 39204 • 601.373.4421  
2368 GROVE STREET • VICKSBURG, MS 39180 • 601.638.3447

189

consent and safety monitoring. All patients in our clinic receive informed consent before beginning treatment.

2. “CMS is seeking public comment on whether there is sufficient evidence to conclude that ESA treatment is **not** reasonable and necessary for beneficiaries with certain clinical conditions including the anemia of myelodysplasia.” Erythropoietin stimulating agents have been used to treat the anemia of myelodysplastic syndrome (MDS) for many years. This is an accepted use and has been supported by our Medicare carrier. Scientific literature beginning in 1991 has shown ESAs to be safe, despite very high doses given to MDS patients (Stein, Abels, Krantz 1991). A special article summarizing the “evidence based clinical practice guidelines” of the American Society of Clinical Oncology and American Society of Hematology stated that the use of ESAs were supported for patients with myelodysplastic syndrome (Rizzo 2002). Denying coverage for ESA therapy for this patient population will be detrimental to the health of patient.

- Stein RS, Abels RI, Krantz SB. Pharmacologic doses of recombinant human erythropoietin in the treatment of myelodysplastic syndromes. *Blood* 1991; 78(7): 1658-63.
- Rizzo JD, Lichtin AE, Woolf SH, et al. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology (ASH). *Blood* 2002; 100(7):2303-20.

3. “ESAs are reasonable and necessary with the following limitations: the Hg levels immediately prior to initiation of dosing for the month should be <9 g/dl in patients without known cardiovascular disease and <10 in patients with documented symptomatic ischemic disease that cannot be treated with blood transfusion.” Both FDA approved package inserts state that patients should be started on therapy when their Hg is at least 10. Most carriers now support the use of ESAs starting at a Hg of 11 so that therapy can be started to keep the patient from dropping to a Hg of 10 or 9. It takes some time for my patients to respond to the ESA and waiting initiate treatment will result in clinical outcomes that are undesirable for my patient, including transfusions and clinical risks and symptoms associated with severe anemia. I have been able to start patients at a Hg of 11 for several years now and have noted that our patients require less medication to reach the target Hg of 12 (I hold ESA treatment at 12 per FDA guidelines and have for many years). Many studies regarding the use of ESA therapy have been published and very few even suggested waiting until the patient reached a Hg of 9. The National Comprehensive Cancer Network expert consensus panel cites multiple randomized studies that support the initiation of ESAs at hemoglobin levels less than 11g/dL.

- Rizzo JD, Lichtin AE, Woolf SH, et al. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology (ASH). *Blood* 2002; 100(7):2303-20.

- Stein RS, Abels RI, Krantz SB. Pharmacologic doses of recombinant human erythropoietin in the treatment of myelodysplastic syndromes. *Blood* 1991; 78(7): 1658-63.
  - Thompson JA, Gilliland DG, Prchal JT, et al. Effect of recombinant human erythropoietin combined with granulocyte/macrophage colony-stimulating factor in the treatment of patients with myelodysplastic syndrome. *Blood* 2000;87(10): 4067-81.
  - Rose EH, Abels RI, Nelson RA, et al. The use of r-HuEpo in the treatment of anaemia related to myelodysplasia (MDS). *Br J Haematol* 1995;89:831-
4. "The maximum covered treatment duration is 12 weeks/year." Some of my Medicare beneficiaries require a long cycle of chemotherapy over 6 months or multiple cycles of chemotherapy. These patients would need ESA treatment to be available to them for the entire cycle of chemotherapy and for long enough following chemotherapy to allow the bone marrow to recover. Please note it takes some older patients longer to achieve this recovery of the bone marrow, so it is even more vital for these patients to receive their ESA treatment until it is no longer medically necessary.
- Rizzo JD, Lichtin AE, Woolf SH, et al. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology (ASH). *Blood* 2002; 100(7):2303-20.
5. "The maximum covered treatment dose is 126,000 units for erythropoietin and 630 g for darbepoetin." Both drugs have FDA approved dose schedules that exceed this limitation. Aranesp, for example, has a Q3 week dose schedule that would require a patient to receive 500 mcg every three weeks. In a month where a patient receives their Aranesp on week 1 and week 4 of the month the dose will be a total of 1000 mcg during the month. Procrit has a once weekly dose of between 40,000 and 60,000 units per week. A patient that receives 60,000 units per week will receive 300,000 units during a month that the patient happens to come in on 5 Mondays, for example. The FDA approved dose for both of these drugs exceeds the dose limitation suggested by CMS.

Thank you for the opportunity to submit these comments. I hope that CMS will continue to create coverage guidelines based on accepted science and in the best interest of the patient. Please feel free to contact me at 601-373-4421.

Sincerely,



Martin Newcomb, MD



# Women's Cancer Research Foundation

## BOARD OF DIRECTORS

John Paul Micha, M.D. / Chairman  
Conley G. Lacey, M.D.  
John G. West, M.D.

## RESEARCHERS

**CALIFORNIA**  
John P. Micha, M.D.  
Mark A. Rettenmaier, M.D.  
John V. Brown, M.D.  
Mark C. Genesen, M.D.  
C. Paul Morrow, M.D.  
Laila I. Munderspach, M.D.  
Paul S. Lin, M.D.  
Lynda D. Roman, M.D.  
Annie Yessaian, M.D.  
Conley G. Lacey, M.D.  
Bridgette D. Duggan, M.D.  
Afshin Bahador, M.D.  
Leo D. Lagasse, M.D.  
Ronald S. Leuchter, M.D.  
William M. Rich, M.D.  
Steven Hager, M.D.  
William Jawien, M.D.  
Rabia Parveez, M.D.  
Michael Moffett, M.D.  
Anantanarayan Padmanabhan, M.D.  
Kate O' Hanlan, M.D.  
Fikret Atamdede, M.D.  
Ramin Mirhashemi, M.D.  
Samuel Im, M.D.  
Christopher Perkins, M.D.  
A. Mustajeeb Haseeb, M.D.  
Dina Ibrahim, M.D.  
Joseph Pascuzzo, M.D.

## ARIZONA

Alan Gordon, M.D.

## ARKANSAS

Alexander Burnett, M.D.

## FLORIDA

Neil J. Finkler, M.D.  
Robert W. Holloway, M.D.  
Hannah B. Ortiz, M.D.

## ILLINOIS

Sudarshan K. Sharma, M.D.

## LOUISIANA

Patricia Braly, M.D.

## NEW MEXICO

Francisco Ampuero, M.D.

## TENNESSEE

Donald Chamberlain, M.D.  
Steve Depasquale, M.D.  
Don Hall, M.D.  
David Martin, M.D.

## TEXAS

Maurie Markman, M.D.

## LEGAL

Sheppard Mullin Richter  
& Hampton LLP

## ADMINISTRATION

Cheri Graham, R.N., BSN / Director  
Bram Goldstein, Ph.D. / Senior Fellow  
Michelle Nickle / Administrator

May 29, 2007

Congressman John Campbell  
610 Newport Center Drive, Suite 330  
Newport Beach, CA 92660

U.S. Department of Health & Human Services  
Centers for Medicare & Medicaid Services  
7500 Security Blvd.  
Baltimore, MD 21244

**Subject:** Proposed coverage decision memorandum for the use of Erythropoiesis Stimulating Agents (ESAs) in cancer and related Neoplastic Conditions (CAG-0038N).

We have reviewed the CMS proposed coverage policy changes for ESAs. These changes would adversely affect our ability to care for gynecologic cancer patients.

Problems in the proposal include:

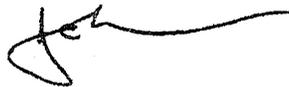
- 1) Ovarian cancer needs to be clearly specified as a covered malignancy.
- 2) Patients treated for hypertension or undergoing anti-angiogenic therapy (e.g., Bevacizumab) or monoclonal antibodies that target epidermal growth factor should be eligible for treatment/coverage with ESAs. Their physicians will explain the risk/benefit issues and the patient/physician should decide if they want treatment with ESAs. Medicare should not decide this.
- 3) We currently treat patients with hemoglobin/hematocrit levels <10g/dl/30% they are all symptomatic. Some patients are symptomatic at 11g/dl/33% and we would also treat them. The suggested new baseline of 9g/dl/27% is simply too low and patients would be suffering unnecessarily. Furthermore, many would require transfusions, interrupting their treatment regimens.
- 4) Maximum proposed coverage is 12 weeks/year. However, our ovarian cancer patients are often on treatment regimens that exceed one year. Many patients with ovarian cancer live normal lives, despite their persistent disease. Therefore, ovarian cancer is often considered a chronic disease, like renal failure. You would not consider telling renal failure patients that they could only receive ESAs for 3 months a year. Similarly, you should not dictate the frequency in which ovarian cancer patients can be treated with ESAs.
- 5) The maximum proposed dose coverage for a 4-week treatment cycle of Erythropoietin is 126,000 units and Darbepoetin is 630 mg. Standard

Erythropoietin treatment is 40,000 units/week. Since 4 weeks of treatment is 160,000 units, how do you propose to pay for only 126,000 units?

- 6) Fluid retention / weight gain issues should be addressed by the physicians and patient. Those specific clinical issues cannot be effectively legislated or mandated.
- 7) Non-coverage for patients with a history of thrombotic episodes related to malignancy is not reasonable. These patients are on Coumadin and have either inferior vena caval filters in place or are treated with various anti-thrombotic agents. Having a stroke or heart attack is not their main concern, whereas dying of cancer is. The choice to use ESAs in this situation should be between the doctor and the patient, and not by legislative fiat.

We appreciate both your concern for the patients and need to control the Medicare budget. However, let's not go overboard of this EPA issue, as the proposed changes would cause much more harm than good.

Sincerely,



John Paul Micha, M.D.  
Chairman  
Women's Cancer Research Foundation  
Website: [www.womenscancerfoundation.com](http://www.womenscancerfoundation.com)  
Email: [research@gynoncology.com](mailto:research@gynoncology.com)



Universitätsklinikum Freiburg • Radiologische Klinik  
Abt. für Strahlenheilkunde • Hugstetter Str. 55 • D-79106 Freiburg

**Radiologische Klinik**  
**Abteilung für Strahlenheilkunde**

To  
Steve Phurrough, MD, MPA  
Director, Coverage and Analysis Group  
Centers for Medicare and Medicaid Services  
Coverage and Analysis  
7500 Security Blvd  
Mail Stop C1-09-06  
Baltimore, MD 21244  
USA – Air Mail

**Michael Henke, MD**  
**Professor of Medicine/Radiooncology**

Telefon: 0761 / 270-9550  
Telefax: 0761 / 270-9497  
e-mail: henke@uni-freiburg.de

24.05.07/hk

**- Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N)**

Dear Dr. Phurrough,

With great sympathy I read the above mentioned memo. It impresses by responsibility for the patients and by scientific seriousness and merits particular credit because it illustrates major weaknesses of the current discussion: (1) ESA studies that were not adequately designed to address safety issues and (2) studies terminated prematurely before generating unwanted results!

I am convinced that ESA treatment negatively affects disease control and survival of head and neck cancer patients. Own (published in 2003) and confirmative findings (RTOG 99-03 and DAHANCA-10) support this view. Comparable safety concerns can be assumed for other cancer sites as well: Leyland-Jones (2005) and Wright (2007) suggest breast and lung cancer.

Unfortunately, we cannot – at present – reliably identify diagnoses, drug dose or potential mechanisms where and how ESAs should be of harm. But the findings from randomized, properly designed and well-controlled trials of more than 2,500 patients (see above) are of major concern and should urge us to address the questions as phrased in your memo (p7/47).

Meanwhile I and many others feel that it is clinically and ethically wise to restrict the use of ESAs for cancer patients. I'd suggest not prescribing ESAs to patients with curable cancer because cure may be hampered. If adequately informed, however, patients receiving palliative cancer treatment and suffering from symptomatic anemia may receive ESAs.

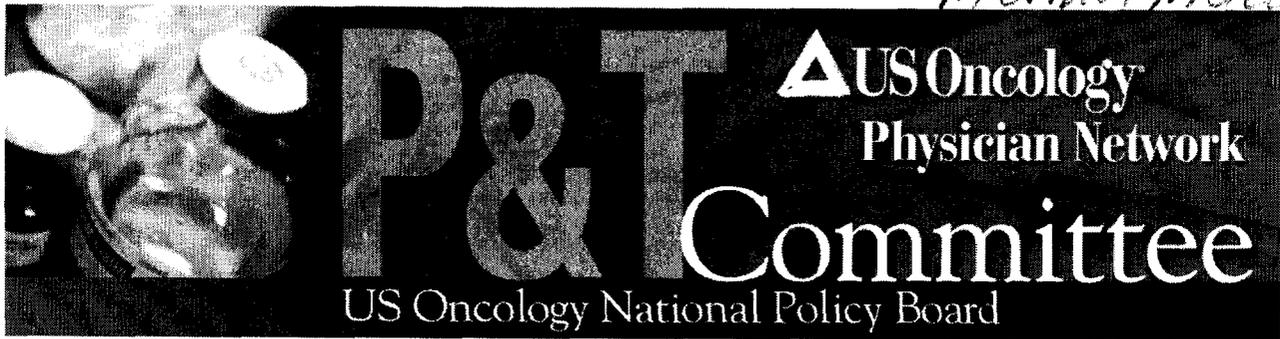
I understand that prescription patterns differ in between countries. Thus, the decision as proposed by CMMS seems to balance necessary restrictions and current US practice. Finally, addressing receptor-positive cancer it encourages dealing more with potential mechanisms how ESAs affect treatment efficacy.

Hopefully patient's safety will rule the ongoing discussion. In case I could support CMMS please let me know.

Sincerely,

Michael Henke, MD  
Professor of Medicine/Radiooncology

*Michael H. Decker*



June 13, 2007

Steve Phurrough, MD, MHA  
Director  
Coverage and Analysis Group  
Centers for Medicare and Medicaid Services  
7500 Security Boulevard  
Baltimore, MD 21244-1850

Maria Ciccanti, RN  
Lead Analyst  
Coverage and Analysis Group  
Centers for Medicare and Medicaid Services  
7500 Security Boulevard  
Baltimore, MD 21244-1850

Shamiram Feinglass, MD, MPH  
Lead Medical Officer  
Coverage and Analysis Group  
Centers for Medicare and Medicaid Services  
7500 Security Boulevard  
Baltimore, MD 21244-1850

**Re: NCD: NCA for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N)**

Dear Drs. Phurrough and Feinglass and Ms. Ciccanti,

On behalf of the oncologists of the US Oncology National Policy Board, the oncologists of the Pharmacy & Therapeutics Committee of the US Oncology National Policy Board and all of the oncologists in the US Oncology network, we are pleased to offer comments in response to the Centers for Medicare and Medicaid Service ("CMS") proposed National Coverage Determination ("NCD") for use of Erythropoiesis Stimulating Agents ("ESAs") in non-renal diseases.

*52*

## **The US Oncology National Policy Board (NPB)**

The US Oncology National Policy Board (the "NPB") advises the US Oncology network and the US Oncology network affiliated practices on policies and strategic initiatives that affect the US Oncology's network of affiliated physician groups. The NPB's charter embraces a commitment to ensuring that neither access to, nor quality of care is compromised for cancer patients in America. The NPB is composed of the physician practice presidents of each of the US Oncology network affiliated practices. The NPB provides an essential platform for physician and management engagement within the US Oncology network and also serves as a platform for the US Oncology physician network's national government relations and public policy voice.

## **The US Oncology Pharmacy and Therapeutics (P&T) Committee**

The P&T Committee of the US Oncology National Policy Board is the physician body that sets quality and efficiency standards for all aspects of drug use in the offices of over 1000 community-based oncologists in 38 states. The P&T Committee has been in place for over 10 years, providing quality of care guidance to the care of over 12% of the nation's cancer patients who are seen in the US Oncology network annually. Of most importance, the primary goal of the P&T Committee is to advance evidence-based pathways to assure the delivery of the highest quality care, with optimal patient outcomes, throughout the network.

## **Overview**

The US Oncology network is committed to national quality of care standards through evidence-based pathways. We strongly support the development of an NCD for ESA use. While the safety issues associated with ESA use are currently being reviewed by the Food & Drug Administration ("FDA"), any NCD promulgated by CMS should be supported by strong clinical evidence and should not rely on speculative theories or hypotheses as to the cause of the safety signals being reviewed by FDA. To protect the integrity of the drug approval and reimbursement process, the final NCD should be based on the total body of evidence, not on a selective review of the evidence or on unpublished, non-public evidence.

It is imperative that the NCD be based on the same evidentiary standards used by professional organizations, reflecting only publicly available medical evidence. It should also respect the patient/physician relationship permitting reasonable discretion in making patient-specific decisions. Specifically, when use of an ESA could provide benefits such as a reduction in transfusion requirements or improved quality of life, the patient and physician should be allowed to weigh those benefits against any risks and make an individual decision as to whether an ESA should be administered. Non-coverage or restricted coverage should only apply when the risks so far outweigh the benefits that no reasonable prudent physician would ever consider administering ESAs.

Therefore, the US Oncology network supports the following CMS proposals:

- Non-coverage of ESAs for use in any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis.
- Non-coverage on anemia associated with radiotherapy.
- Non-coverage of prophylactic use of ESAs to prevent chemotherapy-induced anemia and to reduce tumor hypoxia.

However, the US Oncology network has grave concerns about a number of other CMS proposals that the rest of this comment letter will discuss in detail. They are as follows:

1. CMS appears to have based many of its proposals on an unsubstantiated theory that the alleged presence of erythropoietin (“Epo”) receptors on cancer cells in-vitro causes tumor progression and mitigates the tumorigenic effects of certain anti-cancer agents when used clinically.
2. The draft NCD appears to ignore virtually all the clinical evidence and clinical experience substantiating the safety of ESAs when they are used according to their FDA labeled indications.
3. The proposed coverage for chemotherapy induced anemia (“CIA”) is not consistent with the evidence and the initiation point of less than 9g/dl is too low to avoid most transfusions. Moreover, the policy does not address the black box warning concerning the risks of attaining a Hgb level that exceeds 12g/dl.
4. The proposed treatment duration limit of 12 weeks/yr is grossly inadequate and the proposal to not cover any dose escalation is not consistent with the medical evidence.
5. CMS has ignored the clinical evidence showing that ESAs are safe and effective when used to treat Myelodysplasia (“MDS”) and Multiple Myeloma (“MM”).
6. CMS appears to have misinterpreted the safety signals under FDA review; the signals are limited to off-label uses of ESAs such as prevention of anemia and obtaining hemoglobin levels above 12g/dl but CMS assumes that those safety signals also exist when ESAs are used according to their labeled indications.
7. CMS appears to have not taken into account the effect of its proposal on the US blood supply nor on the number of patients who will catch transmissible illnesses through receipt of blood transfusions that were medically unnecessary but required by its ESA coverage policy.
8. CMS seems not to have considered the effect on patients who for religious or other reasons do not wish to have blood transfusions (e.g., Jehovah’s Witnesses).
9. The proposed CMS policy inappropriately interferes with the patient/physician relationship because it substitutes CMS’ judgment about the benefits and risks of ESAs for the judgments patients and physicians need to make in order to optimize care.

receptor proteins such as heat shock proteins (Elliott, Blood 2006; 107:1892-1895; Brown, Stem Cells 25:718-722; Osterborg, Eur J Cancer 2007; 43:510-519; Agarwal, JCO 2007; 25:1813-1814; Ragione, JCO 2007; 25:1812-1813, Jelkmann, JCO 2007; 25:1627-1628). Heat shock proteins are known cancer promoters that are found in high concentrations in aggressive tumors. This is a significant confounding factor that arises from the very studies that purport to detect Epo-receptors in cancer cell lines.

(2) If Epo-receptors are found in the supernatant of a test tube, are they soluble receptors in the cytosol or are they on the cell membrane where an ESA might bind to them and initiate cell signaling? Investigators who have used Western Blot to specifically detect Epo-receptors have found little evidence that the receptor is membrane bound and accessible to ESA (Sinclair, Proc AACR 2005; 46:5457; Abdalla, Blood 2005; 106:4268). Most of the Epo receptors are found in the cytosol where the receptor is inaccessible to exogenously administered ESAs.

(3) If expression of Epo-receptor mRNA can be detected in cancer cells in vitro, does incubation with ESAs stimulate cancer cell growth? Westphal tested 27 human tumor cell lines and found that ESA did not increase the growth rate of Epo receptor positive tumors (Westphal, Tumori 2002; 88:150-159). Gerwitz demonstrated no tumor proliferation and no interference with Taxol, Adriamycin, or tamoxifen in breast tumor cells in vitro (Gerwitz, Clin Ca Res 2006; 12:2232-2238).

(4) Do tumors transplanted into animal models show progression under the influence of ESAs? We were able to find several animal models that studied syngeneic (mouse tumor into mice) or xenografts (human tumors into mice). None of these tumors showed any effect from ESA administration on tumor growth or progression (xenograft models: LaMontagne, Mol Ca Ther 2006; 5:347-355; Tovari, Ca Res 2005; 65:7186-7193; syngeneic models: Hardee, Mol Ca Ther 2006; 5:356-361; Bianchi, Eur J Cancer 2007; 43:710-717; Hardee, Br J Cancer 2005; 93:1350-1355). In some of these studies, an enhanced effect of chemotherapy was observed.

In summary, there is no clinical evidence to support the CMS theory that cancer cells which may have Epo receptors in vitro will be stimulated to grow by administration of ESAs. However, in spite of this lack of clinical evidence showing that these receptors, if they exist, are functional or promote tumor growth, CMS has proposed to dramatically restrict the use of ESAs for these tumors.

Furthermore, in meetings with the US Oncology network, CMS staff stated that they believed that their theory that tumor progression mediated by erythropoietin receptors on cancer cells explained the data in all the clinical trials showing worse outcomes in patients receiving erythropoietin. CMS staff further stated that the burden was on commenters to disprove their theory with clinical data.

No clinical data exist to disprove the CMS theory. This is because until CMS recently devised this theory there was no reason to study it. Therefore, the theory can not be disproven with clinical evidence. However, it is equally important to note that no studies

of ESA use in CIA have demonstrated an adverse impact on tumor progression. The one trial that alluded to tumor progression under the influence of an ESA was the Henke trial of ESA use in non-anemic patients undergoing radiation treatment where the ESA was used as a radiosensitizer, not as a treatment for chemotherapy-induced anemia.

Extrapolation of data from the Henke study to use of ESAs in CIA is inappropriate and is not evidence based. Further, the CMS theory assumes that if Epo receptors exist in one cancer of a certain tissue type then all cancers from that tissue type will have Epo receptors. There is no evidence to support such an assumption. It is well known that cancer cells express proteins not made in normal tissue of the same type and that they may lose the ability to make proteins that the normal tissue makes. Does CMS have evidence not yet shared with the medical community that every lung tumor has Epo receptors? Unless the NCD requires testing of each tumor for Epo receptors, the proposal makes no sense and is inconsistent with its own premise. Further, if CMS finalized the proposal, what will happen in 5 years when a single tumor cell line is newly discovered to have Epo receptors in vitro? Will this tumor type be added to the restricted coverage list even if there is no clinical evidence the receptors are functional or that administration of ESAs has an adverse effect?

Lastly, it seems that CMS has not considered other explanations for tumor progression in the trials showing poorer outcomes for patients receiving ESAs. As most of these trials were not designed to test for survival, patient stratification was designed for other endpoints (e.g., to achieve a Hgb concentration well above 12g/dl) and the trial arms were not appropriately balanced for a survival analysis. As presented at the ODAC meeting, a number of the trials in question had unbalanced patient groups and drawing conclusions about the effect of ESAs on survival is inappropriate. Additionally, CMS seems not to have considered that disease stage or other patient characteristics may have been causally related to the outcomes or that EPO receptors, if they were present, may have been a marker for some other cause of tumor progression.

**RECOMMENDATION: Withdraw this proposal.**

2. **The draft NCD appears to ignore virtually all the clinical evidence and clinical experience substantiating the safety of ESAs when they are used according to their FDA labeled indications.**

The safety of ESA use in CIA is established from both meta-analyses of over 20,000 patients in trials and one recent large well-designed Phase III clinical trial adds more weight to the safety data.

Two large meta-analyses by different groups were provided with our previous comments (see Exhibit C). The Meta Works analysis looked strictly at CIA trials and found no significant effect of ESAs on overall survival (all cause mortality OR, 1.00; 95% CI 0.69-1.44) ( Ross, Clin Ther 28:801-831). The Cochrane analysis looked at trials conducted in both anemia of cancer and CIA and included the trials under review by the FDA by both Henke and Leyland Jones (Bohlius, Cochrane Database of Systematic Reviews 2006,

Issue 3, Art No. CD003407). The unadjusted hazard for overall survival was 1.08; 95% CI 0.99 to 1.18.

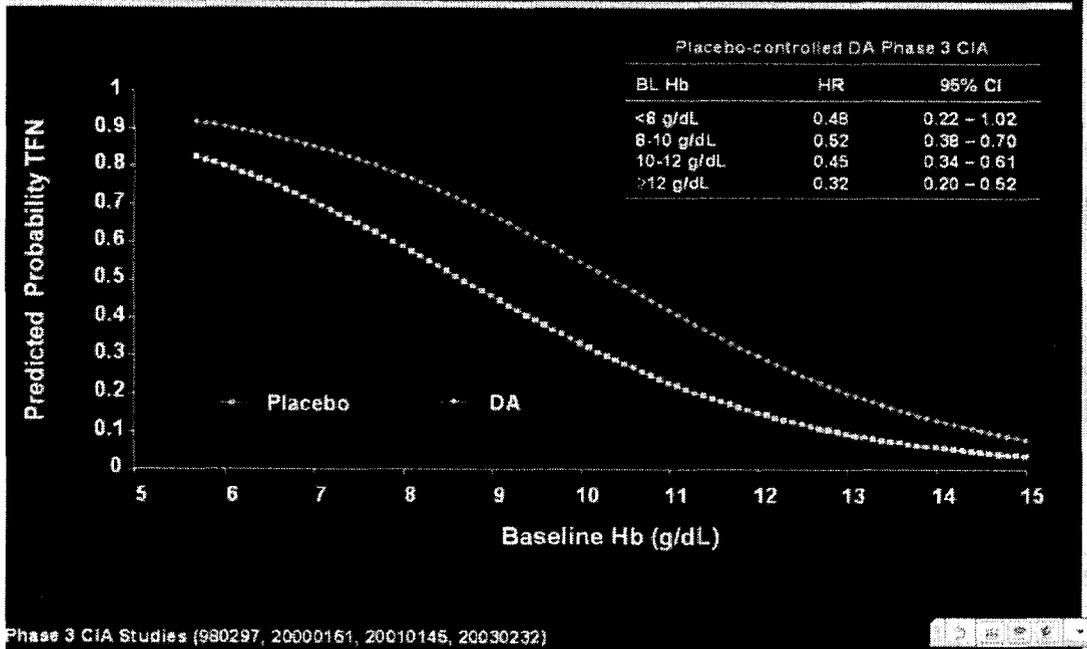
Since this publication, there has been one large randomized placebo-controlled trial of darbepoetin in 600 SCLC patients receiving chemotherapy where overall survival was a primary endpoint. Presented at AACR 2007, this study found no statistically different risk of death (HR 0.93, 95% CI 0.78 to 1.11). The Cochrane group has not yet updated the ESA analysis to include this large trial but it can be anticipated that these data would move the HR closer to 1.0 (Amgen 145, AACR 2007, abstract LB3).

**RECOMMENDATION:** Cover ESA use in CIA consistent with the US Oncology network clinical pathway for ESA use (See Exhibit A).

3. **The proposed coverage for chemotherapy induced anemia (“CIA”) is not consistent with the evidence and the initiation point of less than 9g/dl is too low to avoid most transfusions. Moreover, the policy does not address the black box warning concerning the risks of attaining a Hgb level that exceeds 12g/dl.**

The initiation point for ESA administration, as proposed, places patients at risk of both suboptimal drug performance as well as unnecessary transfusions. Studies have shown that if ESAs are initiated at a Hgb of less than 11g/dl, only 26% of patients will require transfusions. On the other hand, if ESAs are administered at a Hgb of less than 9g/dl then 78% of patients will require transfusions. An analysis of the darbepoetin Phase III trials in CIA shows clearly the impact of delaying the administration of ESAs as Hgb declines under the influence of chemotherapy. The lower the Hgb at the time of ESA initiation, the higher the likelihood of transfusion (Amgen presentation to ODAC, 2007).

## Absolute Risk of Transfusion Depends on Hb Level at Time of ESA Initiation (Phase 3 CIA Studies)



These observations reflect the fact that it often takes 6 weeks for ESAs to increase Hgb level. In patients receiving chemotherapy, Hgb levels keep dropping and once they reach 9g/dl they will continue to drop to lower levels even with ESA administration.

The recent evidence shows that use of a Hgb initiation point at <1g/dl both reduces transfusion requirements and maximizes patient quality of life. Lyman published a systematic review of the literature that evaluated the effect of early versus late intervention on transfusion incidence. Three Phase III trials directly compared the impact of early versus late intervention. The results from all three are depicted below (Lyman, Cancer 2006;106:223-233).

### Randomized Trials of Erythropoietic Agents to Evaluate Early versus Late Intervention: Effect on Transfusion Incidence

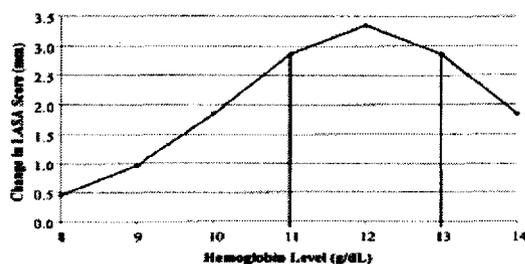
	Straus et al. 2003 <sup>26</sup>		Crawford et al. 2003 <sup>26</sup>		Rearden et al. 2004 <sup>29</sup>	
	rHuEPO QW		rHuEPO QW		Darbepoetin alfa Q3W	
	Early (n = 135)	Late (n = 134)	Early (n = 106)	Late (n = 105)	Early (n = 99)	Late (n = 102)
Hb entry criteria in g/dL	≥ 10 but ≤ 12	< 9	≥ 11 but < 15	≤ 10	≥ 10.5 but ≤ 12.0	≤ 10
Baseline Hb in g/dL Mean (SD)	11.1 (SE 0.7)	11.2 (SE 0.7)	13.1 (1.0)	13 (1.2)	11.1 (0.7)	11.2 (0.6)
No. patients treated	135	26	106	48	99	64
Transfusion incidence	18%	26%	12%	21%	17%	26%

Hb: hemoglobin; SE: standard error; rHuEPO: recombinant human erythropoietin.

Because optimal transfusion avoidance is achieved by early ESA intervention, the preponderance of the clinical trials used a 10-12g/dl as the Hgb initiation point.

Patient quality of life benefits are also optimized when ESAs are used early before transfusion rescue becomes inevitable. Crawford performed a cross-sectional analysis on two large community-based trials of epoetin use for CIA and showed a significant positive correlation between Hgb improvement and quality of life (Crawford, Cancer 2002;95:888-895).

### Relationship Betw/ Hgb and QOL



n = 58 139 225 323 348 316 148

**FIGURE 3.** Incremental changes in Linear Analog Scale Assessment (LASA) overall quality-of-life scores and hemoglobin levels, based on a longitudinal analysis of Community Study 2. Data collected at baseline, Week 8, and Week 16 were included in the analyses.

Crawford, Cancer 2002; 95:888

This is precisely why, over the last 15 years, oncologists have been administering ESAs when Hgb levels reach 11 g/dl. This standard of care optimizes the benefit from ESAs in minimizing the risk of transfusion. Numerous clinical trials and 3 different meta analyses (Cochrane, MetaWorks, and AHRQ) have shown that this use of ESAs is perfectly safe. The studies reviewed by ODAC in May, do not represent this community oncology standard of care. There are no safety signals in chemotherapy induced anemia when ESAs are initiated at Hgb <1g/dl and target Hgb concentrations are 12g/dl or less.

We would also like to point out that the draft NCD is missing a crucial element: a stopping point. The safety signals currently under review by the FDA are seen when Hgb levels rise to greater than 12g/dl after ESA administration. For this reason, we believe that CMS should not cover ESA administration to patients when their Hgb level is greater than 12g/dl.

**RECOMMENDATION:** Cover ESA use in CIA consistent with the US Oncology network clinical pathway for ESA use (See Exhibit A).

4. **The proposed treatment duration limit of 12 weeks/yr is grossly inadequate and the proposal to not cover any dose escalation is not consistent with the medical evidence.**

The CMS proposal limits ESA use in ways that are inconsistent with the clinical evidence and will greatly restrict the number of patients who may benefit from the ESAs. The restriction of coverage to a maximum of 12 weeks per year is grossly inadequate for current medical oncology practice. Many anemia-inducing, life extending regimens extend beyond 12 weeks. A good example is the standard of care dose dense regimen for adjuvant treatment of breast cancer (Burstein, JCO 2005; 23:8340-8347). This regimen is given over 16 weeks and has a 13% risk of transfusion. Patients should not be forced to decide between risking transfusion and seeking a cancer cure from this regimen. In addition, a large proportion of patients with later stage cancers achieve benefit from two to three courses of chemotherapy given sequentially within a year. Not only are these patients at risk for anemia while receiving chemotherapy but they are also at risk for up to 12 weeks after chemotherapy is completed. The US Oncology network believes that 12 weeks of ESA therapy is grossly inadequate for current standard of cancer care.

Additionally, the specification that the ESA should be stopped after 4 weeks if a 1g/dl rise is not achieved does not reflect the clinical trial data for the ESAs. Although there are suggestions that the best responders may be those who achieve a 1g/dl rise in 4 weeks, the average time required to achieve a 1g/dl rise is 5 to 7 weeks (Waltzman, The Oncologist 2005; 10:642-650; Schwartzberg, The Oncologist 2004; 9:696-707). In addition, the NCD does not allow for even a single dose escalation which is the standard of care, is safe, and has been an inherent component of almost every clinical trial. The number of patients who respond is dramatically increased in every trial where dose escalation was permitted.

**RECOMMENDATION: Cover ESA use in CIA consistent with the US Oncology network clinical pathway for ESA use (See Exhibit A).**

5. **CMS has ignored the clinical evidence showing that ESAs are safe and effective when used to treat Myelodysplasia (“MDS”) and Multiple Myeloma (“MM”).**

Both of these are diseases of the elderly where anemia becomes prominent in a majority of patients. Without ESAs, patients are likely to require chronic transfusions earlier and many will experience iron overload and associated organ toxicities. In fact, ESAs are considered to be therapeutic, not supportive, for MDS patients.

CMS seems to have ignored the 59 trials, 4 of which were randomized, showing that ESAs actually improve survival in MDS as provided in our previous comment letter (Randomized trials: Italian Coop Group, Br J Hematol 1998; 103:1070-1074; Casadevall, Blood 2004; 104:321-327; Thompson, Blood 2000; 95:1175-1179; Miller, Blood;104; Abstract 70). In aggregate, 2106 patients were studied over 17 years and no adverse outcomes were reported. It appears that the basis for the CMS proposal was a single case

report of erythroleukemia related to ESA use. Even if CMS does not believe the trials conducted on MDS patients were optimal, the number of patients studied over a long period of time is strong clinical evidence that should outweigh a single case report.

**RECOMMENDATION: Cover ESA use in MDS consistent with the US Oncology network clinical pathway for MDS (Exhibit B).**

- 6. CMS appears to have misinterpreted the safety signals under FDA review; the signals are limited to off-label use of ESAs such as prevention of anemia and obtaining hemoglobin levels above 12g/dl but CMS assumes that those safety signals also exist when ESAs are used according to their labeled indications.**

We reiterate that all the data showing safety signals were collected in trials that are well out of the mainstream of oncology therapy. There is no evidentiary basis for extrapolating those findings to mainstream therapy. Numerous trials and 20 years of clinical experience support ESA use in patients with Hgb levels less than 11g/dl with the intention of attaining a Hgb level of 12g/dl.

- 7. CMS appears to have not taken into account the effect of its proposal on the US blood supply nor on the number of patients who will catch transmissible illnesses through receipt of blood transfusions that were medically unnecessary but required by its ESA coverage policy.**

As noted in our previous comments, the effects of the proposed policy on the US blood supply will be dramatic. In 2006, the American Association of Blood Banks published the results of a nationwide blood collection and utilization survey showing that the percentage difference between red cell collection and transfusion was 4.5% in 2004, the smallest margin ever noted since these surveys have been conducted (The 2005 Nationwide Blood Collection Utilization Survey Report DHHS, Contract HHSP22320042202TE Whitaker BI, Henry R and Sullivan M).

This percentage works out to approximately 1 million surplus units of blood, most of which consists of excess, unneeded Type A blood that will be discarded.<sup>1</sup> Therefore, even with a conservative estimate of the number of MDS, MM, and CIA patients who will require transfusions pursuant to the proposed policy, the US blood supply will be stressed beyond the breaking point and blood will be unavailable either to victims of trauma who will die without it or to cancer patients with crippling anemia.

Thousands of elderly cancer patients who are among the nation's most vulnerable will be unnecessarily exposed to transmissible blood-borne illnesses, known and unknown. Although HIV and Hepatitis C are now detectable in blood, many physicians remember a time in the 1970s, 1980s and 1990s when that was not so and many patients who received blood transfusions thought to have been perfectly safe, got AIDS or Hepatitis

---

<sup>1</sup> Excess Type A blood is collected because it is a common blood type in people who are most likely to donate blood (e.g., Caucasians).

(Blajchman, NEJM 2006; 355:1303-1305; Schriebner, NEJM 1996; 334:1685-1690). Infectious diseases are still transmitted through blood transfusions and not all of them are known. CMS cannot assure the public that an unknown fatal illness is not currently being transmitted through blood transfusions. Physicians have had patients die from tainted blood thought to be safe in recent years. The proposed policy could result in the needless deaths of many patients. Physicians and CMS, as a public health agency, must consider this risk and must help safeguard our blood supply.

**RECOMMENDATION: Cover ESA use consistent with the US Oncology network clinical pathways for CIA and MDS to avoid unnecessary blood transfusions (See Exhibits A and B).**

- 8. CMS seems not to have considered the effect of its policy on patients who for religious or other reasons do not wish to have blood transfusions (e.g., Jehovah's Witnesses).**

There are patients who, for religious or other reasons refuse to have transfusions. The proposed policy would require them to be left untreated. These people could be forced to endure severe anemia and to delay potentially life saving therapy while they wait for the anemia to resolve enough to continue treatment. Again, the proposed policy would have a devastating effect on the quality of care.

- 9. The proposed CMS policy inappropriately interferes with the patient/physician relationship because it substitutes CMS' judgment about the benefits and risks of ESAs for the judgments patients and physicians need to make in order optimize care.**

Cancer care is by its very nature a constant juggling of risks and benefits. The currently available supportive care agents often make it possible and tolerable for patients to undergo high risk outpatient treatments for their cancers in hopes of a cure or prolongation in survival. Many times a patient's willingness to complete aggressive treatment is directly related to our ability to manage the effects of the chemotherapy on his or her well-being.

Patients and physicians are used to and well equipped to evaluate the risks and benefits of drugs like ESAs. The FDA black-box warning for ESAs is a good example. Oncologists commonly treat patients with drugs that have black box warnings. They inform patients of the benefits and risks and work with the patient to make the most appropriate medical decision for that patient. The proposed CMS policy would take that away. Instead of allowing patients and physicians to make individualized decisions about ESAs that include consideration of the black box warning, CMS would dramatically restrict coverage and in some cases, non-cover ESAs because of the black box warning. Such action is not only unwarranted it is tantamount both to practicing medicine and usurping the authority of the FDA.

The proposed policy would have a devastating effect on certain patients. For example, the proposed CMS policy would not allow physicians to administer ESAs **at all** to patients receiving vascular endothelial growth factor (VEGF) or epidermal growth factor receptor (EGFR) inhibitors. The inability to weigh the benefits and risks of ESA therapy on an individualized basis could result in many patients refusing life saving therapy out of fear of transfusions.

More specifically, this policy would require physicians to inform patients for whom VEGF inhibitors and EGFR inhibitors could be life saving therapy that they would not be allowed to have ESAs if they became anemic (e.g., due to concurrently administered chemotherapy such as bevacizumab administered with 5 fluorouracil). The effect of this policy will be to limit access of Medicare beneficiaries to lifesaving cancer therapy and to decrease the overall quality of care.

CMS should only restrict coverage or non-cover ESAs when the risks so far outweigh the benefits of ESAs that no reasonable prudent physician would consider administering them. We believe the US Oncology pathways for ESA, which are based on the available medical evidence reflect the reasonable, prudent use of ESAs and should form the basis of the CMS coverage decision.

**RECOMMENDATION: Cover ESA use consistent with the US Oncology network clinical pathways for CIA and MDS to avoid unnecessary blood transfusions (See Exhibits A and B).**

- 10. The US Oncology network believes that CMS is bound by law and its longstanding policy to cover all FDA labeled indications for ESAs irrespective of whether the label carries a block box warning.**

The US Oncology network counsel has researched the history of CMS policy regarding coverage of cancer drugs. It is our understanding that there was a GAO Report suggesting that restrictive reimbursement policies were having a negative affect on patient access to medically appropriate off-label use of anti-cancer therapies.<sup>2</sup> In response to this report, Congress passed Section 1861(t) of the Social Security Act. Section 1861(t)(2) of the Act was intended to require that Medicare cover anti-cancer drugs when used in accordance with the labeled indications or with off-label indications supported in specified compendia.

Section 1861(t)(2) of the Social Security Act (SSA), in pertinent part, defines drugs and biologics as follows:

(2)(A) For purposes of paragraph (1), the term “drugs” also includes any drugs or biologicals used in an anticancer chemotherapeutic regimen for a medically accepted indication (as described in subparagraph (B)).

---

<sup>2</sup> “Off-Label Drugs: Reimbursement Policies Constrain Physicians in Their Choice of Cancer Therapies,” Sept. 1991. Report to the Chairman, Senate Committee on Labor and Human Resources (GAO/PEMD-91-14).

(B) In subparagraph (A), the term “medically accepted indication”, with respect to the use of a drug, includes any use which has been approved by the Food and Drug Administration for the drug, and includes another use of the drug if—

(i) the drug has been approved by the Food and Drug Administration; and  
(ii)(I) such use is supported by one or more citations which are included (or approved for inclusion) in one or more of the following compendia: the American Hospital Formulary Service-Drug Information, the American Medical Association Drug Evaluations, the United States Pharmacopoeia-Drug Information, and other authoritative compendia as identified by the Secretary, unless the Secretary has determined that the use is not medically appropriate or the use is identified as not indicated in one or more such compendia.

As stated above, this provision was enacted in 1993 specifically for the purpose of ensuring that CMS would cover all anti-cancer drugs when used in accordance with the labeled indications or when used in accordance with off-label compendia supported indications.

Consistent with Congressional intent, CMS promulgated the following Carrier instructions to implement Section 1861(t)(2)<sup>3</sup> (emphasis added):

“Use of the drug or biological must be safe and effective and otherwise reasonable and necessary. (See the Medicare Benefit Policy Manual, Chapter 16, “General Exclusions from Coverage,” §20.) ***Drugs or biologicals approved for marketing by the Food and Drug Administration (FDA) are considered safe and effective for purposes of this requirement when used for indications specified on the labeling.***”

and

“***For purposes of this provision, a cancer treatment regimen includes drugs used to treat toxicities or side effects of the cancer treatment regimen when the drug is administered incident to a chemotherapy treatment.***”

This policy has been uniformly implemented by all Medicare Part B contractors since 1993. Specifically, Medicare Part B contractors have covered anticancer treatments, including ESAs, for their labeled and off-label compendial supported indications since the enactment of the statute.

However, in spite of its own longstanding policy, it appears from our conversations with CMS staff that CMS is now reversing this policy and no longer feels it is obligated to cover labeled indications for ESAs. This raises the question as to whether CMS no longer believes that ESAs are “part of a cancer treatment regimen.”

---

<sup>3</sup> Medicare Benefit Policy Manual 100-02, Chapter 15, Sections 50.4.1 and 50.4.5 (Rev. 1, 10-01-03)

As physicians dedicated to treating cancer patients, we strongly disagree with this position. Many patients can not tolerate otherwise life saving chemotherapy without the use of ESAs. The addition of ESAs to chemotherapy transformed cancer care and was responsible for enabling patients to function normally while undergoing chemotherapy and for enabling oncologists to treat patients in their offices instead of the hospital.

Neither the law nor the Carrier manual addresses conditional or limited coverage of ESAs -- or any other cancer drug. Therefore, we support counsel's belief that CMS does not have the authority to limit its coverage of any labeled indication, even with a block box warning on the label.

CMS should not reverse its policy on ESAs.

**RECOMMENDATION: Cover ESA use in CIA consistent with the US Oncology network clinical pathway for ESA use (See Exhibit A).**

### Summary

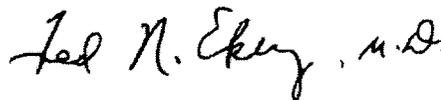
The National Policy Board of the US Oncology physician network and its Pharmacy and Therapeutics Committee appreciate the opportunity to submit these comments to CMS. The final proposal must be supported by strong clinical experience, current medical evidence and valid "best practices". The US Oncology network clinical pathways for ESA use, appended to this letter, meet that evidentiary standard. These should be considered as a model for CMS for the final NCD. We believe that if CMS finalizes an NCD in accordance with our recommendations, that it will facilitate the improvement of cancer care and will promote the establishment of national standards of care.

If you have any questions regarding our recommendations or review of the medical literature on ESAs please feel free to contact us.

Sincerely,



Michael Kolodziej, M.D.  
Chairman  
Pharmacy & Therapeutics Committee  
National Policy Board  
US Oncology



Fred Ekery, M.D.  
Chairman  
National Policy Board  
US Oncology



US Oncology

EXHIBIT A

CONFIDENTIAL AND PROPRIETARY

### Red Cell Growth Factor Pathway

Patient:  DOB:  Physician:

ICD-9 Code(s)  Stage:  PS(ECOG):

**Chemotherapy Induced Anemia:**

Hgb < 11 gm/dl

- Draw transferrin saturation & serum ferritin; If Tsat < 25% and if serum ferritin < 200ng/ml (450pmol/l), consider iron repletion; then begin darbepoetin 100mcg q 1wk or darbepoetin 200mcg q 2wks or darbepoetin 300mcg q 3wks.
- Assess response at 6wks. If Hgb does not increase by 1gm/dl, dose increase to 300mcg q 2wks (or 500 q 3wks or 150mcg q wk)
- If no response (transfusion dependent or falling Hgb despite Epo) DC darbepoetin.
- If patient responding or stable, continue until 8wks after DC of chemotherapy.

Hold darbepoetin for patients with Hgb > 12; restart if Hgb drops below 11.

This pathway excludes Heme malignancies.

**Use of epoetin- $\alpha$  (Prcorit) is considered off pathway.**

**Anemia of Cancer:**

**Suspended by the Pathways Task Force Until Further Notice**

Physician Signature/Date:



EXHIBIT B

Confidential and Proprietary

Myelodysplastic Syndrome Pathway

Patient: [ ] DOB: [ ] Physician: [ ]

ICD-9 Code(s) [ ] Stage: [ ] PS(ECOG): [ ]

**Low risk, Intermediate risk-1**

- Clinical Trial
- darbepoetin{Aranesp™} (see rules below)\*: Hgb less than 11 and epo level less than 500
- azacitadine{Vidaza™}: Hgb less than 10 and epo level greater than 500; and/or neutropenia; and/or thrombocytopenia
- lenalidomide{Revlimid™}: 5q-minus karyotype(simple or complex)
- Supportive care only

---

**Intermediate risk-2, high risk**

- Clinical trial
- Hematopoietic Stem Cell Transplantation (HSCT), if candidate.
- azacitadine {Vidaza™}
- decitabine {Dacogen™}
- lenalidomide{Revlimid™}: 5q-minus karyotype (simple or complex)
- darbepoetin{Aranesp™} (see rules below)\*
- Supportive care only

---

**CMML**

- Clinical Trial
- azacitadine {Vidaza™}
- decitabine{Dacogen™}
- hydroxyurea{Hydrea™}
- Supportive care only

---

**\*Darbepoetin{Aranesp™} rules for MDS**

- Hgb < 11 as starting point
- Serum Epo level < 500 mU/ml
- darbepoetin{Aranesp™} starting dose of 100ug/week or 200ug/qow (6-8 week trial for response)
- If no response increase dose by 50% (150ug/qweek or 300ug/qow)
- If no response then discontinue (further dose escalation requires written pathway exception).
- G-CSF can be added to darbepoetin, particularly if patient is neutropenic, but should potentially be avoided in patients with excess blasts in bone marrow.

Physician Signature/Date: [ ]

**Ciccanti, Maria L. (CMS/OCSQ)**

**From:** CMS CAGInquiries  
**Sent:** Thursday, June 07, 2007 3:58 PM  
**To:** Ciccanti, Maria L. (CMS/OCSQ)  
**Subject:** FW: mfetzer@utahcancer.com

**From:** Michael Gaffney [mailto:Mgaffney@utahcancer.com]  
**Sent:** Tuesday, June 05, 2007 12:38 PM  
**To:** CMS CAGInquiries  
**Subject:** mfetzer@utahcancer.com

Title of NCA/CAL: Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications

Public Comment re: Erythropoiesis Stimulating Agents (ESAs) guidelines

As an employee of Utah Cancer Specialists, and patient care advocate, I am concerned about the proposed erythropoietic stimulating agent (ESA) guidelines under consideration. While I understand the need for proper use of these medications, the proposal falls short of providing the best standard of care recommended by oncology organizations such as NCCN, ASCO and ASH. The current proposals will result in a compromised quality of life for our patients, increased blood transfusion requirements with the associated co-morbidity and risk and, ultimately, prove more costly to society than judicious use of ESAs. Please reconsider these guidelines encouraging physicians to carefully weigh the risk/benefit with patients and allow providers to treat this growing population with the best and most compassionate standard of care.

Chemotherapy-induced anemia is a well-known side effect of myelosuppressive therapy. Furthermore it is quite responsive to ESAs when iron stores, vitamin B12 and folate deficiencies and other underlying processes have been corrected. Holding initiation of ESA until the hemoglobin drops to  $<9\text{mg/dl}$  will delay response and most likely result in transfusion for a greater number of our chemotherapy patients. Most chemotherapy regimens last a minimum of 16 weeks (and many are much longer). Therefore, limiting the covered treatment duration to 12 weeks annually will be inadequate treatment for many of our patients on continued myelosuppressive therapy.

According to the proposed guidelines, the Myelodysplastic Syndrome population will be denied access to any form of ESA under all circumstances. While a portion of the MDS patients will not respond to ESAs, a greater number benefit from these medications; reducing the number of necessary blood transfusions, eliminating the complications of iron overload that results from transfusion, enhanced productivity by limiting time spent in a healthcare facility, and an overall improved quality of life.

We do not dispute the recommendations to discontinue use of the ESAs if the patient is non-responsive to treatment, however:

- The recommended four weeks is an inadequate timeframe in which to evaluate patient responsiveness. Former guidelines allow 12 weeks to determine response. Clearly, four weeks is an irresponsible timeframe.
- The proposed maximum treatment dose is insufficient to provide standard doses within the recommended timeframes. The maximum covered four-week treatment dose is 126,000units of Procrit and 630mcg of Aranesp. At an average dose of 40,000 units of Procrit each week, we would need 160,000 units in four weeks. The average dose of Aranesp is 300mcg per 2 weeks – so the 630mcg would be sufficient.

We encourage you to reconsider the list of specified conditions to include other myeloid and erythroid cancers as well as anemia caused by radiotherapy. Some patients will respond, therefore a trial of an ESA medication seems prudent.

Thank you for your consideration of this request. As a community oncology practice we strive to provide the optimal care to our patients. Please allow us the support we need to continue this practice.

Respectfully,

Michael R. Gaffney, PA-C

06/11/2007

174

May 31, 2007

Sean R. Tunis, MD, MSc. Director, OCSQ  
Chief Medical Officer, CMS  
Department of Health & Human Services  
Centers for Medicare & Medicaid Services  
7500 Security Boulevard, Mail Stop S3-02-01  
Baltimore, Maryland 21244-1850

Dear Dr. Tunis:

Many clients with various diseases have been benefiting from the use of erythropoietin stimulating agents (ESA). The quality of life has been enhanced and should be considered in the evaluation of decreasing the usage criteria that is being proposed. Working in the medical field on a daily basis and seeing positive results from the usage of ESA's is rewarding and extremely real. The positive results are being able to have more energy and complete activities of daily life like climbing stairs and doing a load of laundry. Clients who are unable to receive ESA's are unable to partake in the things in life they enjoy.

I am passionate about this topic because I work in Hematology/Oncology and see clients every day benefiting from this medication. I am proposing that you help our population using ESA's and potentially using ESA's and evaluate how people are feeling and benefiting from them. A number of clients diagnosed with different diseases will benefit and appreciate this added research request.

Thank you for your time.

Sincerely,

A handwritten signature in black ink that reads "Michelle Lewis". The signature is written in a cursive style with a large, stylized initial "M" and "L".

Michelle Lewis



>  
>According to the proposed guidelines, the Myelodysplastic Syndrome  
>population will be denied access to any form of ESA under all  
>circumstances. While a portion of the MDS patients will not respond to  
>ESAs, a greater number benefit from these medications; reducing the  
>number of necessary blood transfusions, eliminating the complications  
>of iron overload that results from transfusion, enhanced productivity  
>by limiting time spent in a healthcare facility, and an overall  
>improved quality of life.  
>  
>  
>  
>We do not dispute the recommendations to discontinue use of the ESAs if  
>the patient is non-responsive to treatment, however:  
>  
> . The recommended four weeks is an inadequate timeframe in which to  
>evaluate patient responsiveness. Former guidelines allow 12 weeks to  
>determine response. Clearly, four weeks is an irresponsible timeframe.  
>  
> . The proposed maximum treatment dose is insufficient to provide  
>standard doses within the recommended timeframes. The maximum covered  
>four-week treatment dose is 126,000units of Procrit and 630mcg of Aranesp.  
>At an average dose of 40,000 units of Procrit each week, we would need  
>160,000 units in four weeks. The average dose of Aranesp is 300mcg per  
>2 weeks - so the 630mcg would be sufficient.  
>  
>  
>  
>We encourage you to reconsider the list of specified conditions to  
>include other myeloid and erythroid cancers as well as anemia caused by  
>radiotherapy. Some patients will respond, therefore a trial of an ESA  
>medication seems prudent.  
>  
>  
>  
>Thank you for your consideration of this request. As a community  
>oncology practice we strive to provide the optimal care to our  
>patients. Please allow us the support we need to continue this practice.  
>  
>  
>  
>Respectfully,  
>  
>  
>  
>  
>  
>Nasfat Shehadeh,MD  
>Utah Cancer Specialists  
>Salt Lake Clinic  
>333 S. 900 E.  
>Salt Lake City, UT 84102  
>Phone: (801) 931-6070  
>Fax: (801) 931-6076  
>e-mail: nshehadeh@utahcancer.com <mailto:nshehadeh@utahcancer.com>  
>

May 31, 2007

Nancy Davenport-Earis  
Chief Executive Officer

**EXECUTIVE BOARD**

William T. McGhee, PhD  
Immediate Past Board President  
Chief Executive Officer  
National Comprehensive Cancer Network  
Edward G. Connette, Esquire  
Board President  
Essex Richards, RI  
Christian Downs, MBA, JD  
Board Vice President  
Executive Director  
Association of Community Cancer Centers  
Leah Arnold, RN, BSN, NECA  
Board Secretary  
Nursing Director, University Health Services  
University of Texas at Austin

John L. Murphy  
Board Financial Officer  
Sagehen Capital, LLC

Don Conway, MD  
Board Financial Officer  
Director, The Healthcare Initiative  
Tuck School of Business  
Dartmouth College

Bruce Avery, MD  
Hematology-Oncology Executive  
Roy A. Beveridge, MD  
Co-Director, Stem Cell Transplant Center  
Inova Fairfax Hospital  
Dennis A. Gustinson, MD  
Director, Human Cell Therapy Laboratory  
Divisions of Transfusion Medicine  
and Hematology  
Mayo Clinic

Richard D. Carter, Esquire  
Carter & Lay

The Honorable Phil Hamilton  
Virginia House of Delegates  
Sheilou Weinhaus, Esquire  
Weinhaus & Polastnick  
Rene S. Cabral-Dantele, JD, MPH  
Director  
Office of Health Policy and Planning  
Virginia Department of Health

**SCIENTIFIC BOARD**

Lari Williams, BSN, RN, AOCN  
Chair, Scientific Board of Directors  
University of Texas  
MD Anderson Cancer Center  
Houston School of Nursing  
Dale W. Brewley, MD  
Professor, Emory School of Medicine  
Emory University

David Weisel, MD  
Professor  
Duke University Medical System  
Radiation Oncology Department  
Robert M. Rifkin, MD, FACP  
Director, Cellular Therapeutics  
Rocky Mountain Blood  
& Marrow Transplant Program  
Rocky Mountain Cancer Centers

H. Marc Stewart, MD  
Medical Director, SCCH  
Professor of Medicine  
University of Washington  
Fred Hutchinson Cancer Research Center  
Richard L. Theriault, DO, MBA  
Professor of Medicine  
MD Anderson Cancer Center

**HONORARY BOARD**

The Honorable Mary T. Christian  
John H. Ennis, Jr., Co-Founder  
Chief Development Officer  
Pearl Moore, MS, MN, EARN  
Director, Essex House  
Paula Trahan-Rieger, RN, MSN, AOCN, EBAN  
Chief Executive Officer  
Oncology Nursing Society  
Leo E. Sands  
Executive Vice President &  
Chief Administrative Officer  
U.S. Oncology  
Doris Simonson

Steve Phurrough, MD, MPA  
Elizabeth Koller, MD, FACE  
Maria Ciccanti, RN  
Coverage and Analysis Group  
Office of Clinical Standards and Quality  
Centers for Medicare and Medicaid Services  
Mail Stop C1-12-28  
7500 Security Blvd  
Baltimore, MD 21244-1849

Re: Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N)

National Patient Advocate Foundation (NPAF) is devoted to the cause of assuring access to appropriate disease related therapy for patients nationwide. National Patient Advocate Foundation represents the voices and experiences of the patients served through our direct patient services organization, Patient Advocate Foundation (PAF), which last year handled 39,780 cases, of which 80% were cancer cases. Additionally, PAF handled requests for information from 6.4 million persons through their website, phones and email inquiries for assistance.

We agree with CMS that caution is required in the use of ESAs, and that appropriate targets of therapy and assessments of response are important. We would urge that our comments submitted to Maria Ciccanti, RN, Centers for Medicare & Medicaid Services RE: Erythropoiesis Stimulating Agents for Non-Renal Indications: CAG#00383N submitted by NPAF on April 13, 2007 be reconsidered. We have attached a copy of those comments for ease of reference. They cite "For many patients experiencing anemia while on chemotherapy for cancer, the benefits of the ESAs remain, and are acknowledged in the FDA alert last updated on 3/9/2007. Access to the ESAs should be preserved for patients undergoing active chemotherapy, and the ability to avoid the largely non-infectious risks of blood transfusions extended." Further, we concur with the recommendations of the American Society of Hematology concerning starting and ending targets, response, the use of ESAs in conjunction with chemotherapy, and the caution that there is no evidence supporting the use of ESAs to potentiate anti-tumor therapy (See Comments on CAG-00383N from Dr. Samuel Silver, MD, PhD, ASH Reimbursement Subcommittee, dated April 25, 2007).

FDA has stated that there is insufficient data at this point to support quality of life labeling for these drugs. As the FDA pointed out on March 9, 2007, the data simply does not exist. At the same time, for the thousands of cancer patients served by our organizations, there is no question that *access to erythropoiesis-stimulating agents is an important adjunct to cancer therapy and supportive care that for the majority of patients receiving them underwrites a higher quality of life including reduced return to work and independent living.*

725 15th Street NW, 10th Floor • Washington, DC 20005 • Tel: 202.347.8009 • Fax: 202.347.5579 • Internet: www.npaf.org

145

We are equally confident, based on our patients' experiences, that erythropoiesis-stimulating agents have a significant role in a number of conditions not recognized by the proposed NCD by CMS. The consensus of a number of professional organizations including ASCO and ASH supports the use of ESAs in selected conditions outside of active chemotherapy.

First, *recent studies* of ESA treatment of patients *not undergoing chemotherapy* have focused on non-hematopoietic malignancies. Among these is a very recent abstract presented at the American Association for Cancer Research (Glaspy J, Smith R, Aapro M, et al. Results from a phase III, randomized, double-blind, placebo-controlled study of darbepoietin alfa for the treatment of anemia in patients not receiving chemotherapy or radiotherapy. #LB-3. Presented at: 2007 Annual Meeting of the American Association for Cancer Research; April 14-18; Los Angeles.). There is consensus that ESA use in hematologic malignancies such as myelodysplasia (MDS) is appropriate while further studies are performed. Low-risk myelodysplastic syndromes with less than five percent blasts in the bone marrow are appropriately treated with ESAs. This group of disorders include refractory anemia, refractory anemia with ringed sideroblasts, refractory cytopenias with multilineage dysplasia, refractory cytopenias with multilineage dysplasia and ringed sideroblasts, unclassified myelodysplastic syndromes, and MDS associated with isolated deletion of a portion of chromosome 5 [del(5Q)].

Second, *the length of time* that ESAs are appropriately used depends on the response to therapy and any arbitrary limit on the length of time for ESA therapy in diseases lasting the remainder of an individual's life should be reconsidered. For instance, MDS responsive to ESAs may be appropriately treated for months or years. Chemotherapy-associated anemia may require 90 days or more to recover after cessation of chemotherapy, so ESAs may be reasonably continued during this time as well.

Third, *the blood supply is increasingly stressed* by more restrictions on donors and increased sophistication of surgical and medical therapy. Even small reductions in the need for blood products have an impact on their availability for the acutely ill trauma patient. In addition, not all patients have easy access to transfusions. Some rural patients may live two hours or more from a transfusing facility.

Patients continue to express concerns relative to blood transfusions including fear of secondary effects such as hepatitis, HIV infection and iron-overload. Patients, such as a recent 45 year old male patient from Arkansas who is fighting Amyloidosis, shared with his PAF case manager the distinct differences that he experiences when taking erythropoiesis stimulating agents as opposed to blood transfusions that he has taken in the past. He cited his improved health status measured by more energy for longer periods of time with no side effects with ESAs. He cited concrete examples of blood transfusions that simply offered to him no improvement in health status with the added familial burden of transportation to the hospital setting and extended time for the type and cross-matching as well as the actual transfusion process itself. His story is consistent with others shared with our case managers through letters from patients in many states.

The studies recently cited raising concern about ESAs have not included enough patients with hematologic malignancies to draw similar conclusions. In the absence of randomized trials supporting the use of ESAs, coverage for patients with hematologic malignancies should be determined by the specific application and not lumped with all non-hematopoietic disorders with high hemoglobin targets. Please note that I join in these comments with members of both the Executive Board and the Scientific Board of National Patient Advocate Foundation; Dr. Dennis Gastineau, Director, Human Cell Therapy Laboratory, Divisions of Transfusion Medicine & Hematology, Mayo Clinic, Rochester, MN, and the immediate past Chair of the Scientific Board and currently a member of the Executive Board of Directors of NPAF, chairs our comment drafting committee authoring these comments. Biographies of the Scientific Advisory Board who have co-signed this letter are also attached.

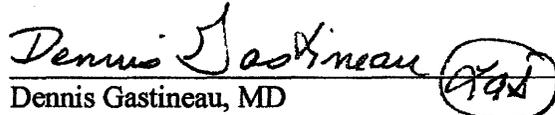
We appreciate the opportunity to share our concerns and support for patients with cancer and look forward to your objective, patient-centric consideration of our comments and those of professional organizations such as ASCO and ASH. Please contact us if we can provide additional information you may be seeking for review and consideration.

Sincerely,

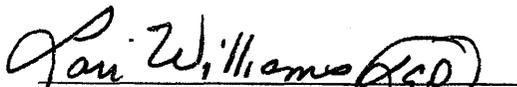


---

Nancy Davenport-Ennis  
CEO, National Patient Advocate Foundation



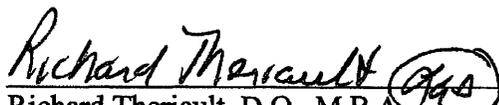
Dennis Gastineau, MD  
Director, Human Cell Therapy Lab  
Mayo Clinic



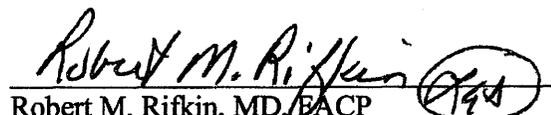
Lori Williams, PhD, DNS, RN, AOCN  
University of Texas  
MD Anderson Cancer Center



David M. Brizel, MD  
Professor of Radiation Oncology  
Associate Professor of Otolaryngology Head  
and Neck Surgery  
Duke University Medical Center



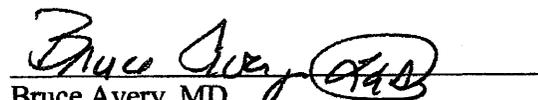
Richard Theriault, D.O., M.B.A.  
Professor of Medicine  
MD Anderson Cancer Center



Robert M. Rifkin, MD, FACP  
Director, Cellular Therapeutics  
Rocky Mountain Blood & Marrow  
Transplant Program  
Rocky Mountain Cancer Centers



Donald P. Conway, MD  
Director, The Healthcare Initiative  
Tuck School of Business  
Dartmouth



Bruce Avery, MD  
Director, Hematology-Oncology Knoxville

  
F. Marc Stewart, MD  
Professor of Medicine, University of  
Washington  
Fred Hutchinson Cancer Research Center

cc: Leslie Norwalk, Acting Director Centers for Medicare and Medicaid Services  
Dr. Barry Staube, Chief Medical Officer, Office of Clinical Standards and Quality

## Ciccanti, Maria L. (CMS/OCSQ)

---

**From:** CMS CAGInquiries  
**Sent:** Tuesday, June 05, 2007 11:24 AM  
**To:** Ciccanti, Maria L. (CMS/OCSQ)  
**Subject:** FW: Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications

>-----Original Message-----

>From: Nathan Rich [mailto:nrich@utahcancer.com]

>Sent: Tuesday, June 05, 2007 9:37 AM

>To: CMS CAGInquiries

>Subject: Erythropoiesis Stimulating Agents (ESAs) for non-renal disease  
>indications

>

>

>

>Public Comment re: Erythropoiesis Stimulating Agents (ESAs) guidelines

>

>As an employee of Utah Cancer Specialists, and patient care advocate, I  
>am concerned about the proposed erythropoietic stimulating agent (ESA)  
>guidelines under consideration. While I understand the need for proper  
>use of these medications, the proposal falls short of providing the  
>best standard of care recommended by oncology organizations such as  
>NCCN, ASCO and ASH. The current proposals will result in a compromised  
>quality of life for our patients, increased blood transfusion  
>requirements with the associated co-morbidity and risk and, ultimately,  
>prove more costly to society than judicious use of ESAs. Please  
>reconsider these guidelines encouraging physicians to carefully weigh  
>the risk/benefit with patients and allow providers to treat this  
>growing population with the best and most compassionate standard of care.

>

>Chemotherapy-induced anemia is a well-known side effect of  
>myelosuppressive therapy. Furthermore it is quite responsive to ESAs  
>when iron stores, vitamin B12 and folate deficiencies and other  
>underlying processes have been corrected. Holding initiation of ESA  
>until the hemoglobin drops to <9mg/dl will delay response and most  
>likely result in transfusion for a greater number of our chemotherapy  
>patients. Most chemotherapy regimens last a minimum of 16 weeks (and  
>many are much longer). Therefore, limiting the covered treatment  
>duration to 12 weeks annually will be inadequate treatment for many of our patients on continued  
>myelosuppressive therapy.

>

>According to the proposed guidelines, the Myelodysplastic Syndrome  
>population will be denied access to any form of ESA under all  
>circumstances. While a portion of the MDS patients will not respond to  
>ESAs, a greater number benefit from these medications; reducing the  
>number of necessary blood transfusions, eliminating the complications  
>of iron overload that results from transfusion, enhanced productivity  
>by limiting time spent in a healthcare facility, and an overall  
>improved quality of life.

>

>We do not dispute the recommendations to discontinue use of the ESAs if  
>the patient is non-responsive to treatment, however:

- >• The recommended four weeks is an inadequate timeframe in which to  
>evaluate patient responsiveness. Former guidelines allow 12 weeks to  
>determine response. Clearly, four weeks is an irresponsible timeframe.
- >• The proposed maximum treatment dose is insufficient to provide  
>standard doses within the recommended timeframes. The maximum covered

>four-week treatment dose is 126,000units of Procrit and 630mcg of Aranesp.

➤At an average dose of 40,000 units of Procrit each week, we would need

>160,000 units in four weeks. The average dose of Aranesp is 300mcg per

>2 weeks – so the 630mcg would be sufficient.

>

>We encourage you to reconsider the list of specified conditions to

>include other myeloid and erythroid cancers as well as anemia caused by

>radiotherapy. Some patients will respond, therefore a trial of an ESA

>medication seems prudent.

>

>Thank you for your consideration of this request. As a community

>oncology practice we strive to provide the optimal care to our

>patients. Please allow us the support we need to continue this practice.

>

>Respectfully,

>

>

>

>

>Nathan Rich M.D.

Title of NCA/CAL: Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications

Public Comment re: Erythropoiesis Stimulating Agents (ESAs) guidelines

As practicing medical oncologist, and an advocate for compassionate and responsible cancer care, I am deeply concerned about the proposed erythropoietic stimulating agent (ESA) guidelines under consideration.

I understand the need for proper use of these medications; however the proposal falls short of providing the best standard of care recommended by oncology organizations such as NCCN, ASCO and ASH. The current proposals will cause a severe reduction in quality of life for cancer patients, increased blood transfusion requirements with the associated co-morbidity and risk and, ultimately, prove more costly to society than the proper use of ESAs. Please reconsider these guidelines and allow skilled practitioners to treat this growing population with the utmost standard of care. I fear you are over-reacting based on a single study. More so, despite the specific study population in said trial, you are applying the changes to other population of patients that were NOT studied in said trial and thus making a potentially dangerous extrapolation. In addition, the proposed changes to the starting hemoglobin for initiation of ESAs is clearly a step backward.

Chemotherapy-induced anemia is a well-known side effect of myelosuppressive therapy. Furthermore it is quite responsive to ESAs when iron stores, vitamin B12 and folate deficiencies and other underlying processes have been corrected. Holding initiation of ESA until the hemoglobin drops to  $<9\text{mg/dl}$  will delay response and will likely result in transfusion for a greater number of our chemotherapy patients. Most chemotherapy regimens last a minimum of 16 weeks (and many are much longer). Therefore, limiting the covered treatment duration to 12 weeks annually is grossly inadequate for many patients requiring continued myelosuppressive therapy. In addition, a number of patients will see more than one regimen in a 12-month period.

According to the proposed guidelines, the Myelodysplastic Syndrome population will be denied access to any form of ESA under all circumstances. While a portion of the MDS patients will not respond to ESAs, a greater number benefit from these medications; reducing the number of necessary blood transfusions, eliminating the complications of iron overload that results from transfusion, enhanced productivity by limiting time spent in a healthcare facility, and an overall improved quality of life.

I do not dispute the recommendations to discontinue use of the ESAs if the patient is non-responsive to treatment, however:

- The recommended four weeks is an inadequate timeframe in which to evaluate patient responsiveness. Former guidelines allow 12 weeks to determine response. Clearly, four weeks is an irresponsible timeframe and is NOT supported by any data.
- The proposed maximum treatment dose is insufficient to provide standard doses within the recommended timeframes. The maximum covered four-week treatment dose is 126,000units of Procrit and 630mcg of Aranesp. At an average dose of 40,000 units of Procrit each week, we would need 160,000 units in four weeks. The average dose of Aranesp is 300mcg per 2 weeks – so the 630mcg would be sufficient.

Your proposed changes will not save any money in the long-run and will put patients at greater risk for harm. It is critical that you reconsider your proposed changes and the list of specified conditions to include other myeloid and erythroid cancers as well as anemia caused by radiotherapy. Some patients will respond, therefore a trial of an ESA medication seems prudent.

Thank you for your consideration and responsible action on this request.

Sincerely,

133

Nitin Chandramouli, MD  
Utah Cancer Specialists



---

# ORTHO BIOTECH

## Ortho Biotech Products, LP Clinical White Paper Submission

June 13, 2007

Proposed National Coverage Decision for  
Erythropoiesis Stimulating Agents (ESAs) for Non-  
Renal Disease Indications (CAG-00383N)

SF

## Table of Contents

1.	Executive Summary .....	3
1.1	Summary of ORTHO BIOTECH's Recommendations on the Proposed NCD.....	3
2.	Introduction.....	9
3.	Patient Benefits of Transfusion Reduction and Improved Quality of Life.....	9
3.1	Transfusion Reduction .....	9
3.2	Favorable Impact of ESAs on Patient-Reported Outcomes.....	11
3.3	Conclusion: Clinical Benefits of ESAs Use in Chemotherapy-Induced Anemia .....	20
4.	Safety of ESAs in the Treatment of Chemotherapy-Induced Anemia.....	20
4.1	Pharmacovigilance Program Evaluating Safety of ESAs in Patients with Cancer.....	21
4.2	Survival Meta-Analysis Demonstrated No Survival Signal When Used Consistent with Label Information.....	21
5.	Response to Proposed Decision Memo Regarding Terminated Epoetin Alfa Trials .....	27
5.1	Reasons for Termination of Trials that Investigated Use of EPO Beyond the Label .....	28
6.	Transfusion/Blood Supply Risks With Decreased ESA Use .....	30
6.1	Increased blood transfusions associated with decreased ESA use have critical patient-related and U.S. blood supply implications .....	30
7.	Ortho Biotech Response to CMS Proposed Decision Memo on ESAs.....	34
7.1	CMS Proposed Non-Coverage of Conditions .....	34
7.2	CMS Proposed Decision Memo: Non-coverage for patients with myelodysplasia (MDS) .....	35
7.3	CMS proposed decision memo: Non-coverage for patients with treatment regimens including anti-angiogenic drugs and antibodies against EGF receptor .....	37
7.4	CMS proposed decision memo: Noncoverage for patient's thrombotic episodes related to malignancy .....	38
7.5	Erythropoietin Receptor.....	39
8.0	CMS Proposed Limitations.....	44
8.1	Hemoglobin Level at ESA Initiation.....	44
8.2	Limited Annual Treatment Duration .....	51
8.3	Dose Limitation.....	52
8.4	Limitation Based on Poor Drug Response.....	54
8.5	Limitation Based on Fluid Retention .....	56
8.6	Limitation Based on Rapid Hemoglobin Rise.....	56
9.	Coverage with Evidence Development .....	57
10.	Conclusion.....	58
11.	References .....	59

## 1. Executive Summary

Erythropoietic stimulating agents [ESAs, (PROCRIT<sup>®</sup> (epoetin alfa) and Aranesp<sup>®</sup> (darbepoetin alfa)], are safe and effective and have an acceptable risk/benefit profile for the treatment of cancer patients with chemotherapy-induced anemia when used to correct anemia. ESAs should be initiated at a baseline hemoglobin (Hb) < 11 g/dL and discontinued for Hb levels > 12 g/dL. ESAs, the only viable alternative to red blood cell transfusions for this patient population, are valuable in reducing the need for transfusions and improving quality of life (QoL). The benefits of reducing transfusions include reduction in hospital visits, avoidance of infectious complications, including the potential for new and emerging pathogens, non-infectious complications, and conservation of the limited national blood supply already constrained with limited marginal capacity, especially at the regional level and during seasonal and holiday periods. In addition to transfusion reduction, epoetin alfa treatment is associated with improvements in patient reported outcomes as demonstrated in multiple clinical trials. ESAs are FDA approved for patients with chemotherapy-induced anemia with compendia listings (DrugPoints<sup>®</sup> (which, in July, 2007, will succeed USP DI<sup>®</sup>, AHFS) for these patients. ESA use has been recommended in anemia treatment guidelines of the National Comprehensive Cancer Network (NCCN) and the American Society of Hematology/American Society of Clinical Oncology.

When ESAs are used according to product labeling (hemoglobin not to exceed 12g/dL) to correct chemotherapy-induced anemia, no effect on survival or tumor growth has been observed. There is an increased risk for TVEs and this risk is well described in product labeling. Safety signals had emerged from investigational cancer studies, particularly when ESAs were used **beyond** the correction of anemia (target hemoglobin >12 g/dL), which showed an increased risk of thromboembolic events (TVEs), reduced survival, and possible tumor proliferation in head and neck cancers. In collaboration with the FDA, Ortho Biotech and Amgen Inc., another marketer of ESAs, updated the ESA labeling safety information and provided recommendations to hold ESA dosing for hemoglobin > 12 g/dL to reflect these safety signals (3/07). In addition, given the data from investigational trials, the Oncologic Drugs Advisory Committee (ODAC) convened on May 10, 2007 to re-assess the safety of ESAs in patients with cancer and to re-evaluate the net clinical benefit of ESAs in this setting. Although the Committee provided recommendations to the FDA urging further study of the drugs and potential labeling changes on the use of ESAs in oncology, the FDA has not completed their review.

### 1.1 Summary of ORTHO BIOTECH's Recommendations on the Proposed NCD

The results of clinical studies, demonstrate that PROCRIT is safe and effective when used for FDA approved indications and for other medically-accepted uses listed in DrugPoints (formerly USP DI). The final NCD should allow for the appropriate use of ESAs for these indications.

CMS proposes thirteen clinical conditions for which ESA treatment would not be reasonable and necessary. We do not object in principle to a determination that ESAs are not reasonable and necessary for the following nine conditions:

- any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis
- the anemia of myeloid cancers
- the anemia associated with the treatment of myeloid cancers or erythroid cancers
- the anemia of cancer not related to cancer treatment
- any anemia associated with radiotherapy
- prophylactic use to prevent chemotherapy-induced anemia
- prophylactic use to reduce tumor hypoxia
- patients with erythropoietin-type resistance due to neutralizing antibodies
- anemia due to cancer treatment if patients have uncontrolled hypertension

However, the final determination should clarify that “myeloid cancers” refers to acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) but not to myelodysplasia or multiple myeloma. Additionally, coverage for the use of ESAs in several of these conditions may be reasonable and necessary when such use is part of an evidence development program.

CMS should specifically allow coverage for ESA use for these conditions:

- **Anemia of myelodysplasia or myelodysplastic syndrome (MDS);**
  - Anemia is the most frequent complication of this irreversible chronic bone marrow disorder, frequently requiring long term transfusions.
  - MDS is commonly treated with epoetin alfa, with benefits that include transfusion reduction and improved hemoglobin levels.
  - While MDS is not considered a malignancy, some MDS patients experience leukemic transformation. There is no evidence that use of EPO accelerates this transformation.
  - Clinical trial evidence has not shown safety signals.
  - Treatment guidelines, e.g. American Society of Hematology/American Society of Clinical Oncology and National Comprehensive Cancer Network, and major compendia [DrugPoints (formerly USP DI) and AHFS] have listed epoetin alfa use for MDS patients.
  - CMS has de facto acknowledged the benefits of ESA treatment in patients with MDS by recently including iron store evaluation in EPO-treated MDS patients as a physician quality measure under the Physician Voluntary Reporting Program (PVRP).
  - **We recommend that epoetin alfa should be covered for anemia of MDS** based on clinical trial results, compendia listings, and the recommendations by MDS/anemia treatment guidelines and American Society of Hematology.

- **Anemia in patients with treatment regimens including anti-angiogenic drugs and/or monoclonal/polyclonal antibodies directed against the epidermal growth factor (EGF) receptor**
  - Non-coverage for patients whose treatment regimens include anti-angiogenic and/or monoclonal/polyclonal antibodies directed against EGF receptor therapies lacks sufficient scientific foundation.
  - No safety signals have been identified with the use of these agents in combination with ESAs.
  - This policy would adversely affect many patients for whom these agents are administered in combination with myelosuppressive chemotherapy regimens that commonly cause anemia.
  - The final coverage determination should be based upon scientific evidence and not highly theoretical constructs.
  - **We recommend these two proposals be withdrawn.**
  
- **Patients with thrombotic episodes related to malignancy.**
  - The prescribing information does not preclude patients with a history of thrombotic episodes to receive ESAs.
  - There are no contraindications for use or warnings in ESA labeling information regarding history of thrombotic episodes
  - No demonstration that TVE risk is increased with EPO treatment, above and beyond the increased risk noted in patients with a prior history of TVEs.
  - The decision to use ESAs in this setting should be left to treating physician after careful assessment of the benefits and risks.
  - **We recommend that this proposal be withdrawn.**

In addition to the conditions noted above, the CMS NCD imposes severe ESA coverage restrictions for many cancer types based on the presence of EPO receptors on normal or malignant tissue, including bone (sarcoma), brain-neurologic, breast, cervical, colo-rectal, gastric, head-and-neck (squamous cell), hepatic, lung, lymphoma, melanoma, multiple myeloma, muscle including cardiac, ovarian, pancreatic (exocrine), prostate, retinal, and uterine. We feel the scientific evidence used as a basis for these restrictions are limited and unreliable. We base our position on the following:

- Conflicting science regarding presence of functional erythropoietin receptors on the surface of tumor cells
- The 18 tumor types listed in the proposed NCD are non-myeloid in origin and therefore are indicated for ESA treatment according to the prescribing information.
- The report developed by FDA scientists described the present scientific evidence regarding erythropoietin receptors in the following manner:

- *“...In addition, a direct relationship between the presence of EPO receptors on tumors and tumor proliferation in response to exogenous EPO has not been established. In vitro and in vivo data do not provide convincing evidence that EPO promotes tumor growth and proliferation...”*
- Detection of EPO receptors to date has used commercial polyclonal antibodies, which have poor specificity for the EPO receptor (substantial cross-reactivity to non-EPO receptor proteins, e.g., heat shock protein 70, an anti-apoptotic protein which predicts for poor outcome in several tumor types)

For the 18 selected tumor types described above, CMS is proposing dosing and administration limitations as follows:

- **CMS NCD draft limitation: Hb levels immediately prior to initiation of dosing for the month should be <9 g/dL; for those with cardiovascular documented ischemic disease, <10 g/dL:**
  - This limitation is neither the current standard of care nor supported by established anemia treatment guidelines
  - The body of evidence showing that ESAs are safe and effective has been in studies where the baseline Hb is < 11 g/dL. The draft NCD is inconsistent with the pivotal trials evaluated by the FDA that demonstrated safety and efficacy at this Hb initiation level.
  - Recent clinical trial analyses have reported higher proportion of patients transfused when initiated at Hb <9 g/dL compared with Hb 9-11 g/dL. Similar findings have been reported when initiating ESA at Hb <10 g/dL versus 10-11 g/dL. No adverse effect on survival has been demonstrated in meta-analyses of studies using baseline Hb initiation levels of 10-12 g/dL.
  - Hb initiation at < 9 g/dL, will have a significant negative impact on patient QoL and result in increased transfusions compared to a Hb initiation of < 11 g/dL.
  - **We suggest coverage for Hb < 11 g/dL at ESA initiation and non-coverage for Hb levels > 12 g/dL.**
- **CMS NCD draft limitation: Maximum covered treatment duration 12 weeks/year**
  - Many standard chemotherapy regimens that are associated with chemotherapy-induced anemia are administered for >12 weeks.
  - Patients may receive more than one chemotherapy treatment regimen in a year particularly those with metastatic or locally advanced malignancies.
  - Frequently, chemotherapy-induced anemia persists for 1-3 months following discontinuation of myelosuppressive treatment.
  - **We recommend that CMS restrict ESA treatment to periods of ongoing chemotherapy plus three months following chemotherapy completion.**

- **CMS NCD draft limitation: Maximum covered 4-week treatment dose is 126,000 Units for EPO; 630mcg for darbepoetin:**
  - The proposed dosing limit is counter to the recommended epoetin alfa dosing described in the prescribing information (eg. 100 kg patient would require 180,000 Units of EPO/4 weeks based on 150 Units/kg TIW or 160,000 Units/4weeks based on 40,000 U QW).
  - A TIW schedule represents an undue burden on patient, caregiver, and office staff time.
  - The prescribing information also recommends dose escalation based upon inadequate response to the starting doses (e.g. 100 kg patient would require 360,000 Units of EPO/4 weeks based on 300 Units/kg TIW or 240,000 Units/4weeks based on 60,000 U QW). Under this proposed NCD maximum covered 4-week treatment dose, the dose escalations recommended in the prescribing information could not be used.
  - Any arbitrary dose limit will create unintended reimbursement incentives to shift use of particular products.
  - **We recommend no maximum covered treatment dose.** Appropriate ESA dosing will be achieved by having non-coverage for patients with a hemoglobin > 12 g/dL, as described in the labeling information. Limiting use based on individual patient specific outcomes, such as Hb levels, provides a more patient focused approach to anemia management than an arbitrary dose cap that must fit all patients.
  
- **CMS NCD draft limitation: Continued use of drug not reasonable and necessary if there is evidence of poor drug response (hemoglobin rise <1 g/dL) after 4 weeks of EPO treatment**
  - Waltzman reported that 29% of patients without a 1 g/dL Hb rise at week 4 went on to have at least a 1 g/dL Hb rise by end of study. This demonstrates that a significant proportion of patients have continued Hb improvements and may avoid transfusion despite not achieving a Hb rise of 1 g/dL after 4 weeks of EPO treatment.
  - Dose escalations at 4 or 8 weeks based on lack of response are recommended as per the EPO prescribing information and anemia treatment guidelines. Placebo-controlled trials have demonstrated that poor drug response at week 4 does not reliably predict ultimate hematologic response by end of study.
  - **We recommend that ESA administration should not be limited based on poor drug response at 4 weeks.** Patients with poor hemoglobin response (hemoglobin/hematocrit rise < 1 g/dL/3% over baseline) should be discontinued after 8 weeks following ESA initiation.
  
- **CMS NCD draft limitation: Continued administration of the drug is not reasonable and necessary if there is an increase in fluid retention or weight (5 kg) gain after 2 weeks of treatment.**

- Patients with fluid retention increase or weight gain are not contraindicated for ESA use according to the prescribing information.
  - Data cited in the proposed NCD to support this limitation pertain to chronic kidney disease patients receiving dialysis and not anemic cancer patients.
  - These data cannot be generalized between the two populations, which are distinctly different with different comorbid states.
  - **We recommend coverage for patients with fluid retention or weight increase be allowed.**
- **CMS NCD draft limitation: Continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin >1g/dL after 2 weeks of treatment.**
    - There is no evidence to support this proposal
    - **We recommend the PROCRT (epoetin alfa) dose should be reduced by 25%, not discontinued, if this situation occurs (as per prescribing information).**

In recognition of our shared interest in developing additional evidence on ESA use, OBI recommends that CMS adopt a Pharmacovigilance and Evidence Development Program for ESAs that will include periodic reports from manufacturers, consideration of the pharmacovigilance plans developed with the FDA.

- **CMS is also interested in public comment on whether coverage for ESA treatment should occur only within the setting of appropriately designed clinical research studies where informed consent and safety monitoring can be ensured.**
  - Such a proposal may be of interest for patients with anemia of cancer not related to chemotherapy, however it would be wholly inappropriate, unreasonable and unnecessary for patients with chemotherapy-induced anemia based on the preponderance of scientific and robust clinical data supporting EPO use and the well described risks and patient monitoring recommendations in the product labeling.

In summary, while Ortho Biotech agrees with several of the proposed coverage changes, we also believe that many of the proposed coverage changes:

- Are not supported by a proper interpretation of available scientific and clinical evidence.
- Do not consider the substantial heterogeneity inherent in oncology patients and their treatments.
- Are contrary, in many instances, to current prescribing information and consensus national treatment guidelines.
- Expose beneficiaries to known and unknown risks of blood transfusions while putting unbearable pressure on the already limited national blood supply and transfusion services.
- Unduly restrict coverage and access to ESAs, which could harm Medicare beneficiaries.

## 2. Introduction

### **PROCRIT (epoetin alfa) safe and effective when used according to labeling information (target Hb levels not to exceed 12 g/dL)**

The safety and efficacy of ESAs have been evaluated in multiple randomized and non-randomized trials in approximately 15,000 patients with chemotherapy-induced anemia in the past 20 years. When used according to the approved prescribing information, ESAs are safe and effective and has an acceptable risk/benefit profile for patients with chemotherapy-induced anemia. Erythropoietic stimulating agents (ESAs) are the only viable alternative to red blood cell transfusions for this patient population. They have proven valuable in reducing the need for transfusions and improving QoL. The benefits of reducing transfusions include reduction in hospital visits, avoidance of infectious complications, including the potential new and emerging pathogens, non-infectious complications, and conservation of the limited national blood supply already constrained with limited marginal capacity, especially at the regional level and during seasonal and holiday periods.

The following section will outline the numerous trials that demonstrate a clinical benefit of ESAs in patients with chemotherapy-induced anemia focusing on transfusion reduction and improved QoL.

## 3. Patient Benefits of Transfusion Reduction and Improved Quality of Life

### 3.1 Transfusion Reduction

Multiple meta-analyses have reported significant transfusion reduction in ESA-treated patients in comparison with control populations. A recent meta-analysis of all randomized controlled studies comparing ESA versus transfusion alone for prophylaxis or treatment of anemia in cancer patients (42 studies with 6,510 subjects) demonstrated that patients treated with epoetin alfa or darbepoetin alfa had a 36% lower risk of transfusion than control subjects (relative risk=0.64 [95% CI: 0.60 to 0.68]) (Bohlius 2006 Cochrane Database). The publication also presented hazard ratio for transfusion categorized by baseline hemoglobin. As shown in the table below, the relative risk for patients initiated at Hb < 10 g/dL was higher (0.70) than for patients initiated at a hemoglobin of 10-12 g/dL, indicating the greater benefit for transfusion reduction is observed in those patients with ESA initiation at 10-12 g/dL (0.46).

Baseline Hb at ESA initiation	Relative risk for transfusion (95% CI)
Hemoglobin < 10 g/dl	0.70 (0.65, 0.75)
Hemoglobin 10-12 g/dL	0.46 (0.40, 0.53)

Another team of investigators conducted meta-analyses of ESA that reported odds ratio for transfusion (EPO:control) of 0.44 (95% CI 0.35-0.55) for EPO and 0.41 (95% CI 0.31-0.55) for DARB when each

agent was compared to the control group (Ross 2006). Additionally, the Agency for Healthcare Research and Quality also investigated transfusion patterns with ESA administration in pooled analyses and reported the relative transfusion risk (EPO:control) for EPO 0.63 (0.59, 0.67) and DARB 0.61 (0.52, 0.72) (Seidenfeld 2006). The Health Technology Assessment published in April 2007, found that treatment with ESAs in patients with cancer-induced anemia reduces the number of patients who receive a RBC transfusion by an estimated 18%. HTA conducted a systematic review of the literature and identified 39 trials that reported the number of patients who were transfused during a trial involving ESA use in cancer-induced anemia. 53 data points were included in a meta-analysis. The relative risk for all trials reporting data on the number of patients receiving a transfusion was 0.63 (95% CI 0.58 to 0.67, fixed effects) favoring EPO. There was statistically significant heterogeneity between the trials. The authors stated that asymmetry was seen in the funnel plot but the pattern was not consistent with publication bias (Wilson 2007).

Witzig et al. (2005) studied weekly administration of EPO in anemic (males Hb < 11.5 g/dL; females Hb < 10.5 g/dL) patients with advanced cancer undergoing myelosuppressive chemotherapy. This was a phase III, randomized, double-blind, placebo-controlled study where patients were randomized to receive either EPO 40,000 U SC (n = 174) or placebo (n = 170) weekly for 16 weeks. The study end points were Hb response, RBC transfusions, and changes in QoL. All enrolled patients were part of the intent-to-treat patient population. A significant reduction in red blood cell transfusion was observed in the epoetin alfa-treated group (RBC transfusion: epoetin alfa group: 25%, control 40%, p < 0.005). The authors concluded that weekly administration of EPO increased Hb levels and reduced transfusion requirements in patients with cancer-related anemia.

Moebus et al. (2007) recently reported the findings of randomized controlled trial in 658 adjuvant breast cancer patients receiving chemotherapy (epirubicin, paclitaxel, and cyclophosphamide) with or without epoetin alfa support. Significant reduction in red blood cell transfusion was observed in the epoetin alfa-treated group (RBC transfusion: epoetin alfa group: 13%, control 28%, p < 0.0001). At a median follow-up of 62 months, there was no difference between the epoetin alfa treated group and control group concerning 5 year disease free survival or overall survival (5 year disease free survival: epoetin alfa group 72%, control 71%, p = 0.86; overall survival: epoetin alfa 81%, control 83%, p = 0.89). The authors concluded the epoetin alfa significantly reduced blood transfusion without influencing disease-free survival or overall survival (Moebus 2007). Similar findings were reported in patients with metastatic breast cancer in a clinical trial with another ESA, epoetin beta. There were no significant differences in overall survival (HR 1.07, 95% CI [0.87; 1.33], p-value 0.52) or progression free survival (HR 1.07, 95% CI [0.89; 1.30], p = 0.45). In patients receiving epoetin beta there was a significant improvement in transfusion free survival (HR 0.59, p = 0.009) (Aapro 2006).

### 3.2 Favorable Impact of ESAs on Patient-Reported Outcomes

*"CMS determines whether an intervention is reasonable and necessary by evaluating its risks and benefits. For all determinations, CMS evaluates whether reported benefits translate into improved net health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses."*  
(Phurrough 2005, CMS)

In accordance with the CMS statement above, the following section will outline studies and analyses that report improved patient reported outcomes (PROs) when used in conjunction with ESAs. While the FDA has issued draft guidance on PRO for purposes of labeling claims, this document has been in development for over five years and has yet to be finalized. CMS should consider the large body of evidence of improved PRO that has been reported with ESA use in patients with chemotherapy-related anemia. It is important to note that QoL studies are described in the ESA product labeling information in Canada (EPREX<sup>®</sup> Prescribing Information [11/06]) and Europe (EPREX<sup>®</sup> Summary of Product Characteristics [7/06]).

Several studies have suggested a relationship between hemoglobin increases during epoetin alfa therapy and corresponding improvements in patient-reported outcomes such as quality of life. One study examined data from two open-label, community-based trials of epoetin alfa therapy in anemic cancer patients undergoing chemotherapy assessed the relationship between Hb changes and QoL changes. This incremental analysis showed a nonlinear relationship between incremental changes in Hb and QoL scores, with the maximum QoL gain occurring at a Hb level of 12 g/dL (range, 11 g/dL - 13 g/dL). The analysis implied that a 1 g/dL increase in Hb from 11 g/dL to 12 g/dL yielded the greatest incremental gain in QoL as measured by the LASA scale. Patients with low baseline QoL scores and longer time periods between baseline and final QoL assessments experienced significantly ( $P < 0.05$ ) greater increases in overall QoL (Crawford 2002). Similar findings were observed in another trial of epoetin alfa-treated patients with chemotherapy-induced anemia (Shasha 2004).

In April 2007, the Health Technology Assessment (HTA) Programme published their findings on the effectiveness of epoetin alfa, epoetin beta and darbepoetin alfa (Wilson 2007). Decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) are directly influenced by research findings from the HTA Programme. The HTA conducted a systematic review of recent randomized controlled trials comparing epo with best standard. Through a MEDLINE search from 1966 to September 2004, the authors identified 20 trials that reported QoL data in conjunction with ESA use. Three thousand one hundred and ninety-five patients were evaluated. The data were tabulated and analyzed qualitatively and a vote-counting method was used to summarize the data. A positive effect was observed in favor of an improved HRQoL for patients on EPO. The noted limitations of this study

include a potential for a variety of within study methodological problems that may bias the results. For example:

- Data may be skewed by missing values
- There may be shifts in patients' responses over time particularly when patients are asked to repeat questionnaires
- Less than half of the trials included in the review were placebo-controlled, therefore some patients would have known their treatment allocation which may have affected how they rated their QoL

However, missing not at random and missing at random techniques used in one of the analyzed trials by the Littlewood (2001) trial greatly assisted in data analysis and minimized these limitations.

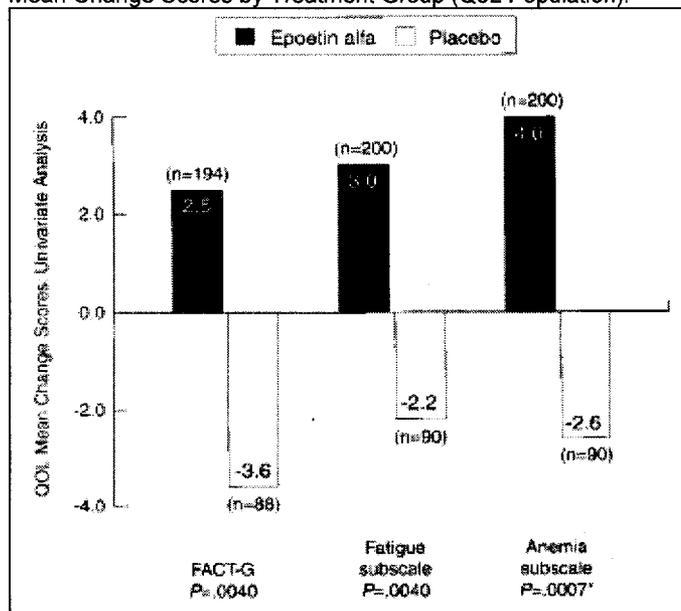
The results of a previous COCHRANE review showed similar results to the HTA review. Changes in health-related, patient-reported outcomes including cancer-related fatigue were analyzed in 16 studies with 3,670 randomized patients as part of the updated Cochrane Review (Bohlius 2006 Cochrane Database). Of the 16 studies, 9 evaluated the effects of treatment on health-related, patient-reported, outcomes as assessed by the FACT instrument and its subscales and generally favored ESA treatment. According to the Cochrane group, the results showed an overall positive effect on health-related patient-reported outcomes from ESAs that seemed unlikely to be due to chance. However, interpretation of results was limited in a similar manner to the HTA study.

A systematic review of the literature has also been performed by the Agency for Healthcare Research and Quality (AHRQ) (Seidenfeld 2006). Outcomes of interest included patient-reported outcomes when assessed with validated tools such as the FACT (includes G-general, F-fatigue, and An-anemia subscales) and the Visual Analog Scale (VAS). AHRQ results also tended to favor ESA treatment over control; however, AHRQ concluded that the evidence was not sufficient for definitive conclusions on the effects of ESA treatment on patient-reported outcomes. Limitations of the data were cited by AHRQ and included potential bias due to missing data and lack of blinding, as well as incomplete correlation of numeric changes on patient-reported outcome scales to clinical differences that are meaningful to patients.

As noted in both the Cochrane and Health Technology Assessment several prospective randomized controlled studies (at least 100 subjects per study) have been conducted to assess the effect of epoetin alfa on patient-reported outcomes using validated instruments such as the Functional Assessment of Cancer Therapy-Anemia (FACT-An), a 47-item questionnaire designed to measure anemia-related and general patient-reported outcomes in patients with cancer, and the Cancer Linear Analog Scale (CLAS), used for assessment of energy level, ability to do activities, and overall patient-reported outcomes. Three studies (Littlewood 2001, Chang 2005, Case 1993) demonstrated significant improvements in cancer and

anemia-specific patient-reported outcomes domains (mean change from baseline) for patients treated with epoetin alfa as compared to placebo/standard of care (i.e. transfusions). In the study by Littlewood et al. (2001), 375 anemic patients with solid or non-myeloid malignancies, receiving non-platinum chemotherapy, were randomly assigned to receive epoetin alfa with the approved 3-times-weekly dosing schedule (150 to 300 IU/kg) or placebo 3 times weekly for 12 to 24 weeks. Mean change scores from baseline in the anemia, fatigue (FACT-F), and general (FACT-G) subscales of the FACT-An was significantly greater for the epoetin alfa group compared with placebo (range of p values from 0.0007 to 0.0040) (Figure 1).

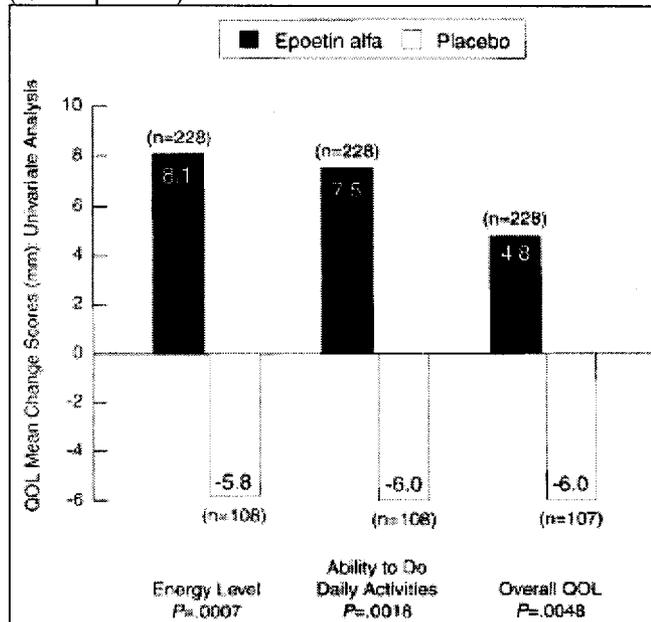
Figure 1: Comparison of Patient-Reported Outcomes (FACT-An, Comprising FACT-G, Fatigue Subscale, and Anemia Subscale) Mean Change Scores by Treatment Group (QoL Population).



\*Indicates that the p value for the Anemia subscale (secondary measure) is unadjusted. All other p values, which correspond to primary measures, are adjusted for multiple comparisons (sequentially rejective Bonferroni procedure).  
 From: Littlewood TJ, et al. *J Clin Oncol* 2001;19:2865-2874 With permission from the American Society of Clinical Oncology. Unauthorized duplication of this content is a copyright infringement and subject to strict penalties.

Consistent with the significant improvement in FACT-An scores, patients receiving epoetin alfa, as compared with placebo (i.e. transfusions), reported significant increases in energy levels (epoetin alfa, +8.1 versus placebo, -5.8; p=0.0007), ability to carry out daily activities (epoetin alfa, +7.5 versus placebo, -6.0; p=0.0018), and patient-reported outcomes (epoetin alfa, +4.8 versus placebo, -6.0; p=0.0048) as assessed by the CLAS (Figure 2).

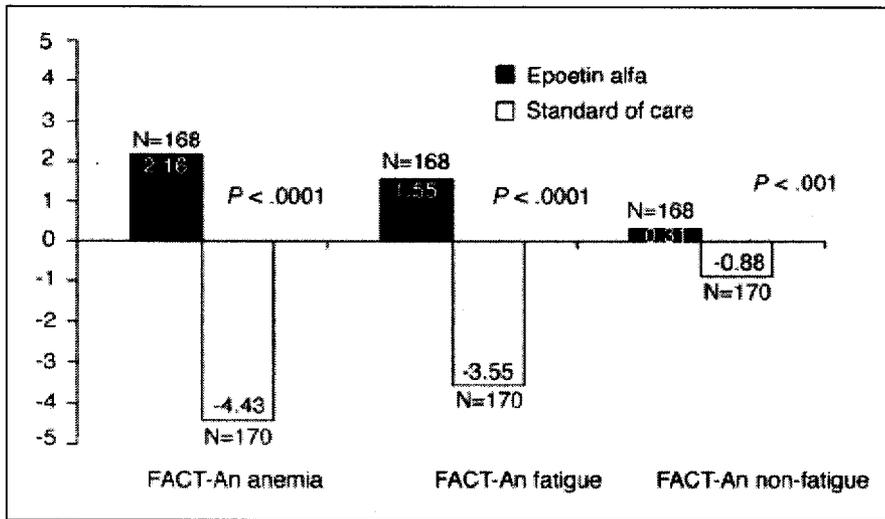
Figure 2: Comparison of Patient-Reported Outcomes (CLAS, Comprising Energy Level, Ability to do Daily Activities, and Overall QoL) Mean Change Scores by Treatment Group (QoL Population).



Note: All p values, which correspond to primary measures, are adjusted for multiple comparisons (sequentially rejective Bonferroni procedure).  
 From: Littlewood TJ, et al. *J Clin Oncol* 2001;19:2865-2874. *With permission from the American Society of Clinical Oncology*  
 Unauthorized duplication of this content is a copyright infringement and subject to strict penalties.

Another randomized Phase III study compared epoetin alfa using a 40,000 U once a week regimen for 16 weeks versus standard of care (transfusions) in 354 anemic patients with breast cancer receiving chemotherapy (Chang 2005). A similar pattern of patient-reported outcomes differences between the epoetin alfa-treated and standard-of-care groups was demonstrated. In this study the mean change in scores from baseline for both the FACT-An anemia and fatigue subscales was significantly better in the epoetin alfa group compared with standard of care ( $p < 0.001$ ) (Figure 3).

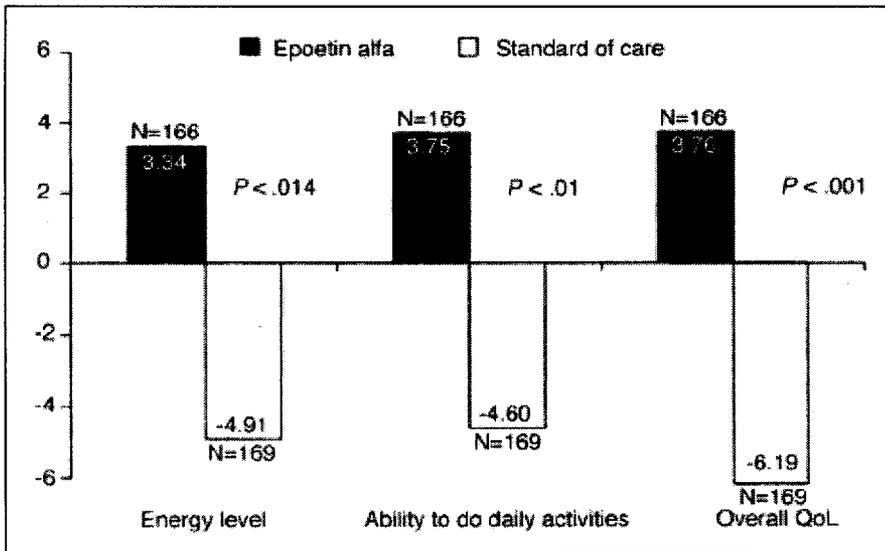
Figure 3: Change in Mean Functional Assessment of Cancer Therapy (FACT)-Anemia Subscale Score Between Baseline and Week 12.



From Chang J, et al. J Clin Oncol 2005;23(12):2597-2605. With permission from the American Society of Clinical Oncology. Unauthorized duplication of this content is a copyright infringement and subject to strict penalties.

Consistent with this patient-reported outcomes benefit, a significant improvement in all 3 CLAS domains (energy level, daily activities, and overall QoL) was demonstrated for the epoetin alfa-treated group compared with the standard-of-care (transfusion only) cohort (Figure 4).

Figure 4: Change in Mean Cancer Linear Analog Scale Score Between Baseline and Week 12.



From Chang J, et al. J Clin Oncol 2005;23(12):2597-2605. With permission from the American Society of Clinical Oncology. Unauthorized duplication of this content is a copyright infringement and subject to strict penalties.

Patient-reported outcomes were measured as secondary endpoints in a third randomized, controlled study of epoetin alfa with the approved 3-times-weekly dosing schedule (150 to 300 IU/kg) or placebo (3 times a week) for 12 weeks in 153 anemic cancer patients receiving chemotherapy. A significant increase in the baseline to final CLAS score for energy level and ability to perform daily activities was observed for

the epoetin alfa-treated population ( $p < 0.05$ ), but not the placebo (transfusion only) group. The difference in mean change of scores from baseline was not compared between the 2 groups (Case 1993).

In another randomized controlled study that included a validated patient-reported outcomes assessment, Thatcher et al. (1999) evaluated whether epoetin alfa could prevent anemia and reduce transfusion requirements in 130 subjects with small cell lung cancer undergoing cyclic chemotherapy. Patients were randomized to receive epoetin alfa at 150 or 300 IU/kg subcutaneously, 3 times a week with 6 cycles of chemotherapy or chemotherapy alone. The impact on patient-reported outcomes was assessed with a linear analogue self-assessment scale, which measures energy level, ability to do daily activities, and overall patient-reported outcomes. A significant improvement in overall patient-reported outcomes was demonstrated in the epoetin alfa group ( $p < 0.05$ ), but the differences in scores for energy level and daily activity were not significant.

In a fifth randomized controlled study of epoetin alfa versus placebo, improvements in patient-reported outcomes (as measured by the FACT-An fatigue scale) were observed in the epoetin alfa group, but they were not significantly different from the placebo group ( $p = 0.18$ ). Hemoglobin responders (regardless of treatment arm) had significantly higher improvements on the FACT-An fatigue scale than nonresponders, suggesting an association between improvement in hemoglobin and an improvement in fatigue (Witzig 2005).

The results of these 5 studies, summarized in Table 1, suggest that ESAs might have important clinical benefit in terms of improved patient-reported outcomes for cancer patients receiving chemotherapy.

Four supplemental publications (Patrick 2003, Fallowfield 2002, Fairclough 2003, Cella 2003) have addressed the limitations of the Littlewood study. Fallowfield et al. (2002) conducted a pre-planned multiple linear regression analysis that controlled for disease progression and several other potential confounding variables, such as baseline disease characteristics that could affect patient-reported outcomes. The multiple regression model confirmed the results of Littlewood (2001), demonstrating statistically significant differences for between-group comparisons of mean patient-reported outcome change scores for all 5 cancer-specific scales (range of p values: 0.01 to 0.04). The improved scores were associated with improvements in hemoglobin concentration. The investigators concluded that "epoetin alfa can improve quality of life in anemic cancer patients undergoing chemotherapy, and this change is associated with increasing hemoglobin levels."

**Table 1: Effect of Epoetin Alfa Treatment on Patient-Reported Outcomes  
(Summary of Results From 5 Studies)**

Study/Tumor Type	Epoetin Alfa Dose Regimen	Treatment Groups	Measures	Results	General Comments
Case (1993)/Varied	150 IU/kg SC TIW x 12 weeks	Non-cisplatin or Cisplatin + EPO (n=63) or placebo (n=61)	LASA-Energy, Daily Activities and Overall QOL	EPO-treated patients had significant improvements in Energy and Daily Activities (P<0.05), and Overall QOL (P=0.083) as compared to baseline values	No intergroup comparisons between EPO-treated and placebo groups conducted
Littlewood (2001)/Varied	150 IU/kg SC TIW x 6 cycles + 4 wk post-CT	Nonplatinum + EPO (n=238) or placebo (n=111)	LASA Energy, Daily Activities, Overall QOL, FACT-G, FACT-F, FACT-An, SF-36	LASA Energy P<0.001, Daily Activities P<0.01, Overall QOL P=0.01, FACT-G P<0.05, FACT F P<0.01, FACT-An P<0.01, SF-36 NS	Adjustments for covariates not included.
Chang (2005) /Breast	40K SC QW x 16 weeks (QOL at 12 weeks)	Nonplatinum+ EPO 40K QW (n=168), or SOC (n=170)	FACT-An, FACT-F, LASA Energy, Daily Activities, Overall QOL	FACT-An and FACT-F P<.0001; LASA Energy P<.014, Daily Activities P<.01, Overall QOL P<.001	
Thatcher (1999) /SCLC	150 IU/kg SC TIW X 6 cycles or 300 IU/kg SC TIW x 6 cycles	Platinum or Nonplatinum+EPO 150 IU TIW (n=42),EPO 300 TIW (n=44), or SOC (n=44)	LASA Energy, Daily Activities, Overall QOL, WHO Performance Score	Overall QOL P<0.05 for EPO 150 IU/kg group. All others NS	Open label design
Witzig (2005) / Varied	40K SC QW x 16 weeks	Platinum or Nonplatinum+ EPO (n=154) or placebo (n=151)	LASA Overall QOL, FACT-An, Symptom Distress Scale	LASA Overall QOL P=0.27, FACT-An P=0.18, SDS NS	QOL higher in placebo group at baseline. Effect of increased transfusion rate in placebo group on Hb could have masked true QOL differences between groups.

CT=chemotherapy; EPO=epoetin alfa; FACT= Functional Assessment of Cancer Therapy; FACT-AN = FACT-anemia; FACT-F=FACT=fatigue; FACT-G= FACT-general; Hb=hemoglobin; LASA=linear analog self-assessment; NS=not significant; SC=subcutaneous; SOC=standard of care; QOL=quality of life; QW=once weekly SCLC=small-cell lung cancer; SDS=Symptom Distress Scale; SF-36; TIW=3 times weekly; 40K=40,000 IU

Fairclough and colleagues (2003) conducted a sensitivity analysis, which included all available patient-reported outcomes data from each patient and adjusted for censored assessments. The results of this sensitivity analysis, when compared to the baseline-to-last available assessment utilized by Littlewood (2001), confirmed the between-group patient-reported outcomes differences favoring epoetin alfa, demonstrating the robustness of the epoetin alfa treatment effect on patient-reported outcomes despite missing data.

The clinical relevance of the observed between-group differences in the FACT-An and CLAS subscales favoring epoetin alfa in the studies by Littlewood (2001) and Chang (2005) has been established by way of anchoring the observed differences to changes in hemoglobin (Patrick 2003) and by comparisons to normative values from the general population (Cella 2003). In the study by Patrick et al. (2003), hemoglobin and patient-reported outcome data from Littlewood (2001) were analyzed to determine the minimally important difference between patients achieving at least a 1 g/dL rise in hemoglobin (improved group) as compared to those who did not deteriorate or improve (stable group). The between group differences in health-related patient-reported outcomes scores between the epoetin alfa and placebo groups observed in the Littlewood (2001) study exceeded the minimally important difference established by Patrick (2003) for all hemoglobin-sensitive, cancer-specific, health-related, patient-reported outcomes evaluations.

Finally, to better characterize the epoetin alfa-associated patient-reported outcomes changes reported by Littlewood (2001), Cella et al. (2003) compared FACT-An data collected from a nationally representative U.S. normative population of 1,400 subjects to the FACT-An results from the study. Comparison of the patient-reported outcomes scores from the normative population norm the Littlewood (2001) clinical study data suggest that the differences in patient-reported outcome scores between the epoetin alfa and placebo (i.e. transfusion only) groups observed in the clinical study are clinically meaningful as well as statistically significant. In fact, most of the patient-reported outcome deficits in the FACT-G and FACT-An fatigue and anemia subscales between the clinical study group and the normative population at baseline were restored with epoetin alfa treatment (95%, 51%, and 49%, respectively).

Gabrilove et al. (2001) conducted a prospective, multicenter, open-label, single-arm, non-randomized 16-week study evaluating the safety, efficacy and QoL of patients receiving EPO in anemic ( $Hb \leq 11$  g/dL) cancer patients receiving chemotherapy. Epoetin alfa was initiated at a dose of 40,000 U administered SC QW. If the Hb did not increase by  $> 1.0$  g/dL after 4 weeks of therapy, the dosage of epoetin alfa was increased to 60,000 U SC QW. Two QoL instruments were used for patient self-analysis at baseline, month 2 and at study completion: the Functional Assessment of Cancer Therapy-Anemia (FACT-An) scale (a 20-item questionnaire that evaluates well-being associated with fatigue and anemia) and a linear analog scale (LASA).

Increases in Hb levels were associated with improvements in QoL as measured by the FACT-An. Mean increases in Hb levels and corresponding point increases in the FACT-An scores are shown in Table 3:

**Table 3. Hemoglobin Increase versus Change in FACT-An Score from Baseline (n = 2,230)**

Increase in Hemoglobin Level (g/dl)	Mean Increase in Anemia Subscale of FACT-An Score (%)
0.0 to 2.0	+4.8 (11.2%) *
>2.0 to 4.0	+7.7 (17.6%) *
> 4.0	+11.0 (25.4%) *

Key: \*p < 0.001

There were significant changes from baseline in LASA scores for energy, activity, and overall QoL, which suggests functional impairment at baseline. The changes from baseline for energy level, activity level, and overall QoL scores were 30.0%, 26.0%, and 19.4%, respectively (P < 0.001). Improvements with QoL parameters correlated significantly (P < 0.001) with increased Hb levels in the LASA scores as shown below in Table 4: Hemoglobin Change versus Change in LASA Scores from Baseline. This direct relationship was sustained over the entire study period.

**Table 4. Hemoglobin Change versus Change in LASA Scores from Baseline (n=2,258)**

Increase in Hemoglobin Level (g/dl)	Mean Increase in LASA Score (%) Overall Quality of Life
0.0 to 2.0	+8.2 (17.2%) *
>2.0 to 4.0	+12.2 (25.2%) *
> 4.0	+15.4 (32.3%) *

Key: \*p < 0.001

The results of this study demonstrated that once-weekly epoetin alfa is effective in increasing Hb levels, decreasing transfusion requirements, and improving QoL in anemic cancer patients receiving chemotherapy.

The evidence in support of epoetin alfa treatment has also been extensively reviewed and summarized in guidelines for chemotherapy-induced anemia. With respect to patient-reported outcomes, the NCCN cited the lack of randomized study data but recommended consideration of the use of erythropoietin in mildly anemic patients (10 to 11 g/dL) who have functional symptoms (NCCN anemia treatment guidelines v.3.2007). Both the Canadian Cancer and Anemia Guidelines Development Group and the European Organization for Research on the Treatment of Cancer concluded that epoetin alfa produces statistically significant and clinically relevant improvements in patient-reported outcomes for the treatment of anemia in patients with cancer (Turner 2001, Bokemeyer 2007).

### 3.3 Conclusion: Clinical Benefits of ESAs Use in Chemotherapy-Induced Anemia

Chemotherapy-induced anemia is an important clinical condition. ESAs have established benefits in reducing the need for transfusions as well as improved quality of life. Recent meta-analyses have shown that ESA use significantly increases hemoglobin response more than three fold and reduces the risk of transfusion by 36 to 59 percent (Bohlius 2006 Cochrane Database, Seidenfeld 2006, Ross 2006). A recent HTA meta-analyses of over 3195 patients found a positive effect in favor of an improved HRQoL for patients on EPO (Wilson 2007). Clinical guidelines continue to recommend ESAs for symptomatic patients with chemotherapy-induced anemia (NCCN anemia treatment guidelines v.3.2007, Rizzo 2002).

### 4. Safety of ESAs in the Treatment of Chemotherapy-Induced Anemia

The risks of PROCRIT and other ESAs in cancer patients are described in the Product labeling (PROCRIT Prescribing Information [3/07]). Increased incidences of thrombotic events have been observed when ESAs are used for the correction of chemotherapy-induced anemia. Adverse effects on survival and possible tumor progression are observed when ESAs are used for non-FDA approved investigational uses, as summarized in the table below. With the exception of the Amgen anemia of cancer trial, all studies evaluated patients with higher Hb initiation levels (> 12 g/dL) and targeted higher Hb levels (> 12 g/dL). These Hb levels are higher than what is currently recommending in the prescribing information (i.e. hold Hb for level > 12 g/dL).

**Table 5. Safety Trials**

Trial	N	Patient Population	Hb initiation (g/dL)	Hb target (g/dL)	FDA-approved use?
Potentiation of radiation therapy					
ENHANCE (Henke 2003)	351	Head and neck cancer patients with radiation therapy	12/13	14/15	No
DAHANCA (Overgaard 2007)	522	Head and neck cancer patients with radiation therapy	14.5	15.5	No
Potentiation of chemotherapy					
BEST (Leyland-Jones 2005)	939	Breast cancer patients with chemotherapy	13	14	No
Anemia of cancer					
Amgen Anemia of cancer (Glaspy 2007)	985	Anemia of cancer	11	12	No
EPO CAN 20 (Wright 2007)	70	Anemia of cancer	12	14	No

In collaboration with the FDA, Ortho Biotech and Amgen Inc, updated (3/07) the safety information in the product labeling for their ESAs to reflect these safety signals. It is our belief that CMS may have applied this safety information to a broader range of clinical settings that are clearly different and unique from the original studies. When used in accordance with the prescribing information, PROCRIT is safe and effective. We urge CMS not to take results of studies investigating off-label uses of ESAs and apply those results broadly to propose non-coverage determinations to areas where ESAs have been shown to be safe and effective.

#### **4.1 Pharmacovigilance Program Evaluating Safety of ESAs in Patients with Cancer**

Both Amgen and Ortho Biotech are working closely with the FDA to provide regular and frequent clinical updates of their respective ongoing pharmacovigilance programs. Each company has established a comprehensive pharmacovigilance program, consisting of several randomized controlled studies, many of which will continue to inform us about the long-term safety of ESAs in various clinical oncology settings over the next 6-18 months. For the epoetin alfa pharmacovigilance program, with the exception of the recently published data on the CAN-20 cooperative group study of off-label use of epoetin alfa in the setting of anemia of cancer not receiving chemotherapy (Wright 2007), no new adverse effect of ESAs on survival, progression-free survival, or other adverse tumor outcomes have been observed. The following tables summarize the clinical trials of the epoetin alfa pharmacovigilance program.

#### **4.2 Survival Meta-Analysis Demonstrated No Survival Signal When Used Consistent with Label Information**

To better define the study and patient-level characteristics associated with key safety events, a predefined pooled analysis was performed. This meta-analysis was based on all eleven completed, randomized, double-blind, placebo-controlled studies in cancer patients totaling 3,104 patients that were conducted with epoetin alfa for which Johnson and Johnson Pharmaceutical Research and Development (J&JPRD) has access to patient-level data. Of the eleven studies, two of these 11 studies investigated hemoglobin targets beyond the correction of anemia. (Grote 2006[N93-004], Leyland Jones 2005[EPO-INT-76, BEST study]).

Studies were classified as "anemia correction" or "beyond correction of anemia" based on a combination of the following: 1) the entry hemoglobin concentration, 2) the hemoglobin range that treatment was intended to achieve, 3) the criterion for study drug dose escalation, 4) the definition of "hemoglobin response," and 5) the hemoglobin at which study drug dosing was suspended and subsequently restarted. For "anemia correction," the primary intent of the studies was to reduce transfusion utilization. Typically, study drug dosing was not escalated as long as there was a satisfactory hemoglobin response (usually a 1g/dL hemoglobin increase from baseline value). Conversely, the intent of the "beyond correction of anemia" studies was generally to keep subjects' hemoglobin  $\geq 12$  g/dL using dose escalation

**Table 6 Epoetin alfa Pharmacovigilance Program Evaluating Safety in Epoetin alfa Safety in Patients with Chemotherapy-induced Anemia**

STUDY # (n, accrual/ planned)	Tumor Type	Primary Endpoint	Secondary Endpoint	Safety Results	Status
N93-004 (224/400)	Lung cancer, treated with chemotherapy, Target Hb 14-16 g/dL	Tumor response (designed to exclude an absolute reduction of 15% in RR between the EPO and control groups)	Overall survival	Objective Tumor response: EPO 72% (95%CI: 64-81%), placebo 67% (95% CI: 58-76%). No more than a 6% difference in RR between the 2 groups was ruled out therefore primary endpoint was met. Overall survival (months): EPO 10.5, control 10.4, (p=0.264)	Stopped in agreement with FDA due to slow accrual secondary to changing standard of care ; Manuscript published (Grote 2005)
EPO- CAN-20 (70/300)	Lung cancer, Target Hb 12-14 g/dL (anemia of cancer; not candidates for further chemotherapy)	Quality of life	Hemoglobin change	Significant difference in the median survival in favor of the patients on the placebo arm of the trial (EPO 63 v placebo 129 days; hazard ratio, 1.84; P .04)	Terminated November 2003 based on unplanned interim analysis; Manuscript published (Wright 2007)
Ger-22 (389/612)	Lung cancer treated with chemotherapy, target 12-14 g/dL <sup>1</sup>	2 year survival rate	Local tumor control	No survival disadvantage for EPO group; Interim analysis, median survival EPO 338 days (95% CI 242-434) Control 299 (95% CI 234-364)	Closed to accrual December 2005; 2-year survival data mature 4Q07(Debus 2006)
RTOG 99-03 (148/372)	Head and neck cancer receiving RT; Target Hb 14-16 g/dL	Local- regional failure	Overall survival	1 yr local-regional control HR 1.18 (95% CI 0.67-2.09); 1 yr overall survival HR 1.57 (95% CI 0.76-3.27)	Closed in November 2003 based on unplanned interim analysis; Abstract published (Machtay 2004); Manuscript submitted
EPO- GBR-7 (301/800)	Head and neck cancer receiving RT; Target Hb 12.5-15 g/dL	2 year local disease free survival	Overall survival	No effect on local tumor control 1 year survival EPO 77.3%, control 79.9% (p=0.867)	Closed to accrual April 2002 due to slow accrual; 5 year follow-up ongoing; Last patient out 2Q07 (Data on file #9, JJPRD; FDA ODAC Briefing Information, May 10, 2007)

**KEY:** Hb, hemoglobin; EPO, epoetin alfa RT, radiation therapy; HR, Hazard Ratio,

<sup>1</sup> Protocol amended in October 2003 to target Hb range of 12-13 g/dL

**Table 6 (continued): Epoetin alfa Pharmacovigilance Program Evaluating Safety in Epoetin alfa Safety in Patients with Chemotherapy-induced Anemia**

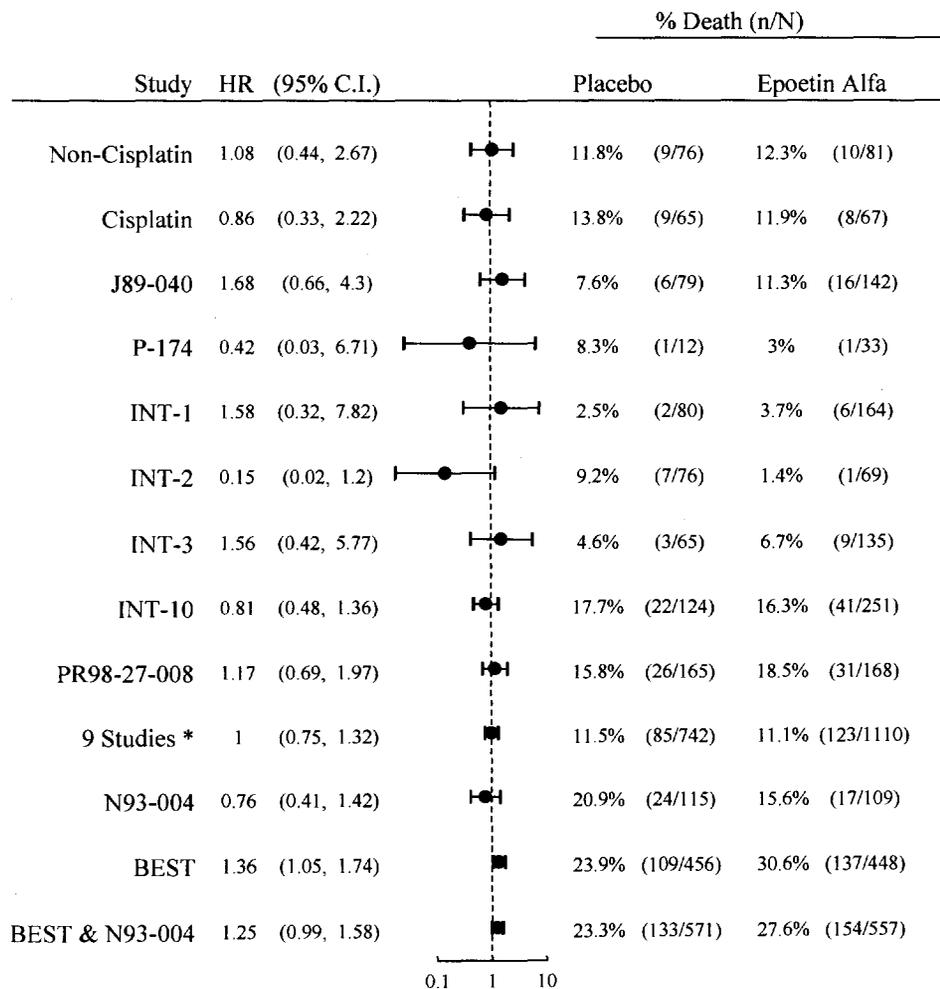
STUDY # (n, accrual/ planned)	Tumor Type	Primary Endpoint	Secondary Endpoint	Safety Results	Status
Moebus	Breast cancer; Target Hb 12.5 -13 g/dl	2 year disease free survival	5 yr DFS, 5 yr Overall survival	5yr disease free survival: EPO 72%, control 71% (p=0.86) overall survival as of Apr. '07: EPO 81%, control 83% (p=0.89)	Closed to accrual October 2002; 5 yr survival data mature 2Q2008; Abstract published (Data on file #7, JJPRD; Moebus 2007)
EPO-ANE- 3010	Breast cancer Target Hb not to exceed 12 g/dl	Progression- free survival	Overall survival	Patient accrual ongoing	Accrual ongoing (JJPRD trial available at <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a> - ID NCT00338286)
EPO-CAN- 17 (354/350)	Breast cancer, treated with chemotherapy Target Hb 12-14 g/dL	Quality of life	2 yr Overall survival	A total of 55 subjects died (27 in the epoetin alfa group and 28 in the SOC group). Kaplan-Meier estimates of the survival curves were similar (log rank test, p=0.82)	Closed to accrual May 2003; Clinical Study Report Submitted to FDA (Chang 2005)
AGO/ NOGGO (264/264)	Cervical cancer, treated with chemotherapy Target Hb 13 g/dL	5 year relapse free survival	Overall survival	Interim analyses Recurrence rate: EPO 11%, control 22% (p=0.04), Median observation time: 64 weeks  The difference in recurrence between the groups at the 105-week observation was less (25% versus 17% for the control and epoetin alfa groups, respectively), but trended toward significance (p=0.074)	Closed to accrual March 2001; Follow-up ongoing, 5 yr relapse free survival data available 3Q'07 (Blohmer 2003)

KEY: Hb, hemoglobin; EPO, epoetin alfa; JJPRD: Johnson & Johnson Pharmaceutical Research & Development, L.L.C; RT, radiation therapy;

(if the hemoglobin was below the target range), or by commencing treatment when the hemoglobin concentration was above 12 g/dL and continuing treatment beyond the usual time frame of 12 to 16 weeks. The safety endpoint analyzed here is on-study mortality, which included all deaths occurring up to 30 days beyond the last dose of study drug.

As demonstrated in the figure below, the mortality hazard ratio from studies in patients evaluating correction of anemia (first nine studies) was 1.00 (95% CI 0.75, 1.32) while those studies investigating beyond the correction of anemia (N93-004 and EPO INT-76 (BEST) was 1.25 (95% CI 0.99, 1.58) (Data on file, JJPRD #8). Such findings support the safety of epoetin alfa use when administered to correct anemia rather than epoetin alfa administration beyond correction of anemia. The subsequent tables describe the studies used for this meta-analysis. (FDA ODAC Briefing Information, May 10, 2007)

Hazard Ratio and 95% Confidence Interval  
(Mortality up to 30 days after double blind phase)



Hazard Ratio and 95% C.I.  
(Log Scale)

\* Without BEST, N93-004 & Non-Chemo Studies

**Table 7: Overview and Design of Completed, Double-Blind, Placebo-Controlled, Multicenter Clinical Studies Used in the Meta-Analysis (FDA ODAC Briefing Information, May 10, 2007)**

No.	Study	Tumor Type	Entry Hb (Hct)/ Upper Hb (Hct) Limit On Study	EPO SC Dose Regimen/ Dose Adjustment	No. of Subjects (DB Phase) <sup>a</sup>		
					EPO	Placebo	Total
<b>Completed, Double-Blind, Placebo-Controlled, Multicenter Clinical Studies of Anemia Correction</b>							
1.	Non-cisplatin CT (I88-037, 87-016, 87-017)	Mixed	Hb: ≤10.5 g/dL/ Hct: 38%-40%	150 U/kg TIW for ≤12 wks/titrated to target	81	76	157
2.	Cisplatin CT (I88-036, 87-018, 87-019)	Mixed	Hb: ≤10.5 g/dL/ Hct: 38%-40%	150 U/kg TIW for ≤12 wks/titrated to target	67	65	132
3.	J89-040	CLL	Hct: <32%/ Hct: 38%-40%	150 U/kg TIW for ≤12 wks/titrated to target	142	79	221
4.	CC2574-P-174	CLL	Hct: <32%/ Hct: 38%-40%	150 U/kg TIW for ≤12 wks/titrated to target	33	12	45
5.	EPO-INT-1 <sup>c,d</sup>	Ovarian	Hb: <11.0 g/dL OR ↓ ≥1.5 g/dL (from BL <14.0 g/dL) OR ↓ ≥2.0 g/dL (from BL ≥14.0 g/dL)/ Hb: 12.5-14 g/dL + ↑<2 g/dL/mo	150 or 300 U/kg TIW for 1 month past last CT cycle/ EPO dose maintained based on reticulocyte count, Hb ↑, and Hb level; if dose held based on above, then restarted at 25% ↓ dose	165 <sup>d</sup>	81	246
16.	EPO-INT-2 <sup>c</sup>	MM	Hb: <11.0 g/dL/ Hb: 12-14 g/dL + ↑<2 g/dL/mo	150-300 U/kg TIW for 12 wks/ EPO dose ↑ if target Hb rise from BL not met; if dose held based on exceeding Hb criterion for dose hold, EPO restarted at 25% ↓ dose	69	76	145

Abbreviations: BL, baseline; DB, double-blind; Hb, hemoglobin; Hct, hematocrit; EPO, epoetin alfa; SC, subcutaneous; CT, chemotherapy; TIW, 3 times weekly; CLL, chronic lymphocytic leukemia; BL, baseline; MM, multiple myeloma; mo, month; QW, once weekly; wks, weeks; ↓, decreases; ↑, increases

<sup>a</sup> Actual number of subjects enrolled.

<sup>b</sup> Under protocol 87-014.

<sup>c</sup> Data available on tumor response and disease progression.

<sup>d</sup> 80 subjects in 300-U/kg group and 85 subjects in 150-U/kg group.

**Table 7: Overview and Design of Completed, Double-Blind, Placebo-Controlled, Multicenter Clinical Studies Used in the Meta-Analysis (Continued)**

No.	Study	Tumor Type	Entry Hb (Hct)/ Upper Hb (Hct) Limit On Study	EPO SC Dose Regimen/ Dose Adjustment	No. of Subjects (DB Phase) <sup>a</sup>		
					EPO	Placebo	Total
<b>Completed, Double-Blind, Placebo-Controlled, Multicenter Clinical Studies of Anemia Correction (Continued)</b>							
7.	EPO-INT-3 <sup>c</sup>	Mixed	Hb: <12.0 g/dL Hb: 14-16 g/dL (men), 12-14 g/dL (women) + ↑<2 g/dL/mo	150-300 U/kg TIW for 12 wks/ EPO dose ↑ if target Hb rise from BL not met; if dose held based on exceeding Hb criterion for dose hold, EPO restarted at 25% ↓ dose	136	65	201
8.	EPO-INT-10 <sup>c</sup>	Mixed	Hb: ≤10.5 g/dL Hb: 12-15 g/dL + ↑<2 g/dL/mo	150-300 U/kg TIW for ≤6 cycles or 24 wks/ EPO dose ↑ based on reticulocyte count and target Hb ↑ not met; dose held based on exceeding Hb criterion for dose hold and restarted at 25% ↓ dose	251	124	375
9.	PR98-27-008 <sup>c</sup>	Mixed	Hb: ≤11.5 g/dL (men), ≤10.5 g/dL (women)/ Hb: 13-15 g/dL	40,000 U QW for 16 wks/ EPO dose ↑ if Hb target rise not met or transfusion; dose held based on exceeding Hb criterion for dose hold and restarted at 25% ↓ dose	174	170	344
<b>Completed, Double-Blind, Placebo-Controlled, Multicenter Clinical Studies Beyond the Correction of Anemia</b>							
10.	N93-004	SCLC	≤14.5 g/dL	150 U/kg SC TIW until 3 wks after completing their initial course of treatment	109	115	224
11.	EPO-INT-76 (BEST) <sup>d</sup>	Breast	No Hb limit specified for inclusion	40,000 U SC QW for 12 months	448	456	904

Abbreviations: BL, baseline; DB, double-blind; Hb, hemoglobin; Hct, hematocrit; EPO, epoetin alfa; SC, subcutaneous; CT, chemotherapy; TIW, 3 times weekly; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; mo, month; QW, once weekly; wks, weeks; ↓, decreases; ↑, increases

<sup>a</sup> Actual number of subjects enrolled.

<sup>b</sup> Under protocol 87-014.

<sup>c</sup> Data available on tumor response and disease progression.

<sup>d</sup> 80 subjects in 300-U/kg group and 85 subjects in 150-U/kg group.

<sup>e</sup> Study drug was discontinued in April 2002.

The above findings are further supported by the independent meta analyses conducted by the Cochrane Group (Bohlius 2006 Cochrane) including all ESAs in which analysis of subgroups of studies found different mortality signals depending on study baseline hemoglobin entry criteria. The hazard ratio for studies with baseline hemoglobin less than 10 g/dL was 1.01 (95% CI: 0.89 to 1.15; 20 studies and 3,765 subjects). For studies with baseline hemoglobin of 10 to 12 g/dL, the hazard ratio was 0.98 (95% CI: 0.82 to 1.16; 8 studies, 1,712 subjects). For studies with baseline hemoglobin greater than 12 g/dL, the hazard ratio for death in the ESA group was 1.27 (95% CI: 1.07 to 2.49, 7 studies, 994 subjects).

Baseline Hb at ESA initiation	Survival odds ratio (95% CI)
Hemoglobin < 10 g/dl	1.01 (0.89, 1.15)
Hemoglobin 10-12 g/dl	0.98 (0.82, 1.16)
Hemoglobin > 12 g/dl	1.27 (1.05, 1.54)

At the 2007 American Society of Clinical Oncology meeting, Gleason et al. (2007) presented meta-analyses of overall survival and risk of venous thromboembolic events in on-label v off-label ESA clinical trials. The overall survival relative risk (ESA:control) for investigator defined on-label studies was 0.97 (95% CI 0.86-1.11) and for off-label studies (eg. anemia of cancer, clinical trials with target hemoglobin levels of 14-16 g/dL) 1.14 (1.02, 1.27). Similar analyses focused on venous thromboembolic events reported a relative risk of 1.38 (0.96, 1.98) for on-label clinical trials and 1.65 (1.28, 2.13) for off-label clinical trials. (Gleason 2007). In an interview with the senior investigator, Dr. Charles Bennett stated,

*"What we do have is what people said all along: When the drug is used on label, there are no hidden safety signals," (Goldberg 2007a)*

## 5. Response to Proposed Decision Memo Regarding Terminated Epoetin Alfa Trials

The CMS Proposed Decision Memo included a table of terminated trials (Table 4). Below is a detailed table describing all the Johnson and Johnson trials involving EPO that were referenced in Table 4. Reasons for trial discontinuation are listed for each study. Trials were terminated either for slow accrual or after safety signals were seen during interim analyses. It is important to note that the FDA has been informed of all terminated trials. Virtually all of the trials listed in Table 4 of the CMS Proposed Decision Memo were actually presented at either the 2004 or 2007 ODAC meeting. Eleven were also included in a recent meta-analysis published by the Cochrane study group (Bohlius 2006 JNCI). One trial was a Phase IV commitment trial (Grote 2005). Seven of the nine trials involving EPO were investigational where the hemoglobin target was beyond what is currently recommended in the prescribing information. Most trials were developed to investigate patient outcomes with higher target hemoglobin levels following clinical findings suggesting a trend toward better outcomes in epoetin alfa-treated patients (Littlewood 2001)

### 5.1 Reasons for Termination of Trials that Investigated Use of EPO Beyond the Label

STUDY #	Tumor Type	Primary Objective	Hemoglobin (g/dL)	Reason for Termination	Investigational Off-label Use?	Publication Status
N93-004	Limited or extensive-stage SCLC	To determine the effect of EPO compared to placebo on tumor response in SCLC patients receiving etoposide and cisplatin	Mean baseline Hb: EPO 12.8 g/dL Placebo: 13.0 g/dl Goal: maintain baseline Hb	Slow accrual associated with changes in standard of care for SCLC (agreed to by FDA, 06/17/01)	Phase 4 commitment	Grote T, et al. J Clin Oncol 2005; 23:9377-86.
INT-76 (Leyland-Jones et al)	Metastatic Breast Cancer (MBC)	To evaluate the effect of maintaining Hb in the range of 12-14 g/dL with Epo on 12-month survival	Goal: maintain Hb btw 12 and 14 g/dL	Unexpected increase in mortality in the Epo-treated group	Yes	Leyland-Jones B et al. J Clin Oncol 2005;23: 5960-5972.
Investigator Sponsored Study	Metastatic Breast Cancer	To measure the impact of Epo on QoL in MBC patients with mild anemia	Mean baseline Hb: NR Entry criteria: Hb < 12.0 g/dl	Increased incidence of thrombotic events in the Epo-treated pts	No	Rosenzweig MQ et al. J Pain Symptom Manage 2004; 27:185-190.
RTOG 99-03	Head & Neck Cancer	To determine if concurrent EPO administration with radiotherapy (± concurrent chemotherapy) could improve LR control in non-operative SCCHN	Target Hb: Males: 16 g/dL Females: 14 g/dL	Unplanned interim analysis after Henke trial revealed NS trend toward poorer outcome with Epo. IDMC concluded futility for demonstrating 1 <sup>o</sup> objective.	Yes	Machtay M, et al. Int J Rad Oncol Biol Phys 2004; 60: S132 (Abs) Manuscript in press.
EPO-GBR-7	Head & Neck Cancer	To evaluate the effect of Epo on local DFS and OS when Hb levels are maintained at 12.5-15 g/dL	Initiation Hb: ≤ 15 g/dL Target Hb: 12.5 g/dL – 15 g/dL	Slow accrual	Yes	Last pt out for 5-year survival (specified endpoint) 2Q'07; Manuscript in preparation. (Data on file, JJPRD #9; FDA ODAC Briefing Information, May 10, 2007)
PR00-03-006	Gastric or Rectal Cancer	To determine if EPO treatment can maintain Hb (≥ 13 g/dL), reduce need for PRBC Tx and improve treatment outcome	Baseline Hb: 13 g/dL	DSMB decision based on imbalance in DVT rate in Epo group	Yes	Vadhan-Raj S, et al. Blood 2004;104: Abs 2915.
PR01-04-005/GOG-191	Cervical Cancer	To determine if Epo treatment to maintain Hb levels ≥ 13 g/dL could prolong PFS	Entry criteria: Hb < 14 g/dl	Interim DMC review of safety showed a higher than expected TVE rate in the Epo group. Due to this	Yes	Clinical study synopsis (25 March 2004) provided to FDA. Study results

STUDY #	Tumor Type	Primary Objective	Hemoglobin (g/dL)	Reason for Termination	Investigational Off-label Use?	Publication Status
				safety concern and accrual, GOG elected to close the study.		have not been published. (Data on file, JJPRD #10; FDA ODAC Briefing Information, May 10, 2007)
EPO-CAN-15	Limited-stage SCLC	To determine if Epo treatment to maintain Hb levels between 14-16 g/dL can enhance chemotherapy effectiveness	Mean baseline Hb: 13.5 g/dl (both groups) Hb Target: 14 –16 g/dl	Higher incidence of TVEs in Epo group	Yes	Goss G, et al. <i>Lung Cancer</i> 2005;49(Suppl 2):S53. (Abst O-154)
EPO-CAN-20	NSCLC (anemia of cancer; not candidates for further chemo)	To determine if Epo treatment to maintain Hb levels between 12-14 g/dL can improve QoL	Hb initiation: 12 g/dL Hb target: 14 g/dL	DSMB review of unplanned safety analysis revealed increased mortality in Epo treated pts	Yes	Wright J et al. <i>J Clin Oncol</i> 2007; 25:1027-1032.

KEY: SCLC, Small Cell Lung Cancer; Hb, hemoglobin; QoL, Quality of Life; LR, loco-regional control; SCCHN, Squamous Cell Carcinoma of the Head and Neck; DFS, Disease Free Survival, OS, Overall Survival; PRBC, Packed Red Blood Cells; Tx, Transfusions; DVT, Deep Venous Thrombosis; IDMC, Independent Data Monitoring Committee; DMC, Data Monitoring Committee; TVE, Thrombotic Vascular Event; GOG, Gynecologic Oncology Group; DSMB, Data Safety Monitoring Board

## **6. Transfusion/Blood Supply Risks With Decreased ESA Use**

### **6.1 Increased blood transfusions associated with decreased ESA use have critical patient-related and U.S. blood supply implications**

Anemia is a common complication of myelosuppressive chemotherapy, with the frequency of occurrence depending on the underlying malignancy and the regimen and intensity of chemotherapy utilized. (Groopman 1999, Mecandante 2000) Anemia is highly associated with fatigue and diminished patient-reported health status in patients with cancer who are receiving chemotherapy. (Cella 1997, Cella 1998) The impact of fatigue on the lives of patients with cancer is significant, with the vast majority reporting that it prevented them from leading a "normal" life, required alterations in their daily routine, (Curt 2000) and was more significant than cancer-related pain. (Vogelzang 1997) Cancer-associated fatigue also has economic repercussions for both employed patients with cancer, who miss an average of 4.2 workdays per month, and their caregivers, who take time off from work to assist them. (Curt 2000) The causes of fatigue are multifactorial and the relationship between hemoglobin concentration and intensity of fatigue is not well understood. However, since patient-reported levels of fatigue in patients who had cancer has been shown to correlate directly with the degree of anemia, (Yellen 1997, Patrick 2003, Witzig 2005) anemia is often treated with red blood cell transfusions or ESAs such as epoetin alfa for palliation of symptoms as per guidelines established by the National Comprehensive Cancer Network (NCCN). (NCCN anemia treatment guidelines v.3.2007)

Blood transfusion patterns in the chemotherapy-treated cancer population are unique from transfusion patterns in other settings (eg. critical care) because of the ambulatory status of this population and the ongoing myelosuppression induced with continued chemotherapy. Translating transfusion Hb triggers used in non-mobile ICU patients to ambulatory cancer patients is problematic. Additionally, transfusion needs may vary based on patient age, co-morbid conditions, underlying malignancy, and chronicity of chemotherapy regimen selected. Barrett-Lee et al. (2000) reported that if the Hb was <10 g/dL prior to chemotherapy initiation, the probability of at least one transfusion at some point during the chemotherapy course was about 70%. Overall, 38% of patients who developed Hb <11 g/dl at some stage during six cycles of chemotherapy and 33% required transfusion (n=902) with 16% of patients requiring multiple transfusion episodes. The mean red blood cell (RBC) utilization was 2.7 units/transfusion. Coffier et al. (2001) reported 14% of patients being transfused with mean transfusion need of 3.83 Units/3 month period in patients receiving non-platinum-based chemotherapy. Estrin et al. (1999) reported a transfusion frequency of 31% of patients and average RBC utilization of 5.1 Units per transfusion event (median of three units per transfusion event).

Transfusions carry quantifiable risks such as infection and hemolytic reactions. In addition, patient attitudes toward blood transfusion are quite negative and most would prefer to avoid them if possible

(Demetri 2001). While some transfusion-associated risks have been quantified, a report prepared jointly by the American Association of Blood Banks (AABB), America's Blood Centers (ABC) and the American Red Cross (ARC), and recognized as acceptable by the Food and Drug Administration, described the uncertainty of blood transfusion in the opening statements, as follows:

*"...WARNING: Because whole blood and blood components are made from human blood, they may carry a risk of transmitting infectious agents, eg, viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent and variant Creutzfeldt-Jakob disease (vCJD) agent. Careful donor selection and available laboratory tests do not eliminate the hazard. Also, septic and toxic reactions can result from transfusion of bacterially contaminated blood and components. Such reactions are infrequent, but may be life-threatening. In addition, blood components may contain certain immunizing substances other than those indicated on the label..." (AABB/ABC/ARC Circular 2002)*

Furthermore, the document identifies contraindication to whole blood and other RBC components as:

*"...Red-cell-containing components should not be used to treat anemias that can be corrected with specific medications such as iron, vitamin B12, folic acid, or erythropoietin..." (AABB/ABC/ARC Circular 2002)*

The complications of RBC transfusions to patients with cancer have been outlined and include risk of infection, allergic or febrile reactions, as well as transfusion-associated immunosuppression (Demetri 2001). A wide range of infectious diseases may be transmitted through allogeneic blood transfusion, although the risk has been dramatically reduced due to enhanced screening (Goodnough 2003). Risks for infection with HIV, hepatitis C, and hepatitis A are all in the range of 1 in 1 to 2 million (Dodd 2003). The risk of infection with hepatitis B is slightly higher at 1 in 30,000 to 250,000 (Goodnough 1999). Infections with human T-lymphotropic virus (HTLV) I and II, and parvovirus B19 are in a similar range (Schreiber 1996, Dodd 1994). Potential for infection with new and emerging pathogens such as West Nile virus, severe acute respiratory syndrome, monkeypox, Trypanosoma cruzi, Plasmodium, Babesia, dengue virus, and variant Creutzfeldt-Jacob disease remains a concern (Alter 2007, Pealer 2003). Bacterial contamination of RBCs occurs in 1 in 500,000 transfusions (Sazama 1990) and is often due to *Yersinia enterocolitica* (Halpin 1997 MMWR).

Hemolytic transfusion reactions are rare but potentially serious. Acute hemolytic reactions are characterized by fever, chills, back pain, or shock. Delayed hemolytic reactions usually occur 2-14 days after transfusion with unexplained fever and decrease in hemoglobin. (AABB/ABC/ARC Circular 2002) Approximately 1 in 1,000 patients has clinical manifestations of delayed reaction to transfusions; however, fatal acute hemolytic reactions occur in only 1 in 250,000 to 1 in 1 million transfusions, and are usually due to clerical error (Linden 1992, Linden 2000, Forgie 1998).

Transfusion-related acute lung injury (TRALI) is similar to acute respiratory distress syndrome in presentation and is the leading cause of transfusion-related mortality worldwide. TRALI occurs with an estimated frequency of 1 in 5,000 RBC transfusions, though the true incidence is probably higher

(Silliman 2005, Toy 2005, Boshkov 2005). Symptoms associated with TRALI can be sudden and fulminant, and most commonly occur between 1-2 hours after the onset of transfusion, but may develop within 30 minutes of transfusion. Almost all reactions occur within 6 hours from the start of a transfusion. Treatment may involve fluid administration or mechanical ventilation (Looney 2004).

Other non-infectious complications of allogeneic blood transfusion include the following: (AABB/ABC/ARC Circular 2002, Perotta 2001)

- febrile non-hemolytic reactions, characterized by fever following blood transfusion, which may occur in 1% of transfusion episodes
- allergic reactions, usually occurring as urticaria, however may include wheezing or edematous reactions
- anaphylactic reactions, characterized by severe shortness of breath, pulmonary edema, bronchospasm.
- post-transfusion purpura, characterized by dramatic decrease in platelet counts, typically 7-10 days after blood transfusion
- circulatory overload leading to pulmonary edema with the elderly and those with chronic anemia particularly at risk for this complication
- iron overload, a complication of repeated red blood cell transfusion with end-organ damage to the heart, liver, and pancreas. Patients with chronic transfusions may be considered for iron chelating agents.
- metabolic disturbances (eg. citrate toxicity with depression of ionized calcium)
- transfusion-associated graft-versus-host disease with immunocompromised patients such as those with prior bone marrow transplant at risk

Despite recent advances to ensure the safety of transfused blood products, patients continue to express concern about the risk of transfusion-related infections, dominated by ongoing fear of contracting HIV (Lee 2006). In one survey, a third of participants expressed this concern (Moxey 2005). Utilizing risk perception research to compare patient perceptions about blood transfusions relative to other hazards, it was found that blood transfusions elicit intermediate ratings of dread and severity comparable to nuclear reactors and pesticides (Lee 2006). Another discrete choice experiment identified several significant predictors of choice for various anemia treatments, including greater level of relief of fatigue, lower risk for infection or allergic reaction, and preference for treatment at the doctor's office versus the hospital (Ossa 2007). All of these predictors indicate a likely patient preference for treatment with an ESA over blood transfusion.

Patients who are already myelosuppressed from chemotherapy and are feeling poorly are particularly risk-adverse to possible allergic and febrile reactions to blood transfusion. A report by the American Red Cross/American Association of Blood Bank stated:

*"... Febrile reactions may accompany about 1% of transfusions; and they occur more frequently in patients previously alloimmunized by transfusion...."( AABB/ABC/ARC Circular 2002)*

Such complications can present management difficulties in cancer patients receiving chemotherapy as differentiation of life-threatening febrile neutropenia and febrile blood transfusion reactions can be difficult. Such complications may be associated with greater diagnostic and therapeutic interventions, including hospitalization.

The nation's blood supply is a limited resource. In 2004, the marginal blood supply was only 6.1% (allogeneic collection: 14.8 million units; transfusion: 13.9 million units) (Whitaker 2005). This situation is further exacerbated by procedures used for qualifying fully screened units. In 2004, 240,000 units were rejected after screening, leaving a margin of only 648,000 units (4.5% of the available supply) (Whitaker 2005). This limited surplus in the blood supply has led to periodic shortages. Based on the 2005 Nationwide Blood Collection and Utilization Survey Report, 8.5% of surveyed hospitals reported postponement of elective surgeries on 1 or more days in 2004 because of blood inventory shortages (mean 3.39 days a year; range: 1 to 39 days a year) (AABB 2004). Sixteen percent of hospitals reported inability to meet their nonsurgical blood needs on at least 1 day (Whitaker 2005). Although demand is fairly constant, the blood supply is actually highly variable throughout the year. This has led to transient shortages during periods typically associated with low donation, e.g., holidays (AABB 2003).

Ortho Biotech performed a modeling simulation to estimate the impact that limiting the use of ESAs in chemotherapy-induced anemia would have on the U.S. blood supply. The excess number of units that would be required if treated patients were not treated with ESAs was contrasted with the available marginal supply using 2004 data (the most recently available). Model inputs were drawn from the published literature or expert opinion where evidence was lacking. Estimates were developed for a range of scenarios and incorporated into appropriate sensitivity analyses.

The model predicts that up to a third of the marginal U.S. blood supply would be required to cover the incremental demand for blood that would arise from a 25% decrease in the use of ESAs. Nearly two-thirds of the marginal blood supply could be compromised with a 50% reduction of ESA use in patients with chemotherapy-induced anemia. Recent Wall Street Analysts report that the CMS Proposed Decision Memo on ESAs as written may decrease ESA sales from 25% to 70% (Porges 2007, Werber 2007, Ende 2007, Hopkins 2007). Such changes in ESA utilization are associated an incremental demand of 118,000-237,000 units of blood. (Data on file, Ortho Biotech #1, Excel model attached) This added pressure on the blood supply could be even larger due to regional variation in the number of available

units and the variable frequency of donation. The American Red Cross has reviewed the model and welcomes CMS to inquire with them regarding the model and the blood supply impact. (Richard Benjamin, MD, Chief Medical Officer American Red Cross, personal communication, 6/4/2007 [benjaminr@usa.redcross.org]).

## **7. Ortho Biotech Response to CMS Proposed Decision Memo on ESAs**

### **7.1 CMS Proposed Non-Coverage of Conditions**

- The CMS proposed decision memo lists certain conditions for which ESAs are not reasonable and necessary. We do not object in principle to a determination that ESAs are not reasonable and necessary for the following nine conditions:
  - any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis
  - the anemia of myeloid cancers
  - the anemia associated with the treatment of myeloid cancers or erythroid cancers
  - the anemia of cancer not related to cancer treatment
  - any anemia associated with *primary* radiotherapy
  - prophylactic use to prevent chemotherapy-induced anemia
  - prophylactic use to reduce tumor hypoxia
  - patients with erythropoietin-type resistance due to neutralizing antibodies
  - anemia due to cancer treatment if patients have uncontrolled hypertension

However, the final determination should clarify that “myeloid cancers” refers to acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) but not to myelodysplasia or multiple myeloma. Additionally, coverage for the use of ESAs in several of these conditions may be reasonable and necessary when such use is part of an evidence development program.

While Ortho Biotech can agree with some of what CMS has proposed based on our review of the available evidence, we do not believe the evidence supports many of the restrictions that have been proposed.

We disagree with the CMS interpretation of the evidence that ESAs are not reasonable and necessary and support the ESA coverage for the following conditions:

- Anemia of MDS
- Patients with treatment regimens including anti-angiogenic drugs such as bevacizumab (Avastin®)

- Patients with treatment regimens including monoclonal/polyclonal antibodies directed against the epidermal growth factor (EGF) receptor e.g., trastuzumab (Herceptin®), cetuximab (Erbix®) and panitumumab (Vectibux™)
- Patients with thrombotic episodes related to malignancy

## **7.2 CMS Proposed Decision Memo: Non-coverage for patients with myelodysplasia (MDS)**

**OBI position: Epoetin alfa should be covered for MDS based on clinical trial results, Compendia listings, and the recommendations by MDS/anemia treatment guidelines and American Society of Hematology. Additionally, CMS has incorporated ESA use in MDS patients as a physician quality measure under the Physician Voluntary Reporting Program (PVRP).**

Myelodysplastic syndromes (MDS) are a group of bone marrow stem cell diseases characterized by progressive bone marrow failure. The diseases are largely incurable with the exception of a bone marrow transplant. Up to 85% of MDS patients develop anemia during the course of their disease and most ultimately require red blood cell transfusions (Hellstrom-Lindberg 1997). Epoetin alfa (EPO) does not have a label indication for the treatment of anemia with myelodysplastic syndromes (MDS); however, the AHFS compendium describes the use of epoetin alfa in MDS patients (McEvoy 2007). Since 1998, the USP DI/DrugPoints compendium has reviewed evidence in the peer-reviewed literature, and in addition to the FDA-approved indications, DrugPoints currently lists PROCRT as beneficial for use in anemia related to MDS (USP DI has denoted as acceptance of use not established). The NCCN, MDS treatment guidelines and ASH/ASCO anemia treatment guidelines also include the use of EPO in MDS patients (NCCN MDS guidelines v.1.2007, Rizzo 2002). In the April 12, 2007 letter to CMS regarding ESAs, the American Society of Hematology endorsed the coverage of ESA for patients with myelodysplasia (Silver 2007).

There are two randomized, double-blind, placebo-controlled clinical trials evaluating the role of EPO monotherapy in MDS. (Stein 1991, Ferrini 1998) In the larger study, patients were randomized to receive 150 U/kg/day (N=37) or placebo (n=38) for 8 weeks. Overall response rates were 36.8% for the EPO arm vs 10.8% on the placebo arm ( $p=0.007$ ). (Ferrini 1998) Several open-label studies have evaluated the role of EPO in MDS. (Aloe Spiriti 2005, Stasi 2004, Terpos 2002, Wallvik 2002, Stasi 1997, Rose 1995) The newer, more recently conducted open label studies have shown that not only was EPO more effective in treating the anemia of MDS, the incidence of pRBC transfusions was found to be lower following EPO treatment in these patients. (Aloe Spiriti 2005, Terpos 2002) Moyo et al. (2006) reported a meta-analysis of 20 studies and 890 patients, in which the cumulative erythroid response rate was 42% overall and 58% for the more recent studies that used the International Working Group Criteria (IWG) for response assessment, compared to 28% ( $p=0.02$ ) for the older group of studies that used the alternative

(non-IWG) research criteria. This meta-analysis confirms that response rates have improved over time as a result of better classification systems and the adoption of uniform response assessment criteria (Moyo 2006).

Most ( $\geq 70\%$ ) MDS patients within lower risk categories do not die from leukemia transformation. Instead they die from non-leukemic causes of death, which include cardiac conditions (50%), infections (30%), liver failure (8%) and bleeding events (8%). With the exception of bleeding, these non-leukemic causes of morbidity and mortality have been associated with iron overload following chronic transfusion in thalassemia and other disease states. (Ladis 2005, Gordeuk 1994) The development of transfusion dependence and iron overload in MDS has been associated with decreased survival. (Malcovati 2006, Malcovati 2005)

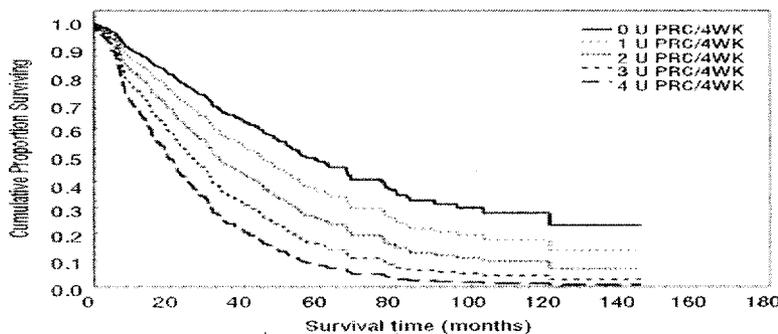


Figure 1. Survival of MDS patients according to the intensity of their red cell transfusion requirement, calculated as the number of packed red cell (PRC) units per month (U/4WK) (data obtained from 426 patients diagnosed with MDS according to WHO criteria at the IRCCS Policlinico San Matteo, Pavia, Italy, between 1992 and 2004. The between-group comparison was performed by applying a Cox proportional hazard regression model with time-dependent covariates).

Figure 5: Malcovati et al Haematologica 2006; 91; 12 (Permission pending)

Bone marrow transplant is the only curative option for MDS but even in this setting the presence of high iron stores related to pre-transplant RBC transfusions may be associated with increased transplant related mortality and lower overall survival. (Armand 2007)

Although epoetin alfa reduces transfusions in low risk MDS patients, there are no prospective data showing improved survival with treatment. There are several retrospective studies suggesting that the use of growth factors including epoetin alfa may be associated with improved survival in low risk MDS patients, compared to historical controls (Golshayan 2007, Park 2006, Jadersten 2006, Musto 2006).

Because the natural history of MDS has been associated with a proportion of patients transforming to acute leukemia, there is concern that the use of an erythropoietic agent would protect malignant cells and enhance the development of leukemia. In MDS, there have been no clinical studies to date that have been associated with increased leukemia transformation rates following the use of EPO. Data from randomized studies have not shown an increase in AML transformation rates in EPO treated patients

(Stein 1991, Thompson 2000, Nair 2006, Casadevall 2004, Miller 2004). In the Eastern Cooperative Oncology Group (ECOG) randomized clinical trial, in which 109 patients were randomized to receive EPO +/- G-CSF or transfusion support there was no difference in leukemia rates between the treatment arms after 1 year of hematopoietic growth factor support (Miller 2004)

Measure 68 of the physician quality research initiative (PQRI) will be used by CMS to reward physicians for the quality of care they provide. (Measure 68, 2007) This measure includes the provision for documenting iron stores prior to *initiating EPO therapy in pts 18 years or older with MDS*.

***“Myelodysplastic Syndrome(MDS): Documentation of Iron Stores in Patients Receiving Erythropoietin Therapy***

*Percentage of patients aged 18 years and older with a diagnosis of MDS who are receiving erythropoietin therapy with documentation of iron stores prior to initiating erythropoietin therapy”*

If this has been established as a quality measure for ESA treatment of MDS by CMS, then by inference ESA use for MDS must be reasonable and necessary.

Additionally, during the May 10, 2007 FDA ODAC Dr Richard Pazdur, Director of the FDA's Office of Oncology Drug Products commented on the differentiation of chemotherapy-induced anemia and anemia of myelodysplasia.

*“I think those are two opposite different things, and unfortunately, I do not want them (MDS patients) to get swept away with this, and we will discuss with our colleagues in CMS to make sure that does not occur.”*

**7.3 CMS proposed decision memo: Non-coverage for patients with treatment regimens including anti-angiogenic drugs and antibodies against EGF receptor**

**OBI Position: The scientific evidence is insufficient to support a NCD. Coverage of ESA with treatment regimens including anti-angiogenic drugs and antibodies against EGF receptor should be allowed.**

**Rationale:**

The theoretical concern that EPO will promote angiogenesis in humans is based on preclinical studies. There is no scientific data in humans to support this coverage decision. An extensive literature search failed to reveal clinical studies that suggested an adverse safety signal of ESA and anti-angiogenic drugs or antibodies against the EGF receptor. One clinical trial that investigated concurrent use of chemotherapy, epoetin alfa and an antibody to the EGR receptor did not report adverse safety outcomes associated with the combination (Hurley 2006).

In all bevacizumab trials (current and completed) ESA use has never been contraindicated or discouraged. There is no data demonstrating that combining ESAs with bevacizumab containing

chemotherapy regimens results in increase in any toxicities or decreased of survival. A large observational registry of Avastin (BRIGHT) does not contain any information about potential risk of adverse events in patients receiving ESAs. This was not specifically collected or analyzed for ESA use vs no use, but there is no signal, which would trigger such analysis (e.g. unexpected higher number of deep vein thromboses or pulmonary emboli). (Genentech Medical Information, oral communication, 5/23/07).

Concurrent ESA administration is neither contraindicated nor discussed in the Warnings section of the bevacizumab (Avastin) package insert. Recent published drug reviews of panitumomab (Vectibix) and bevacizumab (Avastin) by authors from the FDA have not reported safety warnings regarding concurrent use with ESAs (Giusti 2007, Cohen 2007).

#### **7.4 CMS proposed decision memo: Noncoverage for patient's thrombotic episodes related to malignancy**

**OBI Position: Based on lack of contraindication or warnings in ESA labeling information, and no demonstration that TVE risk is increased with EPO treatment, above and beyond the increased risk noted in patients with a prior history of TVEs, the decision to use ESAs in this setting should be left to treating physician after careful assessment of the benefits and risks.**

##### **Rationale:**

Thrombotic vascular events are a recognized risk in patients with cancer, and that risk increases with use of ESAs (Otten 2004, Khorana 2005). Certain anti-cancer therapies can also increase TVE risk (Bohlius 2006 JNCI). Johnson and Johnson Pharmaceutical Research and Development (J&JPRD) has previously performed an analysis of TVEs in 10 double-blind, randomized, placebo-controlled studies of epoetin alfa that focused on treatment of anemic cancer patients receiving chemotherapy, excluding Study N93-004 [Grote 2005] and the BEST [Leyland-Jones 2005] study, as these studies included treatment of non-anemic subjects. All studies were part of regulatory submissions made by J&JPRD. In brief, the odds ratios for TVEs were variable in these 10 studies. The combined analysis of all 10 studies yielded an odds ratio of 1.55 (95% CI: 0.96 to 2.50) suggesting a higher incidence of TVEs with epoetin alfa treatment (FDA ODAC Briefing Information, May 2004). This increased risk is recognized in the product labeling worldwide.

An independent, systematic review of 30 randomized, controlled studies evaluating 6,092 subjects with cancer, assessed the relative risk of TVEs between subjects receiving epoetin alfa therapy and placebo/no therapy (Seidenfeld 2006). The studies included in the analysis investigated a variety of cancer types and concomitant anti-cancer therapies (including no anti-cancer therapy) and a variety of entry and target hemoglobin levels. The overall risk of thrombo-embolic complications was increased by 69% in Epo treated subjects (relative risk = 1.69 [95% CI: 1.36 to 2.10]). Subgroup analyses of TVE

relative risk by studies conducted according to “labeled” criteria with respect to dose and maximum Hb stopping value as compared to those studies evaluating epoetin alfa treatment beyond correction of anemia were performed. Treatment to target a hemoglobin of greater than 12 g/dL (studies beyond correction of anemia) leads to greater TVE risk and is strongly warned against in prescribing information. Although cancer patients with a prior history of TVEs are more likely to have subsequent TVEs, it is unclear if concomitant erythropoietin therapy contributes to that risk. In a study by O’Connell et al. (2006), the clinical correlates of cancer patients with unsuspected pulmonary emboli diagnosed by computed tomography were compared to matched controls. Although prior history of TVE, fatigue, and dyspnea were more common in patients with unsuspected pulmonary emboli than in controls, there was no difference in erythropoietin use between the two groups (O’Connell 2006).

In the current National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for treatment of TVEs, it is recommended that patients with advanced cancer experiencing a TVE be maintained on anticoagulation therapy for at least six months and indefinitely for patients with persistent risk factors or active cancer (NCCN venous thromboembolism guidelines v.2.2006). Thus, most patients with a recent cancer-associated TVE history will already be on anticoagulation therapy and in this setting there is no evidence that concomitant erythropoietin treatment of chemotherapy-induced anemia as per the labeled guidelines will further increase the TVE risk. Moreover, the alternative to ESAs for treatment of chemotherapy-induced anemia, namely blood transfusions, in patients with thrombotic episodes related to malignancy may result in worse outcomes in this setting. Accordingly we believe there is insufficient evidence to conclude that ESA coverage for patients with thrombotic episodes related to malignancy is not reasonable and necessary. The decision to use ESAs in patients with thrombotic episodes related to malignancy should be left to the treating physician after a careful assessment of the product’s risk/benefit profile as per the labeled guidelines.

## **7.5 Erythropoietin Receptor**

**CMS has proposed limitations based on the erythropoietin receptor (EPO-R) to guide policy decisions; however, the erythropoietin receptor lacks predictive use for use in cancer patients, which is confirmed by FDA reviewers and Oncology Drug Advisory Committee Chair.**

The draft CMS NCD suggests that ESAs should be limited for specific tumor types that express the EPO-R. This proposal may be partially due to recent ESA clinical trials in breast and head and neck cancer where an imbalance between treated and placebo arms were observed. Although this proposal warrants further study, no data to date exists to discriminate/segregate specific tumor types unequivocally for exclusion.

The EPO-R discovery and characterization was concomitant with the launch of the first ESA (Winkelman 1990). At that time, the EPO-R was thought to be a receptor restricted to erythropoietic precursors.

Subsequently, the EPO-R has been reported on numerous cell types of non-hematopoietic origin including endothelial and brain cells (Farrell and Lee, 2004). Moreover, its expression has been reported on numerous tumor types/cells including bladder, breast, female reproductive tissue, gastrointestinal tract, head and neck, kidney, liver, lung, melanoma, pancreatic, prostate, nervous system and thyroid (Hardee 2006). The methodologies to ascertain expression are equally broad including reverse transcriptase-polymerase chain reaction (RT-PCR), northern and western blotting and immunohistochemistry. In summary, EPO-R expression is not limited to hematopoiesis as assessed by numerous methodologies. On the other hand, although recent literature has purported a role of the EPO-R in tumor progression, rigorous biochemical analysis of the receptor on tumors is lacking due to non-specific EPO-R antibodies, inability to generate an EPO binding affinity due to low or absent cell surface expression and weak to absent cell signaling.

Erythropoiesis is driven by ESAs binding to the EPO-R leading to the promotion and maturation of red blood cell precursors (D'Andrea 1998). Biochemical analysis utilizing *in vitro* and *in vivo* systems has shown that ESAs bind to erythroid precursors with an affinity of  $\approx 200$  pM and exert a biological response at extremely low levels, 12 pM ( $EC_{50}$ ), the level at which 50% of maximal stimulation is observed. When similar analyses were performed on tumor cells, no detectable binding could be ascertained (LaMontagne 2006). Furthermore, no increase in proliferation was observed. When reviewing the conflicting data reporting an effect of ESA on tumors, an amount of ESA far exceeding that necessary to drive erythropoiesis or that utilized clinically showed minimal effect on signaling. In summary, no reports describing an  $EC_{50}$  for an ESA on tumor proliferation have been reported.

As stated above the ability of ESAs to stimulate cell proliferation has been assessed by numerous groups. Numerous investigations have reported that ESAs do not stimulate cell proliferation (Berdel 1991; Westphal 2002; Rosti 1993; Hardee 2005). This result has been confirmed by our internal studies. On the other hand, others have reported that ESAs stimulate cell proliferation (Westenfelder 2000; Acs 2001; Yasuda 2003, Lai 2005). A potential explanation of these two opposing conclusions is that the data to support that ESAs stimulate tumor cell proliferation are based on a minimal proliferative response at supra-pharmacological concentrations (i.e., greater than 10 Units/mL). Secondly, the proliferative response was not concentration-dependent. This is in contrast to hematopoietic cells, which reach maximal proliferative response at approximately 0.06 Units/mL. Full agonist activities are observed at 0.12 U/mL (1ng/mL) *in vitro*. The progression of a cell to a malignant phenotype is associated with dysregulated changes in gene expression and growth factor independent of cell growth. For this reason, it is possible for ESAs to have no effect on proliferation even though the EPO-R is up regulated as the cell progresses to a malignant state. An intact and competent signal transduction pathway is necessary to confer ESA responsiveness upon binding to its receptor. In summary, the presence of the EPO-R on a cell does not confer ESA responsiveness on all cell types.

In the manuscript by Acs (2001), the authors propose that EPO may be detrimental to cancer due to increased expression of the EPO-R on human breast tissue. Various experiments were performed to demonstrate expression by immunohistochemical analysis and western blotting. Moreover, this result was confirmed by use of breast cancer cells lines. Although this is a plausible hypothesis, the authors do not provide unequivocal data to support their hypothesis. For example, the authors demonstrate the presence of EPO-R on human breast cancer cells by western blot analysis; however, the antibody C20, directed against the carboxyl terminal domain is used, negating the ability to assess cell surface expression. Moreover, this antibody has been shown to lack specificity for the EPO-R, (Elliott 2006). Furthermore, there are examples in the literature of hematopoietic and non-hematopoietic malignant cell lines that possess EPO-R but do not proliferate in response to EPO, (Rosti 1993). In hematopoietic cells, a large percentage of the EPO-R synthesized is sequestered to the endoplasmic reticulum and thus never reaches the cell surface to bind EPO and commence a signal transduction pathway.

The authors state that EPO or an EPO mimetic peptide can elicit tyrosine phosphorylation, a hallmark of EPO signaling, however, the data does not support that EPO elicits a signaling cascade through the JAK/STAT pathway. For example, the EPO-R receptor is rapidly phosphorylated on cytoplasmic tyrosine residues. As shown, a reactive band corresponding to the EPO-R is not tyrosine phosphorylated. Secondly, no reactive band is observed at 95 kDa indicative of STAT phosphorylation. A second point is a concentration of 250 Units/mL is used to demonstrate tyrosine phosphorylation. This concentration is 100 fold higher than would be seen in human serum where concentrations of 2-4 IU/mL are observed after EPO administration (Cheung 1998). Also, UT-7 cells, a hematopoietic cell line possessing endogenous EPO-R, demonstrate robust tyrosine phosphorylation after EPO administration at concentrations below 10 Units/mL. Lastly, the authors show a cellular proliferation stimulation of 125 % of control (no stimulation). This amount of stimulation is within the noise of a cell proliferation assay and would suggest no effect. For reference, UT-7 cells demonstrate 300-500% of control at low EPO (ng/mL) concentrations. In summary, this article does not adequately demonstrate the existence of EPO-R on human breast cancer tissue or that the cell lines have an effect.

A follow-up manuscript from Acs (2002), describes the immunohistochemical expression of EPO and EPO-R in breast carcinoma. The authors propose that EPO-R may play a role in breast carcinogenesis. The authors state that the induction of autocrine and paracrine EPO signaling may represent a novel mechanism by which hypoxia can promote breast carcinoma. A few points should be stated to address this paper. Firstly, EPO-R is expressed in benign mammary epithelial cells with an increase in invasive mammary carcinoma. This result is not surprising since breast cancer tumors are in general very hypoxic and given that EPO and EPO-R are upregulated under hypoxic conditions, this phenomena is a normal physiological process. Secondly, the authors did not find a correlation between EPO-R immunostaining

and tumor size, tumor grade, presence of necrosis, lymphovascular invasion, lymph node status hormone receptor status, or HER2/neu overexpression. No control cytokine and/or cytokine receptor was evaluated in this study. The analysis of VEGF/VEGFR and/or EGF/EGFR would be extremely interesting since VEGF is regulated by hypoxia and is a pharmacological intervention currently studied for therapeutic utility. Although these factors, i.e., EPO, VEGF and EGF share common features, they are actually quite different. EPO signals through an associated tyrosine kinase, JAK2 while VEGF and EGF signal through an intrinsic kinase in the receptor itself that is mutated and amplified in some cancers.

In another manuscript by Arcasoy (2002) evidence is presented to support a role of erythropoietin receptors (EPO-R) in breast cancer. This is shown by demonstrating both EPO and EPOR expression in cancerous tissue as compared to surrounding normal tissue. Moreover, a correlation of tumor hypoxia and EPO/EPO-R expression is proposed. This was investigated since tissue hypoxia has been associated with tumor progression coupled with the fact that hypoxia is the mechanism that governs EPO expression. Although the authors can demonstrate that both hypoxia and EPO/EPOR expression are up regulated in breast cancer tissue, a correlation of both occurring together in the same tissue section is not established. The progression of normal tissue to a cancerous state results from dysregulated/aberrant gene expression. For this reason, it is not surprising that EPO is up regulated during tumor progression. Furthermore numerous genes have been shown to be up regulated including both epidermal and fibroblast growth factors.

Additional experiments to understand the functional significance of EPO-R on breast cancer tissue were performed by implanting rat adenocarcinoma cells into rats and observing if EPO-R antagonists have an effect on tumor progression. Briefly, cells were implanted subcutaneously in the presence or absence of test compound and maximal tumor depth was analyzed seven days post-implantation. The authors demonstrate that soluble EPO receptor; anti-EPO antibody and a JAK kinase inhibitor can decrease tumor depth in a dose dependent manner. This result suggests that the EPO signaling pathway is involved in tumor progression. Although this result supports their hypothesis since attenuation of the signal leads to decreased tumor depth, numerous parameters need to be tested. First, the experiment was performed with one administration of test compound. The relevance to current clinical practice whereby EPO is administered during the course of chemotherapy is unknown. Research has shown in animal models that multiple administrations of EPO either has no effect (La Montagne 2006) or leads to tumor regression. Lastly, EPO has been shown to increase survival in a murine multiple myeloma model (Mittleman 2001).

Several groups have explored whether ESAs confer an anti-apoptotic effect or interfere with the effectiveness of chemotherapeutic agents on tumor cells. Numerous studies have shown that ESAs increase the expression of the anti-apoptotic genes, *bcl<sub>x</sub>* and *bcl2* in hematopoietic and neuronal cells. In

the study by Batra et al. (2003), up-regulation of  $bcl_x$  and  $bcl2$  was demonstrated at EPO concentrations greater than 30 Units/mL, a supra-pharmacological concentration; however, expression of these genes was also observed in the absence of ESAs. Furthermore, this EPO concentration necessary to impact gene expression is 1000-fold higher than EPO levels in the normal physiological range and 10-to 100-fold higher than that seen after high-dose EPO administration in the clinical setting.

In the study by Gewirtz (2006) EPO failed to interfere with the antiproliferative and cytotoxic effects of antitumor drugs. Both taxol and tamoxifen exhibit identical cytotoxicity on MCF-7 cells in the absence or presence of 10 Units/mL EPO. MCF-7 cells, a human breast cancer cell line, have been previously shown to express the EPO-R (Acs 2001). In addition to this *in vitro* result, several published studies have reported that ESAs increase the chemo- and radio-sensitivity of tumors in normal and anemic animal models (Silver 1999, Thews 2001; Stuben 2001).

To answer the question pertaining to exclusion of tumor types for ESA treatment, one must explore this question with extreme diligence. For example, select tumor types must be obtained in high quality under similar conditions. Secondly, tumors should be processed and evaluated with specific reagents that detect the EPO-R with high confidence. Thirdly, all positive tumors should be further evaluated with a bioassay to ascertain functionality. Both RT-PCR and IHC provide a qualitative not quantitative assessment of EPO-R protein and function that may not reflect the actual situation *in situ*. In summary, no comprehensive evaluation of tumors linking expression, binding and functionality exist to adequately address ESA and tumor exclusivity presently.

Mechanisms other than epoetin-tumor cell interactions may explain the findings of less favorable outcomes in investigational (non-FDA approved) ESA trials targeting higher hemoglobin levels. The CMS proposed decision memo (p. 18-19) discussed the evidence of cancer-related changes in the coagulation cascade and epoetin-associated alterations of coagulation, platelet function and blood viscosity. Tumor-related coagulation changes have been reported by others (Khorana 2007). Such epoetin- and tumor-related changes may synergize to cause microthrombi within or surrounding the tumor resulting in altered blood flow and attenuation of chemotherapy or radiation anti-tumor effect. This hypothesis of epoetin-induced vascular change as a mechanism for less favorable outcomes has recently been described in the *JNCI* (Journal of the National Cancer Institute) (Tuma 2007)

Discordant findings of cell surface receptors and clinical outcomes have been reported with other hematopoietic growth factors, specifically receptors that stimulate white blood cell maturation. Acute myelogenous leukemia cells (a malignancy of white blood cells) are known to have cell surface receptors for granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) (Armitage 1998, Kawada 1998), yet two hematopoietic growth factors that act on these

receptors—filgrastim (G-CSF, Neulasta®) and sargramostim (GM-CSF, Leukine®)--are FDA approved to reduce the time of neutrophil recovery in patients with acute myelogenous leukemia. (Neulasta® package insert, Leukine package insert®) Both agents have been evaluated by regulatory agencies and found to have beneficial rather than deleterious effects on patients with acute myelogenous leukemia despite receptor interaction. Additionally, American Society of Clinical Oncology white blood cell growth factor treatment guidelines recommend colony-stimulating factors for patients with acute myelogenous leukemia, particularly those over the age of 55. (Smith 2006)

Independent reviewers, including FDA reviewers, have also described the uncertainty of the present state of the art regarding erythropoietin receptor science. Comments in the FDA briefing document developed by FDA scientists for the May 2007 Oncology Drug Advisory Committee included the following:

*“... a direct relationship between the presence of erythropoietin receptors on tumor and tumor proliferation in response to exogenous erythropoietin has not been established. In vitro and in vivo data do not provide convincing evidence that erythropoietin promotes tumor growth and proliferation...” (FDA-authored Briefing Document, May 2007)*

Additionally, Dr Gail Eckhardt, Oncology Drug Advisory Committee Chair, recently commented on the erythropoietin receptor:

*“... Eckhardt said the CMS decision to base its actions on the hypothesis that response to EPO is regulated by EPO receptors is premature. “There is a huge amount of conflicting science on that issue, so I don’t think that anybody can say definitively one way or the other, certainly not at ODAC.”... (Goldberg 2007b)*

## **8.0 CMS Proposed Limitations**

The CMS proposed decision memo describes six potential coverage limitations with the CMS draft limitations, and Ortho Biotech positions are described below.

### **8.1 Hemoglobin Level at ESA Initiation**

CMS draft limitation: *“the hemoglobin/hematocrit levels immediately prior to initiation of dosing for the month should be <9 g/dl/27% in patients without known cardiovascular disease and <10 g/dl/30% in patients with documented symptomatic ischemic disease that cannot be treated with blood transfusion (The latter patients should be alerted to the increased potential for thrombosis and sequelae.) (We suggest that patients, especially those in the latter category, be alerted to the increased potential for thrombosis and sequelae.)”*

**OBI position: Coverage for Hb < 11 g/dL at ESA initiation, which is consistent with labeling information, anemia treatment guidelines, and ESA clinical trial designs. Initiating ESA use at a Hb < 9 g/dL will have a negative effect on patient quality of life and increase risk of transfusion. Clinical trial and ESA registry analyses reported higher transfusion frequency in patients with hemoglobin of <9 g/dL compared with Hb 9-11 g/dL at time of ESA initiation. Clinical data is**

**lacking for ESA initiation based on the CMS proposed limitation. Published practice pattern studies have reported hemoglobin levels consistent with NCCN anemia treatment guidelines. This position is for the initiation of ESA dosing for the entire treatment course rather than for one month at a time.**

**Rationale:**

**Quality of life (QoL)**

If patients are initiated at a Hb < 9 g/dL, their QoL will be negatively impacted compared to initiating at a Hb level of < 11 g/dL. Several publications have examined QoL differences at various Hb levels. Crawford et al (2002) demonstrated that anemic patients undergoing chemotherapy experience the greatest gain in quality of life with Hb improvements from 11 g/dL to 12 g/dL in association with ESA administration. A much smaller incremental gain in QoL was observed with Hb improvements of 8.0 g/dL to 9.0 g/dL or Hb improvements of 9.0 g/dL to 10.0 g/dL.

A separate randomized, open label trial of 359 evaluable patients receiving chemotherapy and radiotherapy noted similar incremental gains in QoL. The greatest incremental gain in QoL associated with a 1 g/dL rise in Hb occurred around Hb 12 g/dl (range 11-13 g/dL). There was an increase in LASA Overall QOL score of 1.4 mm when Hb increased from a midpoint range of 8 to 10 g/dL. This is in contrast to an increase of 13.5 mm points when Hb increased from 10 to 12 g/dl. (Shasha 2004)

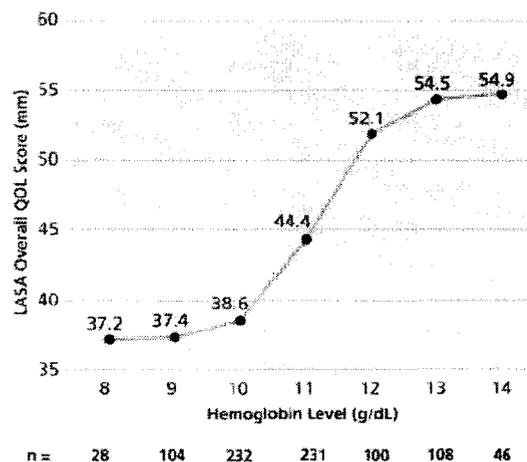


Figure 6: Longitudinal analysis of the relationship between changes in Hb levels and changes in LASA scores for overall QoL during epoetin alfa therapy. (Permission pending)

Straus et al (2006) conducted an open label multicenter trial examining early vs late epoetin alfa use in patients with anemia associated with chemotherapy. The objective was to examine if there was any differences in patient reported QoL if epoetin alfa was initiated at Hb < 9.0 g/dL (late group) vs Hb  $\geq$  10 -  $\leq$  12 g/dL (early group). Patients initiated at Hb < 9.0 g/dL (late group) had significantly lower QoL scores for total FACT-General, FACT-General physical and functional well-being subscales, total anemia scale,

and fatigue subscale and daily activity, energy compared to patients initiated at higher Hb levels (ESA Hb initiation 10-12 g/dL). The late group (ESA Hb initiation < 9.0 g/dL) also had more bed rest days and restricted activity days. (Straus 2006)

Initiating ESA use at Hb < 9.0 g/dL will have a significant and detrimental impact on patient QoL. We recommend initiating at a higher Hb levels in order to improve the quality of life benefit ESAs confer to anemic chemotherapy induced cancer patients.

#### Labeling information

A baseline Hb level of < 9 g/dL for ESA initiation is inconsistent with pivotal trials that led to FDA approval of ESAs in patients with chemotherapy-induced anemia. Both FDA-approved ESAs, each with two approved dosing schedules, have been evaluated in randomized clinical trials following regulatory agency discussions. In each case, baseline Hb at ESA initiation in pivotal trials has been 10.5-11.5 g/dL, including FDA approval of one ESA regimen as recently as March 2006.

FDA-approved ESA regimen*	Year of FDA approval	Baseline Hb in FDA-approved registration trial
Aranesp 500 mcg Q3W	2006	< 11 g/dL
Aranesp 2.25 mcg/kg QW	2002	≤ 11 g/dL
PROCRIT 40,000 U QW	2004	< 10.5 g/dL females, < 11.5 males
PROCRIT 150 U/kg TIW	1993	≤ 10.5 g/dL

\* PROCIT Prescribing Information [3/07], Aranesp Prescribing Information [4/07]

Information regarding baseline Hb of pivotal trials has been included in the "Clinical Studies" section of the Aranesp labeling information:

*"... This study was conducted in anemic (Hgb ≤ 11 g/dL) patients with advanced, small cell or non-small cell lung cancer, who received a platinum-containing chemotherapy regimen. Patients were randomized to receive Aranesp® 2.25 mcg/kg (n = 156) or placebo (n = 158)..."*

*"... This study was conducted in anemic (Hgb < 11 g/dL) patients with non-myeloid malignancies receiving multicycle chemotherapy. Patients were randomized to receive Aranesp® at 500 mcg Q3W (n = 353) or 2.25 mcg/kg (n = 352) administered weekly as a SC injection for up to 15 weeks..."* (Aranesp Prescribing Information [4/07])

The National Comprehensive Cancer Network (NCCN) anemia treatment guidelines provide recommendations regarding ESA initiation at a hemoglobin level of < 11 g/dL for cancer patients with chemotherapy-induced anemia:

*"Following the identification of anemia (defined for the purpose of considering intervention as hemoglobin levels equal to or less than 11 g/dL) and the evaluation for anemia specific causes, an initial risk assessment should be completed... The history should assess whether accompanying symptoms are present, such as chest pain or dyspnea. Comorbidities such as cardiac disease or underlying pulmonary disease must be considered... Observation or*

*erythropoietic therapy should be considered for asymptomatic patients with risk factors for developing anemia. The decision of whether to use epoetin immediately or to wait until hemoglobin levels fall closer to 10 g/dL should be determined by clinical circumstances. For symptomatic patients, transfusion and/or erythropoietic therapy are recommended. If the patient's hemoglobin level is between 10-11 g/dL, the panel recommends the consideration of erythropoietic therapy with or without transfusion. If the patient's hemoglobin level is <10 g/dL, the panel strongly recommends erythropoietic therapy..." (NCCN anemia treatment guidelines v.3.2007)*

Additionally, the American Society of Hematology/American Society of Clinical Oncology (ASH/ASCO) published anemia treatment guidelines recommend ESA initiation at an Hb of 10-12 g/dL in certain clinical conditions, such as the elderly.

*"...The guideline panel found good evidence to recommend use of epoetin as a treatment option for patients with chemotherapy-associated anemia with a hemoglobin level less than 10 g/dL. Use of epoetin for patients with less severe anemia (hemoglobin < 12 g/dL but never below 10 g/dL) should be determined by clinical circumstances... Examples of patients at this higher degree of absolute risk, who may be considered reasonable candidates for this agent, based on clinical judgment, include but are not limited to elderly individuals with limited cardiopulmonary reserve or patients with underlying coronary artery disease and symptomatic angina..." (Rizzo 2002)*

Post hoc analyses of multiple controlled clinical trials reported a higher proportion of patients requiring blood transfusions and higher blood utilization in patients treated with baseline hemoglobin <9 g/dL compared with those initiated at hemoglobin of 9-11 g/dL. The placebo-controlled registration trial used to support the FDA approval of PROCRIT (epoetin alfa) 40,000 Units QW was analyzed to investigate the transfusion patterns of patients initiated at a hemoglobin level of < 9 g/dL v. 9-11 g/dL. A consistent reduction of proportion of patients requiring transfusion was observed in both subgroups categorized by baseline hemoglobin of hemoglobin 9-11 g/dL v < 9 g/dL in the epoetin alfa-treated group compared to the placebo-treated group. (Data on file, Ortho Biotech #2). Moreover, 38% of patients required blood transfusion when PROCRIT was initiated when Hb < 9 g/dL whereas only 22% required blood transfusions when initiated with Hb 9-11 g/dL.

Hb at ESA initiation	Registration trial of EPO 40,000 Unit QW			
	EPO < 9 g/dL	EPO 9-11 g/dL	Placebo < 9 g/dL	Placebo 9-11 g/dL
Patients requiring PRBC or whole blood transfusion – Day 1 to end of study	38%	22%	63%	31%
Number of units transfused/transfused patient	3.3	2.8	4.1	3.9

Additionally, post hoc analyses of two controlled ESA clinical trials (clinical trial #1: Waltzman (2005); clinical trial #2 Henry (2006)) also reported similar results: higher transfusion rates (50%) in patients initiated at Hb < 9 compared with those initiated at Hb 9-11 g/dL (13-18%). (Data on file, Ortho Biotech #3)

	Clinical trial #1	
Hb at ESA initiation	< 9 g/dL	9-11 g/dL
Patients requiring PRBC or whole blood transfusion – Day 1 to end of study (95% CI)	50% (33, 67)	18% (14, 22)
Mean number of units transfused/transfused patient (SD) <sup>1</sup>	4.6 (3.8)	2.9 (1.8)

<sup>1</sup>P value of mean number of units transfused (ESA initiation < 9 g/dL vs 9-11 g/dL): 0.01

	Clinical trial #2	
Hb at ESA initiation	< 9 g/dL	> 9-11 g/dL
Patients requiring PRBC or whole blood transfusion – Day 1 to end of study (95% CI)	50% (33, 67)	13% (9,17)
Mean number of units transfused/transfused patient (SD) <sup>2</sup>	3.6 (1.5)	3.0 (1.8)

<sup>2</sup>P value of mean number of units transfused (ESA initiation < 9 v 9-11): 0.30

Similarly observational data from an ongoing patient registry study ESA in U.S. oncology clinics reported higher transfusion frequency in the patients initiated at Hb <9 g/dL compared to those initiated at Hb levels 9-11 g/dL. (Data on file, Ortho Biotech #4)

	ESA registry data	
Hb at ESA initiation	< 9 g/dL (n=25)	9-11 g/dL (n=145)
Patients requiring PRBC or whole blood transfusion – Day 1 to end of study (SD)	46% (32.9%, 59.7%)	18% (15.9%, 21.1%)
Mean number of units transfused/transfused patient (mean SD)	3.2 (2.38) 95% CI: 2.22, 4.18	3.2 (2.18)* 95% CI: 2.83, 3.52

\* p = 0.96

Similar findings have been reported in analyses comparing patients initiated at a Hb < 10 g/dL compared with those with ESA initiation of 10-11 g/dL. In clinical trials and observation studies, data have reported a higher proportion of patients requiring blood transfusion in the Hb < 10 g/dL v Hb 10-11 g/dL.

	Type of study	Proportion of patients transfused Hb at ESA initiation	
		< 10 g/dL	10-11 g/dl
Vansteenkiste (2004)	Clinical trial	31%	15%
Boccia (2006)	Clinical trial	28%	12 %
Szczudlo (2007)	Clinical trial	36%	9%
Szczudlo (2007)	Clinical trial	29%	3%
Wang (2007)	Observational	31%	13%

A recent meta-analysis of all randomized controlled studies comparing ESA versus transfusion alone for prophylaxis or treatment of anemia in cancer patients (42 studies with 6,510 subjects) demonstrated that patients treated with epoetin alfa or darbepoetin alfa had a 36% lower risk of transfusion than control subjects (relative risk=0.64 [95% CI: 0.60 to 0.68]) (Bohlius 2006 Cochrane Database). The publication also presented relative risk for transfusion categorized by baseline hemoglobin. As shown in the table below, the relative risk for patients initiated at Hb < 10 g/dL was higher (0.70) than for patients initiated at a hemoglobin of 10-12 g/dL, indicating the greater benefit for transfusion reduction is observed in patients with ESA initiation at 10-12 g/dL (0.46).

Baseline Hb at ESA initiation	Relative risk for transfusion (95% CI)
Hemoglobin < 10 g/dL	0.70 (0.65, 0.7)
Hemoglobin 10-12 g/dL	0.46 (0.40, 0.53)

ESA clinical trials evaluating anemia management have used baseline hemoglobin levels of < 11 g/dL to investigate ESA use in the oncology population receiving chemotherapy.

Clinical trial publication	Baseline hemoglobin
Demetri (1998)	≤ 11 g/dl
Gabrilove (2001)	< 11 g/dl
Vansteenkiste (2002)	≤ 11 g/dl
Vadhan-Raj (2003)	≤ 11 g/dl
Shasha (2003)	≤ 11 g/dl
Schwartzberg (2004)	≤ 11 g/dl
Waltzman (2005)	≤ 11 g/dl
Glaspy (2006)	≤ 11 g/dl
Boccia (2006)	< 11 g/dl
Henry (2006)	≤ 11 g/dl
Steensma (2006)	< 12 g/dL males; < 11 g/dL females
Canon (2006)	< 11 g/dl
Witzig (2005)	< 10.5 g/dL females, < 11.5 males
Abels (1993)	≤ 10.5 g/dL
Justice (2005)	≤ 11 g/dl
Glaspy (2005)	≥ 9 & ≤ 11 g/dL
Hesketh (2004)	≤ 11 g/dl
Glaspy (2003)	≤ 11 g/dl

Multiple ESA practice pattern studies have reported that hemoglobin levels prior to ESA initiation. In each study, the team of health care professionals made the decision for ESA initiation caring for the individual

patient. Mean baseline hemoglobin levels from three studies are consistent with NCCN treatment guidelines (mean Hb at ESA initiation < 11 g/dL).

	N	Mean hemoglobin at ESA initiation (SD)	
		EPO	DARB
Chen (2006)	861	10.4 (0.9)	10.5 (1.0)
Mark (2005)	1005	9.78 (0.86)	9.94 (0.82)
Schwartzberg (2003)	1391	10.2 (1.1)	10.3 (1.2)

As currently written, this limitation is unclear in the meaning of "dosing for the month should be..." If this infers that for each new month a patients Hb must be less than 9 g/dl to receive coverage, it would result in disjointed and irregular Hb levels as well as increased transfusions. It is important to note that it after ESAs are administered it takes 3-4 weeks to see a Hb effect. For example, a hypothetical case of adjusting each month to align with Hb < 9.0 g/dL is as follows:

Date	Hb Level (g/dL)	Treatment received
July 1	8.9	Patient receives one dose of ESA
July 8	8.0	Patient receives a transfusion + 1 dose ESA
July 15	8.8	Patient receives one dose of ESA
July 22	9.2	Patient receives one dose of ESA
July 29	9.9	Patient receives one dose of ESA
Aug 5	10.1	No ESA given since it is a new month and Hb > 9 g/dl
Aug 14	9.7	No ESA given since it is a new month and Hb > 9 g/dl
Aug 21	9.3	No ESA given since it is a new month and Hb > 9 g/dl
Aug 29	8.8	Patient receives one dose of ESA
Sept 5	8.5	Patient receives one dose of ESA
Sept 12	8.0	Patient receives a transfusion + 1 dose ESA

We do not recommend dividing ESA dosing into monthly intervals where certain parameters must be obtained on a monthly basis in order to receive coverage. We propose CMS stipulate that for each contiguous treatment course of ESAs, the Hb levels prior to initiation of ESA dosing should be less than 11 g/dL.

At the May 2007 ODAC meeting there was discussion surrounding Hb initiation, but the committee suggested no specific Hb initiation level. It is important to note that the ESA prescribing information does not provide guidance on Hb initiation for patients with chemotherapy-induced anemia.

## 8.2 Limited Annual Treatment Duration

CMS draft limitation: *the maximum covered treatment duration is 12 weeks/year*

**OBI Position: No annual treatment duration restriction; consider limitation of ESA administration to 3 months following completion of chemotherapy regimen**

### Rationale:

An arbitrary annual limit of ESA administration to 12 weeks is without merit in that most chemotherapy regimens exceed treatment duration of 18 weeks. As anemia is a frequent complication of many regimens (Groopman 1999), the duration and intensity of ESA support will depend on individual patient age, co-morbidities, underlying malignancy, and previous cancer-related treatments. Additionally, the 12-week annual limit in the draft NCD severely restricts ESA use in patients with refractory or relapsed malignancies that may require multiple chemotherapy regimens within a given year. Patients experiencing a clinical benefit to ESA could lose such benefits imposed by the treatment duration limits described in the draft NCD.

The chart below highlights the treatment duration of a variety of chemotherapy regimens. Many patients treated with relapsed or refractory disease may experience multiple chemotherapy regimens, and therefore, have a much longer chemotherapy treatment duration that described with various treatment regimens.

Tumor type	Chemotherapy regimen	Chemotherapy-related treatment duration
Non-Hodgkin's lymphoma (Feugier 2005)	R-CHOP	24 weeks
Hodgkin's lymphoma (NCCN Hodgkin disease/lymphoma v.1.2007)	ABVD	16-32 weeks
Colon cancer (NCCN colon cancer v.2.2007)	5FU-leucovorin	32 weeks
Breast cancer (NCCN breast cancer v.2.2007)	CAF	24 weeks
Breast cancer (NCCN breast cancer v.2.2007)	AC followed by paclitaxel	24 weeks
Lung cancer (Ihde 1994)	cisplatin-etoposide	24 weeks

Medical claims analyses from two large U.S. managed care databases found that the mean duration of ESA administration was 105-119 days in the age > 65 population receiving concurrent chemotherapy and ESA. Additionally, 44-52% of patients received an ESA for more than 12 weeks. This indicates that approximately 50% of the age > 65 population would have ESA agents terminated prematurely based treatment duration limits of 12 weeks as described in the draft CMS NCD. (Data on file, Ortho Biotech #4)

ESA treatment duration for age > 65 population receiving concurrent chemotherapy

	Mean (SD)	Median (25 <sup>th</sup> -75 <sup>th</sup> percentile)	% of patients with ESA treatment duration > 12 weeks
Database 1	105 (100)	71 (29-148)	44%
Database 2	119 (109)	86 (29-170)	52%

CMS inquired about ESA treatment duration in patients initiated late in the chemotherapy treatment regimen. Discussions with CMS at the June 6, 2007 meeting, mentioned ESA administration late in the cycle; however, to clarify chemotherapy cycle is typically administered every 3-4 weeks with most chemotherapy treatment regimens given as a series of 4-8 cycles. For patients that experience anemia (baseline Hb < 11 g/dL) during the latter part of the chemotherapy regimen (eg. month six), ESA coverage should be supported, thus allowing physicians to decide on ESA intervention based on the individual patient's condition. Implementation of policy to hold ESA dosing for Hb > 12 g/dL, consistent with labeling information, will lead to a self-limited ESA treatment duration in such patients.

### 8.3 Dose Limitation

CMS draft limitation: *the maximum covered 4 week treatment dose is 126,000 units for erythropoietin and 630 µg for darbepoietin*

**OBI Position: A maximum covered 4 week treatment dose should not be considered due to patient and chemotherapy treatment heterogeneity. Furthermore, such proposals position a financial disincentive for the use of one product over the other. A more evidence-based approach could focus on the appropriate ESA use based on patient-specific outcomes limiting coverage (Initiation of ESA at Hb < 11 g/dL with non-coverage for Hb > 12 g/dL). Such recommendations are supported by FDA-approved labeling information and recent clinical trials.**

Rationale:

Dosing limitations described in the draft CMS NCD preclude epoetin alfa administration consistent with FDA-approved dosing. FDA approved epoetin alfa labeling information defines initial dosing and dosing based on initial response as follows:

PROCRIT (epoetin alfa)

*"Starting Dose: Adults 40,000 Units SC..Increase Dose if: response is not satisfactory (no increase in hemoglobin by ≥ 1g/dL after 4 weeks of therapy, in the absence of a RBC transfusion) to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL: Adults: 60,000 Units SC Week"*

*"Starting Dose: Adults 150 Units/kg SC TIW..Increase Dose to 300 Units/kg TIW if: response is not satisfactory (no reduction in transfusion requirements or rise in hemoglobin) after 8 weeks to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL" (PROCRIT Prescribing Information [3/07])*

Anemia treatment guidelines developed by the NCCN and ASH/ASCO have also incorporated FDA-approved dosing that included potential dose escalation based on initial response. The draft NCD limitation would not allow for dosing in accordance with anemia treatment guidelines.

Clinical studies have described a mean weight of approximating 70 kg in patients receiving ESA however the standard deviation is wide [Weight, kg (SD): Study 1: 69.3 (13.7) (Canon 2006); Study 2: 74 (18) (Mark 2005); Study 3: 75.6 (19.2) (Chen 2006)] demonstrating patient heterogeneity with respect to weight. These findings highlight patient variability with regard to weight and potential dosing implications. For example, a 100-kg patient would require a four week epoetin alfa dose of 360,000 Units<sup>2</sup> should dose escalation be required.

The proposed dosing limitations have tremendous implications for patients; as such limitations may cause interruption of ESA treatment. Two data base analyses of medical claims showed 4-week cumulative ESA dosing which exceeds the proposed limitations (EPO: 126,000 Units/4 weeks: DARB 630 mcg/4 weeks) in 28-29% of patients over age 65 receiving concurrent ESA and chemotherapy (Data on file, Ortho Biotech #5, #6). These data suggest that a proportion of Medicare beneficiaries would have ESA treatment interrupted if the proposed dose maximums were adopted, denying Medicare beneficiaries the benefits of avoiding transfusion and better quality of life. In particular, patients with higher BMIs or those who receive particularly myelosuppressive chemotherapy will be unnecessarily discriminated against. Maximum dose limits also ignore patient heterogeneity in response, which may be a function of their inherent physiology and not something that patients have any control over.

Additionally, the proposed dosing limitations could result in shifting usage to the ESA whose dose maximum accommodates the most patients. An unintended consequence is that this could force the selection of the ESA with the highest cost, without any corresponding additional benefit. For instance, the 4-week dose maximums proposed in the NCD would result in a payment limit for Aranesp, which is 66% higher than the payment limit for PROCRIT. This would put CMS in the position of picking winners and losers in a therapeutic category, limiting choice, paying more than it would otherwise, and increasing beneficiary co-pays.

Based on 2<sup>nd</sup> quarter Average Sales Price (ASP) the following price premium is calculated for ARANESP:

	Dose	Cost based on ASP	ARANESP Price Premium
PROCRIT	126,000 Units	\$1,190.95	66%
ARANESP	630 mcg	\$1,980.09	

NOTE: 2<sup>nd</sup> Qtr ASP: PROCRIT -\$9.452/1,000 Units; ARANESP - \$3.143/mcg

Source: CMS. <http://www.cms.hhs.gov/McrPartBDrugAvgSalesPrice/> Accessed June 5, 2007

<sup>2</sup> 100 kg patient x 300 U/kg TIW (FDA-approved epoetin alfa dose with dose escalation) = 30,000 Units TIW (90,000 Units/week) or 360,000 Units/4 week period

We also believe that ESAs should remain a covered treatment for beneficiaries with MDS, and since patients with MDS require doses well beyond those needed by patients with chemotherapy-induced anemia, maximum doses for the latter would impede effective doses in the former.

The only way to avoid the arbitrary advantaging of one product over another is to not set maximum dose limits on either product. ESA dose can and will be appropriately and effectively constrained through implementation of an ESA initiation hemoglobin of < 11 g/dL and holding ESA dosing at Hb > 12 g/dL, obviating the need for separate maximum dose limits which interfere with patient care.

#### **8.4 Limitation Based on Poor Drug Response**

CMS proposed limitation: *“continued use of the drug is not reasonable and necessary if there is evidence of poor drug response (hemoglobin/hematocrit rise < 1 g/dL/< 3%) after 4 weeks of treatment”*

**OBI Position: ESA administration should not be limited based on poor drug response at 4 weeks. Patients with poor hemoglobin response (hemoglobin/hematocrit rise < 1 g/dL/3% over baseline) should be discontinued after 8 weeks following ESA initiation.**

##### Rationale

We agree that coverage for ESA administration in patients with documented non-response should be limited; however, restrictions based on poor initial drug response (< 1 g/dL Hb rise after 4 weeks of ESA treatment) as proposed in the draft NCD does not allow for ESA dosing as described in FDA-approved labeling information, anemia treatment guidelines, and clinical trial evidence. Such limitations preclude patient benefits of hemoglobin response and transfusion reduction in those patients that do not achieve an initial response however respond with subsequent ESA dose escalation, as described in labeling information.

The actual ESA treatment duration in assessing an individual patient response may vary depending on the selected dosing schedules. FDA approved PROCRIT (epoetin alfa) labeling information defines dosing for patients with inadequate initial response as follows:

##### PROCRIT (epoetin alfa)

*“Starting Dose: Adults 40,000 Units SC...Increase Dose if: response is not satisfactory (no increase in hemoglobin by  $\geq$  1g/dL after 4 weeks of therapy, in the absence of a RBC transfusion) to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL: Adults: 60,000 Units SC Week”*

*“Starting Dose: Adults 150 Units/kg SC TIW...Increase Dose to 300 Units/kg TIW if: response is not satisfactory (no reduction in transfusion requirements or rise in hemoglobin) after 8 weeks to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL” (PROCRIT Prescribing Information [3/07])*

Based on FDA-approved labeling, patients treated with the weekly PROCRIT (epoetin alfa) dosing schedule are initiated at 40,000 Units weekly and then dose escalated, if initial poor response, to 60,000 Units weekly at week four. In those patients with continued poor response (hemoglobin improvement < 1 g/dL over baseline) following four weeks of 60,000 Units weekly, PROCRIT (epoetin alfa) should be discontinued, which allows an 8 week PROCRIT treatment duration in assessing the individual patient response.

For patients treated with the TIW PROCRIT (epoetin alfa) dosing schedule are initiated at 150 U/kg weekly and then dose escalated, if initial poor response, to 300 U/kg TIW at week eight. In those patients with continued poor response (hemoglobin improvement < 1 g/dL over baseline) following four weeks of 300 U/kg TIW, PROCRIT (epoetin alfa) should be discontinued, which allows an 12 week PROCRIT treatment duration in assessing the individual patient response.

Anemia treatment guidelines have also commented on the ESA treatment duration for patients with poor response. The NCCN anemia treatment guidelines recommend ESA dose escalation if lack of initial response and continuation of therapy based on individual patient response.

*"An initial response assessment distinguishes patients with a response (Hb increase by 1 g/dL) from those with no response to erythropoietic therapy. In patients with a response, erythropoietin should be continued to maintain an optimal hemoglobin (12 g/dL). Assessment of patients with no response to therapy should be performed at 4 weeks for epoetin alfa and 6 weeks for darbepoetin. If no response is detected, a dose increase of the erythropoietic agent is recommended with or without iron supplementation as indicated. If the hemoglobin level increases by 1 g/dL at 8-12 weeks of erythropoietic therapy then a dosage titration should be performed to maintain an optimal hemoglobin level at 12 g/dL. Erythropoietic therapy should be discontinued and transfusion initiated as indicated if there is no hemoglobin response at 8-12 weeks of therapy..." (NCCN anemia treatment guidelines v.3.2007)*

ASH/ASCO guidelines recommend appropriate dose escalation prior to considering a patient as a non-responder

*"...Continuing epoetin treatment beyond 6 to 8 weeks in the absence of response (eg, < 1 to 2 g/dL rise in hemoglobin), assuming appropriate dose increase has been attempted in nonresponders, does not appear to be beneficial..." (Rizzo 2002)*

Clinical trial evidence has reported continued patient benefits when dosed with potential dose escalation based on initial response. Waltzman (2005) reported that 29% of epoetin alfa-treated patients and 35% of darbepoetin alfa-treated patients without a 1 g/dL Hb rise at week 4 went on to have at least a 1 g/dL Hb rise by end of study. Henry (2006) reported 35% of patients that did not achieve a Hb response (> 1 g/dL) within the first four weeks, achieved a Hb response during the course of study. Patterns of decreased transfusion use throughout the clinical trial duration have been observed in multiple ESA clinical trials (Duh 2005, Demetri 1998, Gabrilove 2001, Shasha 2003). This demonstrates that a significant proportion of patients have continued benefits throughout ESA treatment.

## **8.5 Limitation Based on Fluid Retention**

CMS draft limitation: *"continued administration of the drug is not reasonable and necessary if there is an increase in fluid retention or weight (5 kg) after 2 weeks of treatment"*

**OBI position: Scientific evidence is insufficient to support a NCD on ESA administration and fluid retention in cancer patients at this time.**

Rationale:

Fluid retention or weight (5 kg) gain after 2 weeks of treatment is not a contraindication for use of PROCRIT (epoetin alfa) according to the FDA approved prescribing information. Also, warnings are not described in the prescribing information for fluid retention or weight gain (5 kg) after 2 weeks of treatment. The studies listed in the proposed NCD for ESAs citing fluid retention all involve chronic kidney disease patients receiving dialysis. (Maschio 1995, Roger 1993, Winearls 1986) The articles focus on hypertension and platelet reactivity and not fluid retention or weight gain. Chronic kidney disease patients receiving dialysis are a distinctly different population than anemic oncology patients receiving chemotherapy. Uremic patients undergoing dialysis are at an increase risk of pulmonary edema, and several factors unique to this population, such as the inability to excrete a fluid load or to adjust to increased intravascular volume by increased urine output. These unique factors are attributed to a higher incidence of weight gain. Extrapolating data from a dialysis population and inferring similar results in oncology patients is not scientifically sound.

To date, there are no data in the published literature linking an increase in fluid retention in anemic patients receiving chemotherapy to poor outcomes. An updated COCHRANE meta-analysis by Bohlius et al. (2006) showed an increase risk of hypertension that was not statistically significant in oncology patients receiving epoetin alfa or darbepoetin alfa. The authors concluded that there was insufficient evidence to judge whether ESAs increases the risk of hypertension in this population.

## **8.6 Limitation Based on Rapid Hemoglobin Rise**

CMS draft limitation: *"continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin/hematocrit > 1 g/dL/>3% after 2 weeks of treatment"*

**OBI position: Although this is an appropriate safety signal, the ESA dose should be reduced by 25%, not discontinued, as per the prescribing information.**

Rationale:

The prescribing information for PROCRIT (epoetin alfa) lists specific recommendations for managing patients who experience a rapid rise in hemoglobin. The recommendation is:

*Reduce dose by 25% when Hgb approaches 12 g/dL or increases > 1 g/dL in any 2 weeks (PROCRIT Prescribing Information [3/07])*

Similar information is described in the Aranesp (darbepoetin alfa) labeling information:

*"If the hemoglobin increases by more than 1.0 g/dL in a 2-week period, the dose should be decreased by approximately 25%." (Aranesp Prescribing Information [4/07])*

The prescribing information does not recommend discontinuing use in the event of a rapid rise as proposed in the CMS NCD. Reducing the dose by 25% is also in accordance with the recently updated NCCN guidelines (NCCN anemia treatment guidelines v.3.2007).

## **9. Coverage with Evidence Development**

In its proposal on ESAs, CMS expressed interest in comments on whether coverage for ESAs for "Medicare beneficiaries with cancer" should occur only within appropriately designed clinical research studies where informed consent and safety monitoring can be assured. It is unclear from this language whether CMS means to refer to patients with anemia of cancer not related to cancer treatment, or to patients undergoing treatment for cancer who experience chemotherapy-induced anemia. Both patient groups can be described as beneficiaries "with cancer".

Requiring beneficiary participation in clinical research studies in order to receive Medicare coverage appears to be Coverage with Study Participation (CSP), one of the two options outlined in recent CMS guidance on Coverage with Evidence Development (CED), a type of national coverage determination (NCD) that includes capture and reporting of data as a condition for payment.

If by "Medicare beneficiaries with cancer" CMS means those patients suffering from anemia of cancer not related to treatment, then Ortho Biotech may have interest in CSP under Coverage with Evidence Development. That interest will, however, depend on the details of any proposed study design and its execution.

Alternatively, if by "Medicare beneficiaries with cancer" CMS is referring to cancer patients with chemotherapy-induced anemia, then applying Coverage with Study Participation is clearly unacceptable given the body of evidence demonstrating that ESAs are reasonable and necessary for the treatment of CIA. Such an action suggests that the current level of evidence is inadequate and, in the past, would have prompted a *non-coverage* decision. This is an extreme, overreaching and unprecedented interpretation of the current body of evidence, one that is simply without merit or broad-based support from a wide range of interested parties, including health care practitioners, patients and the organizations that represent them, caregivers, manufacturers, researchers, and commercial insurers. While CMS is asserts that it does not make coverage determinations based on costs or cost-effectiveness, Coverage with Study Participation in CIA would lend substantial credibility to the increasingly popular belief that

CMS is advocating unsupportable coverage restrictions on ESAs due primarily to budgetary considerations.

## **10. Conclusion**

While Ortho Biotech agrees with several of the proposed coverage changes, we also believe that many of the proposed coverage changes:

- Are not fully supported by a proper interpretation of available scientific and clinical evidence, which is inconclusive
- Do not consider the substantial heterogeneity inherent in oncology patients and their treatments
- Are contrary, in many instances, to current prescribing information and independent national treatment guidelines
- Expose beneficiaries to known and unknown risks of blood transfusions while putting unbearable pressure on the already limited national blood supply and transfusion services
- Unduly restrict coverage and access to ESAs, which could harm Medicare beneficiaries

## 11. References

- Aapro M, Barnadas A, Leonard RC, et al. Effects of epoetin beta treatment in patients with metastatic breast cancer receiving chemotherapy. Results of the BRAVE trial [abstract]. Presented at the 29th San Antonio Breast Cancer Symposium 2006, December 14-16, San Antonio, Texas. <sup>(Abs 6095)</sup> Available at: <http://www.abstracts2view.com/sabcs06/search.php?search=do&intMaxHits=10&where%5B%5D=&andnot%5B%5D=&query=aapro>
- Abels R. Erythropoietin for anaemia in cancer patients. *Eur J Cancer* 1993;29A (Suppl 2):S2-S8.
- Acs G, Acs P, Beckwith SM, et al. Erythropoietin and erythropoietin receptor expression in human cancer. *Cancer Res* 2001;61:3561-3565.
- Acs G, Zhang PJ, Rebbeck TR, et al. Immunohistochemical expression of erythropoietin and erythropoietin receptor in breast carcinoma. *Cancer* 2002;95:969-81.
- Aloe Spiriti MA, Latagliata R, Niscola P, et al. Impact of a new dosing regimen of epoetin alfa on quality of life and anemia in patients with low-risk myelodysplastic syndrome. *Ann Hematol* 2005;84(3):167-76.
- Alter HJ, Stramer SL, Dodd RY. Emerging infectious diseases that threaten the blood supply. *Semin Hematol* 2007;44(1):32-41.
- American Association of Blood Banks, America's Blood Centers & American Red Cross. Circular of information: for the use of human blood and blood components. July 2002. Available at: <http://www.fda.gov/cber/qdlns/crclr.pdf>
- American Association of Blood Banks. Blood banking community issues national appeal for immediate donations to address winter blood shortage. January 12, 2004. Available at: [http://www.aabb.org/Content/News\\_and\\_Media/Press\\_Releases/pr011204.htm](http://www.aabb.org/Content/News_and_Media/Press_Releases/pr011204.htm). Accessed June 5, 2007.
- American Association of Blood Banks. Blood banking industry issues national appeal for immediate donations to address summer blood shortage. July 7, 2003. Available at: [http://www.aabb.org/Content/News\\_and\\_Media/Press\\_Releases/pr070703.htm](http://www.aabb.org/Content/News_and_Media/Press_Releases/pr070703.htm). Accessed June 5, 2007.
- Aranesp<sup>®</sup> (darbepoetin alfa) Prescribing Information. Amgen Inc., Thousand Oaks, CA. Rev'd April 2007.
- Arcasoy MO, Amin K, Karayal AF, et al. Functional significance of erythropoietin receptor expression in breast cancer. *Lab Invest* 2002;82:911-918.
- Armand P, Kim HT, Cutler CS et al. Prognostic impact of elevated pre-transplant serum ferritin in patients undergoing myeloablative stem cell transplantation. *Blood* 2007;109(10):4586-8.
- Armitage JO. Emerging applications of recombinant human granulocyte-macrophage colony-stimulating factor. *Blood* 1998;92(12):4491-508.
- Avastin<sup>®</sup> (bevacizumab) Prescribing Information. Genentech, Inc. San Francisco, California. October 2006. <http://www.gene.com/gene/products/information/pdf/avastin-prescribing.pdf>
- Barrett-Lee PJ, Bailey NP, O'Brien MER, et al. Large-scale UK audit of blood transfusion requirements and anaemia in patients receiving cytotoxic chemotherapy. *Br J Cancer* 2000;82(1):93-97.
- Batra S, Perelman N, Luck LR, et al. Pediatric tumor cells express erythropoietin and a functional erythropoietin receptor that promotes angiogenesis and tumor cell survival. *Lab Invest* 2003;83:1477-1487.

Berdel WE, Oberberg D, Reufi B, et al. Studies on the role of recombinant human erythropoietin in the growth regulation of human nonhematopoietic tumor cells *in vitro*. *Ann Hematol* 1991;63:5-8.

Blohmer JU, Wurschmidt F, Petry U, et al. 6th interim analysis of a prospective, randomized, open and controlled AGO- and NOGGO-intergroup study: Sequential adjuvant chemo-radiotherapy with vs without epoetin alfa for pts with high-risk cervical cancer. *Pro Am Soc Clin Oncol* 2003;22:447. <sup>(Abst 1798)</sup>  
**(hardcopy not provided)**

Boccia R, Malik IA, Raja V, et al. Darbepoetin alfa administered every three weeks is effective for the treatment of chemotherapy-induced anemia. *Oncologist* 2006;11:409-17.

Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. *J Natl Cancer Inst* 2006;98:708-14.

Bohlius J, Wilson J, Seidenfeld J, et al. Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database of Systemic Reviews* 2006, Issue 3. Art. No. CD003407. DOI: 10.1002/14651858.CD003407.pub4. Available at: <http://www.cochranelibrary.com>. Accessed June 5, 2007.

Bokemeyer C, Aapro MS, Courdi A, et al. EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 Update. *Eur J Can* 2007;43(2):258-70.

Boshkov LK. Transfusion-related acute lung injury and the ICU. *Crit Care Clin* 2005;21:479-495.

Canon J-L, Vansteenkiste J, Bodoky G, et al. Randomized, double-blind, active-controlled trial of every-3-week darbepoetin alfa for the treatment of chemotherapy-induced anemia.

Casadevall N, Durieux P, Dubois S, et al. Health, economic and quality-of-life effects of erythropoietin and granulocyte colony-stimulating factor for the treatment of myelodysplastic syndromes: a randomized, controlled trial. *Blood* 2004;104:321-327.

Case DC, Bukowski RM, Carey RW, et al. Recombinant human erythropoietin therapy for anemic cancer patients on combination chemotherapy. *J Natl Cancer Inst* 1993;85(10):801-806.

Cella D, Zagari MJ, Vondoros C, et al: Epoetin alfa treatment results in clinically significant improvements in quality of life in anemic cancer patients when referenced to the general population. *J Clin Oncol* 2003;21(2):366-373.

Cella D. Factors influencing quality of life in cancer patients: anemia and fatigue. *Semin Oncol* 1998;25(Suppl 7):43-46.

Cella D. The functional assessment of cancer therapy-anemia (FACT-An) scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. *Semin Hematol* 1997;34(3, Suppl 2):13-19.

Centers for Medicare and Medicaid Services. "Medicare Part B Drug Average Sales Price: Payment Allowance Limits for Medicare Part B Drugs, Effective April 1, 2007 through June 30, 2007." <http://www.cms.hhs.gov/McrPartBDrugAvgSalesPrice/> Accessed June 5, 2007.

Chang J, Couture F, Young S, et al. Weekly epoetin alfa maintains hemoglobin, improves quality of life and reduces transfusion in breast cancer patients receiving chemotherapy. *J Clin Oncol* 2005;23(12):2597-2605.

Chen E, Peake C, Buscaino E, et al. Hematologic outcomes and erythropoiesis-stimulating therapy costs in epoetin alfa (EPO)- and darbepoetin alfa (DARB)-treated cancer patients: results of the dosing and outcomes study of erythropoiesis-stimulating therapies (D.O.S.E. Registry). Poster presented at the 48<sup>th</sup> Annual Meeting of the American Society of Hematology (ASH); Dec 9-12, 2006; Orlando, Florida.

Cheung WK, Goon BL, Guilfoyle MC, Wacholtz MC. Pharmacokinetics and pharmacodynamics of recombinant human erythropoietin after single and multiple subcutaneous doses to healthy subjects. *Clin Pharmacol Ther* 1998;64(4):412-23.

Cohen MH, Gootenberg J, Keegan P, et al. FDA drug approval summary: bevacizumab plus FOLFOX4 as second-line treatment of colorectal cancer. *Oncologist* 2007;12:356-61.

Coiffier B, Guastalla J.-P., Pujade-Lauraine E, et al. Predicting cancer-associated anaemia in patients receiving non-platinum chemotherapy: results of a retrospective survey. *Eur J Cancer* 2001;37:1617-23.

Crawford J, Cella D, Cleeland CS et al. Relationship between changes in hemoglobin level and quality of life during chemotherapy in anemic cancer patients receiving epoetin alfa therapy. *Cancer* 2002;95(4):888-95

Curt GA, Breitbart W, Cella D, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. *Oncologist* 2000;5:353-60.

D'Andrea AD, Lodish HF, Wong GG. Expression cloning of the murine erythropoietin receptor. *Cell* 1989;57(2):277-85. **(hardcopy not provided)**

Data on file #1. Ortho Biotech Products, L.P. U.S. impact model of suppressing the use of erythropoietic stimulating therapies in chemotherapy-induced anemia on the blood bank.

Data on file #2. Ortho Biotech Products, L.P. Clinical trial analyses for Henry, Waltzman, Witzig, and Littlewood studies. May 18, 2007.

Data on file #3. Ortho Biotech Products, L.P. Clinical trial analyses for Henry and Waltzman studies. May 24, 2007.

Data on file #4. Ortho Biotech Products, L.P. D.O.S.E. Registry analysis memo. June 1, 2007.

Data on file #5. Ortho Biotech Products, L.P. CMS 2007: IHCIS Medical Claims Analysis. May 28, 2007.

Data on file #6. Ortho Biotech Products, L.P. CMS 2007: Pharmetrics Medical Claims Analysis. May 28, 2007.

Data on file #7. Johnson & Johnson Pharmaceutical Research & Development, L.L.C. Moebus 2007 study.

Data on file #8. Johnson & Johnson Pharmaceutical Research & Development, L.L.C. Mortality Hazard Ratio Plot.

Data on file #9 - Johnson & Johnson Pharmaceutical Research & Development, L.L.C. EPO-GBR-7.

Data on file #10 - Johnson & Johnson Pharmaceutical Research & Development, L.L.C. PR01-04-005/GOG-191.

Debus J, Hindermann S, Morr H, et al. Epoetin alfa (EPO) and survival in patients with non-resectable NSCLC – Interim results [abstract]. Presented at the 27<sup>th</sup> German Cancer Congress; March 22-26, 2006; Berlin, Germany. Available at: <http://www.egms.de/en/meetings/dkk2006/06dkk257.shtml> **(hardcopy not provided)**

Demetri GD, Kris M, Wade J, Degos L, Cella D. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. *J Clin Oncol* 1998;16(10):3412-3425.

- Demetri GD. Anaemia and its functional consequences in cancer patients: current challenges in management and prospects for improving therapy. *Br J Cancer* 2001;84(Suppl 1):31-37.
- Dodd RY. Adverse consequences of blood transfusion: quantitative risk estimates. In: Nance ST, ed. *Blood supply: risks perceptions, and prospects for the future*. Bethesda, MD: American Association of Blood Banks, 1994:1-24.
- Dodd RY. Emerging infections, transfusion safety, and epidemiology. *New Engl J Med* 2003; 349(13):1205-1206.
- Duh MS, Mark TL. Cost-effectiveness of epoetin alfa and darbepoetin alfa in patients with chemotherapy-related anemia. *Expert Rev Pharmacoeconomics Outcomes Res* 2005;5:383-394.
- Elliott S, Busse L, Bass MB, et al. Anti-Epo receptor antibodies do not predict Epo receptor expression. *Blood* 2006;107(5):1892-5.
- Ende E, Newman J, Christiansen P. Amgen Inc: Expect more volatility post-CERA PDUFA. Merrill Lynch Research Report. United States: Merrill Lynch: May 17, 2007.
- Epoetin alfa. DrugPoints® System. In: Stat!Ref®. Thomson Micromedex Healthcare. Accessed June 5, 2007. Available at <http://online.statref.com>
- Eprex® Prescribing Information. Janssen-Ortho, Inc. Toronto, Ontario, Canada. November 2006. [http://www.janssen-ortho.com/JOI/pdf\\_files/Eprex\\_E.pdf](http://www.janssen-ortho.com/JOI/pdf_files/Eprex_E.pdf)
- Eprex® Summary of Product Characteristics In: Electronic Medicines Compendium. Janssen-Cilag Ltd. High Wycombe, United Kingdom. July 2006. <http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=889> Accessed June 6, 2007
- Erbix® (cetuximab) Prescribing Information. ImClone Systems, Inc. and Bristol-Myers Squibb Co. Branchburg NJ & Princeton NJ. August 2006.
- Estrin JT, Schocket L, Kregenow R, et al. A retrospective review of blood transfusions in cancer patients with anemia. *Oncologist* 1999;4:318-24.
- Fairclough DL, Gagnon DD, Zagari MJ et al. Evaluation of quality of life in a clinical trial with nonrandom dropout: the effect of epoetin alfa in anemic cancer patients. *Qual Life Res* 2003;12(8):1013-1027.
- Fallowfield L, Gagnon D, Zagari M, et al. Multivariate regression analysis of data from a randomised, double-blind, placebo-controlled study confirm quality of life benefit of epoetin alfa in patients receiving non-platinum chemotherapy. *Br J Cancer* 2002;87(12):1341-1353.
- Farrell F, Lee A. The erythropoietin receptor and its expression in tumor cells and other tissues [review]. *Oncologist*. 2004;9 Suppl 5:18-30.
- FDA Oncology Drug Advisory Committee hearing on May 10, 2007. Food and Drug Administration. Oncologic Drugs Advisory Committee. Available at: <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4301b2-00-index.htm>. Accessed June 5, 2007.
- FDA Oncology Drug Advisory Committee hearing on May 4, 2004. Food and Drug Administration. Oncologic Drugs Advisory Committee. Available at: <http://www.fda.gov/ohrms/dockets/ac/04/slides/4037s2.htm> and <http://www.fda.gov/ohrms/dockets/ac/04/briefing/4037b2.htm>. Accessed June 5, 2007.
- Ferrini PR, Grossi A, Vannucchi AM, et al. A randomized double-blind placebo controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes. *Br J Haematol* 1998;103:1070-4.

Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol* 2005;23(18):4117-26.

Forgie MA, Wells PS, Laupacis A, et al. for the International Study of Perioperative Transfusion (ISPOT) Investigators. Preoperative autologous donation decreases allogeneic transfusion but increases exposure to all red blood cell transfusion: results of a meta-analysis. *Arch Intern Med* 1998;158:610-616.

Gabrilove JL, Cleeland CS, Livingston RB, et al. Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. *J Clin Oncol* 2001;19:2875-82.

Gerwitz DA, Xu D, Teneille WD, et al. Erythropoietin fails to interfere with the antiproliferative and cytotoxic effects of antitumor drugs. *Clin Cancer Res* 2006;12:2232-38.

Giusti RM, Shastri KA, Cohen MH, et al. FDA drug approval summary: panitumumab (Vectibix™). *Oncologist* 2007;12:577-83.

Glaspy J, Henry D, Patel R, et al. Effects of chemotherapy on endogenous erythropoietin levels and the pharmacokinetics and erythropoietic response of darbepoetin alfa: a randomized clinical trial of synchronous versus asynchronous dosing of darbepoetin alfa. *Eur J Cancer* 2005;41:1140-49.

Glaspy J, Smith R, Aapro M, et al. Phase III, randomized, double-blind, placebo-controlled study of darbepoetin alfa for the treatment of anemia in patients not receiving chemotherapy or radiotherapy. Proceedings from the 2007 American Association for Cancer Research (AACR) Annual Meeting, April 14-18, 2007, Los Angeles, CA.  
<http://www.abstractsonline.com/viewer/viewAbstractPrintFriendly.asp?CKey={0F449D11-0E8D-43DF-85E7-77E5F4589E7D}&SKey={FA30AEE6-5964-4270-8253-C16F6E2F75DA}&MKey={E3F4019C-0A43-4514-8F66-B86DC90CD935}&AKey={728BCE9C-121B-46B9-A8EE-DC51FDFC6C15}>

Glaspy J, Vadhan-Raj S, Patel R, et al. Randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia: the 20030125 study group trial. *J Clin Oncol* 2006; 24:2290 – 2297.

Glaspy JA, Jadeja JS, Justice G, et al. A randomized, active-control, pilot trial of front-loaded dosing regimens of darbepoetin-alfa for the treatment of patients with anemia during chemotherapy for malignant disease. *Cancer* 2003;97:1312-20.

Gleason KJ, Djulbegovic B, Courtney DM, McKoy JM, Edwards B, Raisch D, Yarnold P, West D, Bennett CL. Venous thromboembolism and mortality concerns with erythropoietin and darbepoetin before and after 2003: did something change? Poster presented at the 43rd American Society of Clinical Oncology (ASCO) 2007 Annual Meeting, June 1 - June 5, Chicago, Illinois. **(hardcopy not provided)**

Goldberg P. Scientist's interpretation of meta-analysis on ESAs turns 180 degrees over 72 hours. In Goldberg KB, Goldberg P, eds. *The Cancer Letter*. Vol 33. No. 22. Washington, DC. June 8, 2007a.

Goldberg P. After ODAC: Questions on ESA claims, advertising, reimbursement gain urgency. In: Goldberg KB, Goldberg P, eds. *The Cancer Letter*. Vol 33. No. 19. Washington, DC. May 18, 2007b.

Golshayan AR, Jin T, Maciewjewski J, Fu AZ, et al. Efficacy of growth factors compared to other therapies for low-risk myelodysplastic syndromes. *Br J Hematol* 2007;137:125-32.

Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine: first of two parts: blood transfusion. *New Engl J Med* 1999;340(6):438-447.

Goodnough LT. Risks of blood transfusion. *Crit Care Med* 2003;31(12 Suppl):S678-686.

Gordeuk VR, McLaren GD, Samowitz W. Etiologies, consequences, and treatment of iron overload. *Crit Rev Clin Lab Sci* 1994;31:89-133.

Goss G, Feld R, Bezjak A, et al. Impact of maintaining Hb with epoetin alfa on time to progression (TTP), overall survival (OS), quality of life (QOL) and transfusion reduction in limited disease SCLC patients. *Lung Cancer* 2005;49(Suppl 2):S53. (Abst O-154)

Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. *J Natl Cancer Inst* 1999;91(19):1616-34.

Grote T, Yeilding A L, Castillo R, et al. Efficacy and safety analysis of epoetin alfa in patients with small-cell lung cancer: A randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2005;23(36):9377-86.

Halpin TJ, Moore W, Waterman SH, et al. Red blood cell transfusions contaminated with *Yersinia enterocolitica* — United States, 1991–1996, and initiation of a national study to detect bacteria-associated transfusion reactions. *MMWR-Morb Mortal Wkly Rep* 1997;46:553-555.

Hardee ME, Kirkpatrick JP, Shan S, et al. Human recombinant erythropoietin (rEpo) has no effect on tumour growth or angiogenesis. *Br J Cancer* 2005;93(12):1350-5.

Hardee ME, Arcasoy MO, Blackwell KL, et al. Erythropoietin biology in cancer. *Clin Cancer Res* 2006;12:332-9.

Hellstrom-Lindberg E, Negrin R, Stein R, et al. Erythroid response to treatment with G-CSF plus erythropoietin for the anemia of patients with myelodysplastic syndromes: proposal for a predictive model. *Br J Hematol* 1997;99:344–51.

Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet* 2003;362(9392):1255-60.

Henke M, Mattern D, Pepe M, et al. Do erythropoietin receptors on cancer cells explain unexpected clinical findings? *J Clin Oncol* 2006;24(29):4708-13. Erratum in: *J Clin Oncol*. 2007;25(11):1457.

Henry DH, Gordan LN, Charu V et al. Randomized, open-label comparison of epoetin alfa extended dosing (80000 U Q2W) vs weekly dosing (40000 U QW) in patients with chemotherapy-induced anemia. *Curr Med Res Opin* 2006;22(7):1403-1413.

Herceptin® (trastuzumab) Prescribing Information. Genentech, Inc. San Francisco, California. November 2006.

Hesketh PJ, Arena F, Patel D, et al. A randomized controlled trial of darbepoetin alfa administered as a fixed or weight-based dose using a front-loading schedule in patients with anemia who have nonmyeloid malignancies. *Cancer* 2004;100:859-68.

Hopkins B. JNJ: Procrit proposal an overhang. Lehman Brothers Research Report. United States: Lehman Brothers: May 15, 2007.

Hurley J, Doliny P, Reis I, et al. Docetaxel, cisplatin, and trastuzumab as primary systemic therapy for human epidermal growth factor receptor 2-positive locally advanced breast cancer. *J Clin Oncol* 2006;24(12):1831-38.

Ihde DC, Mulshine JL, Kramer BS, et al. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 1994;12(10):2022-34.

Jädersten M, Malcovati L, Dybedal I, et al. Treatment with erythropoietin and G-CSF improves survival in MDS patients with low transfusion need. *Blood* 2006;108(11):158a. <sup>(Abs 521)</sup>

Johnson & Johnson Pharmaceutical Research & Development, L.L.C. A Study of Epoetin Alfa Plus Standard Supportive Care Versus Standard Supportive Care Only in Anemic Subjects With Metastatic Breast Cancer Receiving Standard Chemotherapy (ID: NCT00338286). Available at: <http://www.clinicaltrials.gov/ct/show/NCT00338286?order=1> Accessed June 5, 2007

Justice G, Kessler JF, Jadeja J, et al. A randomized, multicenter study of subcutaneous and intravenous darbepoetin alfa for the treatment of chemotherapy-induced anemia. *Ann Oncol* 2005;16:1192-98.

Kawada H, Sasao T, Yonekura S, et al. Clinical significance of granulocyte colony-stimulating factor (G-CSF) receptor expression in acute myeloid leukemia. *Leuk Res* 1998;22(1):31-7.

Khorana AA, Ahrendt SA, Ryan CK, et al. Tissue factor expression, angiogenesis, and thrombosis in pancreatic cancer. *Clin Cancer Res* 2007;13(10):2870-5.

Khorana AA, Francis CW, Culakova E, et al: Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. *Cancer* 2005;104:2822-29.

Ladis V, Chouliaras G, Berdousi H, Kanavakis E, Kattamis C. Longitudinal study of survival and causes of death in patients with thalassemia major in Greece. *Ann NY Acad Sci* 2005;1054:445-450.

Lai, SY, Childs, EE, Xi, S, et al., Erythropoietin-mediated activation of JAK-STAT signaling contributes to cellular invasion in head and neck squamous cell carcinoma. *Oncogene* 2005;24:4442-4449.

LaMontagne KR, Butler J, Marshall DJ, et al. Recombinant epoetins do not stimulate tumor growth in erythropoietin receptor-positive breast carcinoma models. *Mol Cancer Ther* 2006;5:347-355.

Lee D. Perception of blood transfusion risk. *Transfusion Med Rev* 2006;20:141-148.

Leukine<sup>®</sup> (sargramostim) Prescribing Information. Bayer Healthcare Pharmaceuticals Inc., Seattle, WA. Rev'd December 2006.

Leyland-Jones B. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *J Clin Oncol* 2005;23(25):5960-72.

Linden JV, Paul B, Dressler KP. A report of 104 transfusion errors in New York State. *Transfusion* 1992;32:601-606.

Linden JV, Wagner K, Voytovich AE, Sheehan J. Transfusion errors in New York State: an analysis of 10 years' experience. *Transfusion* 2000;40:1207-1213.

Littlewood TJ, Bajetta E, Nortier JW, et al: Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2001;19(11):2865-2874.

Littlewood TJ, Zagari M, Pallister C, et al. Baseline and early treatment factors are not clinically useful for predicting individual response to erythropoietin in anemic cancer patients. *Oncologist* 2003;8(1):99-107.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Cancer- and Treatment-Related Anemia v.3.2007. The Complete Library of NCCN Practice Guidelines in Oncology may be found at [www.nccn.org](http://www.nccn.org). Accessed June 5, 2007.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Venous Thromboembolic Disease. v.2.2006. The Complete Library of NCCN Practice Guidelines in Oncology may be found at [www.nccn.org](http://www.nccn.org). Accessed June 5, 2007.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Hodgkin Disease/Lymphoma v.1.2007. The Complete Library of NCCN Practice Guidelines in Oncology may be found at [www.nccn.org](http://www.nccn.org). Accessed June 5, 2007.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Colon Cancer v.2.2007. The Complete Library of NCCN Practice Guidelines in Oncology may be found at [www.nccn.org](http://www.nccn.org). Accessed June 5, 2007.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Breast Cancer v.2.2007. The Complete Library of NCCN Practice Guidelines in Oncology may be found at [www.nccn.org](http://www.nccn.org). Accessed June 5, 2007.

National Comprehensive Cancer Network (NCCN). Practice Guidelines in Myelodysplastic Syndromes, v.1.2007, The Complete Library of NCCN Practice Guidelines in Oncology may be found at [www.nccn.org](http://www.nccn.org). Accessed June 5, 2007.

Neulasta® (pegfilgrastim) Prescribing Information. Amgen Inc., Thousand Oaks, CA. Rev'd January 2007.

O'Connell CL, Boswell WD, Duddalwar V, et al. Unsuspected pulmonary emboli in cancer patients: clinical correlates and relevance. *J Clin Oncol* 2006;24:4928-32.

Ossa DF, Briggs A, McIntosh E, et al. Recombinant erythropoietin for chemotherapy-related anaemia: economic value and health-related quality of life assessment using direct elicitation and discrete choice experiment methods. *Pharmacoeconomics* 2007;25:223-237.

Otten HMB, Mathijssen J, ten Cate H, et al: Symptomatic venous thromboembolism in cancer patients treated with chemotherapy: An underestimated phenomenon. *Arch Intern Med* 2004;164:190-194.

Overgaard J. Danish Head and Neck Cancer Group. Interim Analysis of DAHANCA 10: Study of the importance of novel erythropoiesis stimulating protein (Aranesp®) for the effect of radiotherapy in patients with primary squamous cell carcinoma of the head and neck. Available at: [http://www.dahanca.dk/get\\_media\\_file.php?mediaid=125](http://www.dahanca.dk/get_media_file.php?mediaid=125). Accessed June 5, 2007.

Park S, Kelaidi C, Grabar S, et al. Prognostic factors and response duration in 419 MDS treated with erythropoietin ± GCSF: the GFM experience. *Blood* 2006;108(11):158a. <sup>(Abs 522)</sup>

Patrick DL, Gagnon DD, Zagari MJ, et al. For the Epoetin Alfa Study Group: assessing the clinical significance of health-related quality of life (HrQoL) improvements in anaemic cancer patients receiving epoetin alfa. *Eur J Cancer* 2003;39:335-345.

Pealer LN, Marfin AA, Petersen LR, et al. for the West Nile Virus Transmission Investigation Team. Transmission of West Nile Virus through blood transfusion in the United States in 2002. *New Engl J Med* 2003;349(13):1236-1245.

Perrotta PL, Snyder EL. Non-infectious complications of transfusion therapy. *Blood Reviews* 2001;15:69-83.

PROCRIT (Epoetin alfa) Prescribing Information. Distributed by Ortho Biotech Products, L.P., Raritan, NJ. Rev'd March 2007.

Porges GC, Nudell BM, Guha A, Schneider EJ. AMGN, JNJ: End of evidence based regulation - CMS proposal could cut the EPO market by 50% or more. Bernstein Research Report. New York: Sanford Bernstein & Co., LLC, a subsidiary of Alliance Bernstein L.P.; May 15, 2007.

Phurrough S, Jacques L, Daily K, Rollins J. Centers for Medicare and Medicaid Services. "Decision Memo for Aprepitant for Chemotherapy-Induced Emesis (CAG-00248N)." April 4, 2005. <http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=133>. Accessed June 5, 2007.

Rizzo JD, Lichtin AE, Woolf SH, et al. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology (ASH). *Blood* 2002;100(7):2303-20 and *J Clin Oncol* 2002;20(19):4083-107.

Roger S, Piper J, Tucker B, Raine A, Baker L, Kovacs I. Enhanced platelet reactivity with erythropoietin but not following transfusion in dialysis patients. *Nephrol Dial Transplant* 1993;8:213-7.

Rose EH, Abels RI, Nelson RA, et al. The use of r-HuEpo in the treatment of anaemia related to myelodysplasia (MDS). *Br J Haematol* 1995;89:831-7.

Rosenzweig MQ, Bender CM, Lucke JP, et al. The decision to prematurely terminate a trial of R-HuEPO due to thrombotic events. *J Pain Symptom Manage* 2004;27(2):185-90.

Ross SD, Allen E, Henry DH, et al. Clinical benefits and risks associated with epoetin and darbepoetin in patients with chemotherapy-induced anemia: a systematic review of the literature. *Clin Ther* 2006;28:801-31.

Rosti V, Pedrazzoli P, Ponchio L, et al. Effect of recombinant human erythropoietin on hematopoietic and non-hematopoietic malignant cell growth *in vitro*. *Haematologica* 1993;78:208-12.

Sazama K. Reports of 355 transfusion-associated deaths: 1976 through 1985. *Transfusion* 1990;30:583-90.

Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. *N Engl J Med* 1996;334:1685-1690.

Schwartzberg L, Shiffman R, Tomita D, et al. A multicenter retrospective cohort study of practice patterns and clinical outcomes of the use of darbepoetin alfa and epoetin alfa for chemotherapy-induced anemia. *Clin Ther* 2003;25(11):2781-96.

Schwartzberg LS, Yee LK, Senecal FM, et al. A randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia in patients with breast, lung, or gynecologic cancer. *Oncologist* 2004;9:696-707.

Seidenfeld J, Piper M, Bohlius J, et al. Comparative effectiveness of epoetin and darbepoetin for managing anemia in patients undergoing cancer treatment. Comparative Effectiveness Review No. 3 (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Cancer Evidence-based Practice Center under Contract No. 290-02-0026) Rockville, MD: Agency of Healthcare Research and Quality. May 2006. Pages 35, 58-69, 94-100. Available at: [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm)

Shasha D, Cremieux P, Harrison L. Relationship between hemoglobin levels and quality of life during radiation therapy plus concomitant or sequential chemotherapy in patients with cancer and anemia treated with epoetin alfa. *J Natl Compr Canc Netw* 2004;2(5):509-517.

Shasha D, George MJ, Harrison LB. Once-weekly dosing of epoetin- $\alpha$  increases hemoglobin and improved quality of life in anemic cancer patients receiving radiation therapy either concomitantly or sequentially with chemotherapy. *Cancer* 2003;98:1072-9.

Silliman CC, Ambruso DR, Boshkov LK. Transfusion-related acute lung injury. *Blood* 2005;105:2266-2273.

Silver DF, Piver MS. Effects of recombinant human erythropoietin on the antitumor effect of cisplatin in SCID mice bearing human ovarian cancer: a possible oxygen effect. *Gynecol Oncol* 1999;73:280-284.

Silver S. ASH Comments to the Centers for Medicare and Medicaid Services on coverage for Erythropoiesis Stimulating Agents (ESAs) filed electronically on April 12, 2007.

Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006;24(19):3187-205.

Stasi R, Brunetti M, Bussa S, et al. Response to recombinant human erythropoietin in patients with myelodysplastic syndromes. *Clin Cancer Res* 1997;3:733-9.

Stasi R, Brunetti M, Terzoli E, et al. Once-weekly dosing of recombinant human erythropoietin alpha in patients with myelodysplastic syndromes unresponsive to conventional dosing. *Ann Oncol* 2004;15:1684-1690.

Steensma DP, Molina R, Sloan J, et al. Phase III study of two different dosing schedules of erythropoietin in anemic patients with cancer. *J Clin Oncol* 2006;24(7):1079-1089.

Stein RS, Abels RI, Krantz SB. Pharmacologic doses of recombinant human erythropoietin in the treatment of myelodysplastic syndromes. *Blood* 1991;78(7):1658-63.

Straus DJ, Testa MA, Sarokhan BJ, et al. Quality-of-life and health benefits of early treatment of mild anemia: a randomized trial of epoetin alfa in patients receiving chemotherapy for hematologic malignancies. *Cancer* 2006;107(8):1909-17.

Stuben G, Thews O, Pottgen C, et al. Recombinant human erythropoietin increases the radiosensitivity of xenografted human tumours in anaemic nude mice. *J Cancer Res Clin Oncol* 2001;127:346-350.

Szczudlo T, Croot C, McKenzie R, et al. Epoetin alfa initiation at Hb 10-11 or Hb <10 g/dL: analysis of safety and efficacy. *J Clin Oncol* 2007;25(18S Part 1 of 2).<sup>(Abs 1962B)</sup> Available at: [www.asco.org](http://www.asco.org)

Terpos E, Mougiou A, Kouraklis A, et al. Prolonged administration of erythropoietin increases erythroid response rate in myelodysplastic syndromes: a phase II trial in 281 patients. *Br J Haematol* 2002;118:174-80.

Thatcher N, De Campos ES, Bell DR, et al. Epoetin alpha prevents anaemia and reduces transfusion requirements in patients undergoing primarily platinum-based chemotherapy for small cell lung cancer. *Br J Cancer* 1999;80(3-4):396-402.

Thews O, Kelleher DK, Vaupel P. Erythropoietin restores the anemia-induced reduction in cyclophosphamide cytotoxicity in rat tumors. *Cancer Res* 2001;61:1358-1361.

Thompson JA, Gilliland DG, Prchal JT, et al. Effect of recombinant human erythropoietin combined with granulocyte/macrophage colony-stimulating factor in the treatment of patients with myelodysplastic syndrome. *Blood* 2000;95:1175-9.

Toy P, Popovsky MA, Abraham E, et al. Transfusion-related acute lung injury: definition and review. *Crit Care Med* 2005;33:721-726.

- Tuma RS. Amid health concerns, FDA reviews safety of several heavily used anemia drugs. *J Natl Cancer Inst* 2007;99(10):746-7, 753.
- Turner R, Anglin P, Burkes R, et al. Epoetin alfa in cancer patients: evidence-based guidelines. *J Pain Symptom Manage* 2001 Nov;22(5):954-65.
- Vadhan-Raj S, Mirtsching B, Charu V, et al. Assessment of hematologic effects and fatigue in cancer patients with chemotherapy-induced anemia given darbepoetin alfa every two weeks. *J Support Oncol* 2003;1:131-38.
- Vadhan-Raj S, Skibber JM, Crane C, et al. Randomized, double-blind, placebo-controlled trial of epoetin alfa (Procrit) in patients with rectal and gastric cancer undergoing chemo-radiotherapy (CT/RT) followed by surgery: early termination of the trial due to increased incidence of thrombo-embolic events (TEE). *Blood* 2004;104(pt 1):797a. (Abst 2915)
- Vansteenskiste J, Pirker R, Massuti B, et al. Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. *J Natl Cancer Inst* 2002;94:1211-20.
- Vansteenkiste J, Tomita D, Rossi G, Pirker R. Darbepoetin alfa in lung cancer patients on chemotherapy: a retrospective comparison of outcomes in patients with mild versus moderate-to-severe anaemia at baseline. *Support Care Cancer* 2004;12(4):253-62.
- Vaupel P, Mayer A, Hockel M. Impact of hemoglobin levels on tumor oxygenation: the higher, the better [Review]? *Strahlenther Onkol* 2006;182(2):63-71.
- Vectibix™ (panitumumab) Prescribing Information. Amgen Inc. Thousand Oaks, California. June 2007.
- Vogelzang NJ, Breitbart W, Cella D, et al. Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey. *Semin Hematol* 1997;34(3 Suppl 2):4-12.
- Wallvik J, Stenke L, Bernell P, et al. Serum erythropoietin (EPO) levels correlate with survival and independently predict response to EPO treatment in patients with myelodysplastic syndromes. *Eur J Haematol* 2002;68:180-6.
- Waltzman RJ, Croot C, Justice GR, et al. Randomized comparison of epoetin alfa (40,000 U weekly) and darbepoetin alfa (200 µg every 2 weeks) in anemic patients with cancer receiving chemotherapy. *Oncologist* 2005;10(8):642-650.
- Wang Q. Hematologic outcomes of epoetin-alfa treated cancer patients based on initial intervention of Hb <10 v. Hb 10-11 g/dL: results from a prospective observational study. *J Clin Oncol* 2007;25(18S Part 1 of 2). (Abs 19542) Available at: [www.asco.org](http://www.asco.org)
- Werber Y. Amgen Inc (AMGN): It all comes down to the final CMS NCD decision - cardiorenal panel might not be nearly as bad as ODAC. Citigroup Research Report. North America: Citigroup Global Markets Inc.: May 25, 2007.
- Westenfelder C, Baranowski RL. Erythropoietin stimulates proliferation of human renal carcinoma cells. *Kidney Int* 2000;58:647-657.
- Westphal G, Niederberger E, Blum C, et al. Erythropoietin and G-CSF receptors in human tumor cells: expression and aspects regarding functionality. *Tumori* 2002;88:150-159.
- Whitaker BI, Sullivan M. The 2005 nationwide blood collection and utilization survey report. Department of Health & Human Services, pp. 31-32, 51-53. Available at: <http://www.hhs.gov/bloodsafety/2005NBCUS.pdf>. Accessed June 5, 2007.

Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, et al. A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment. *Health Technol Assess* 2007;11(13). Available at: [http://www.hta.ac.uk/ProjectData/3\\_project\\_record\\_published.asp?PitId=1442](http://www.hta.ac.uk/ProjectData/3_project_record_published.asp?PitId=1442)

Winearls C, Oliver D, Pippard M, Reid C, Downing M, Cotes P. Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic dialysis. *Lancet* 1986;2:1175-8.

Winkelmann JC, Penny LA, Deaven LL, et al. The gene for the human erythropoietin receptor: Analysis of the coding sequence and the assignment to chromosome 19p. *Blood* 1990;76:24-30.

Witzig TE, Silberstein PT, Loprinzi CL, et al. Phase III, randomized, double-blind study of epoetin alfa versus placebo in anemic patients with cancer undergoing chemotherapy. *J Clin Oncol* 2005;23(12):2606-2617.

Wright JR, Ung YC, Julian JA, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. *J Clin Oncol* 2007;25(9):1027-32.

Yasuda Y, Fujita Y, Matsuo T, et al. Erythropoietin regulates tumour growth of human malignancies. *Carcinogenesis* 2003;24:1021-1029.

Yellen SB, Cella DF, Webster K, et al. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage* 1997;13(2):63-74.

T.O.P.S.

## TENNESSEE ONCOLOGY PRACTICE SOCIETY

June 7, 2007

President:

Patrick B. Murphy, M.D.  
(Franklin)

Vice President:

Benton M. Wheeler, M.D.  
(Memphis)

Secretary-Treasurer:

Elaine Griffin Galindez, M.D.  
(Hixson)

Immediate Past President:

Ruth T. Young, M.D.  
(Franklin)

At-Large Members:

W. Charles Penley, M.D.  
(Nashville)

Anthony A. Meluch, M.D.  
(Nashville)

Medicare CAC Representative

Charles McKay, M.D.  
(Nashville)

Steve Phurrough, MD, MPA  
Director, Coverage and Analysis Group  
Centers for Medicare and Medicaid Services  
Department of Health and Human Services  
Mailstop: C1-13-18  
7500 Security Blvd.  
Baltimore, MD 21244

Re: Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for Non-Renal Disease Indications (CAG-00383N).

Dear Dr. Phurrough:

As President of the Tennessee Oncology Practice Association, I represent over 100 practicing oncologists and their groups in the state of Tennessee. I am writing on behalf of them, and more importantly on behalf of the patients for whom we care, regarding the Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for the Non-Renal Disease Indications (CAG-00383N).

We have followed with great interest the recent publications suggesting a possible safety signal for the ESA class. Our evaluation shows that of the studies published in the 7 publications (5 in oncology patients) with safety concerns, ESAs were used in a method that is outside the norm for how these agents are used in the community oncology setting. These studies either investigated the use of ESAs with a high hemoglobin target or investigated the use in patients with cancer not undergoing chemotherapy and near the end of life, neither of which is a standard practice in community oncology. The standard of care in the community is to follow accepted national clinical guidelines such as those published by ASCO and NCCN.

Upon review of the significant literature, we are unable to find any suggestion of a safety signal when these agents are used while following these accepted clinical guidelines. There is actually a large literature, including pooled analysis, that would strongly suggest that these agents are indeed safe when used according to widely accepted guidelines. In view of these data, it seems less than reasonable to extrapolate a safety signal seen in an experimental setting that does not apply to current clinical practice. Our assessment shows that the limitations listed in the proposed NCD are not supported by the available science.

In addition, there are aspects of the proposed NCD that appear completely arbitrary. There is no literature to support limiting initiation of ESA to hemoglobin of 9, but there is literature that shows the risk of requiring a transfusion goes up the lower the initiation hemoglobin, with an initiation level of 11 appearing to be optimal. Likewise, there are no data to support an arbitrary 12-week limit to therapy. Review of the 7 publications showing a safety signal does not reveal a relationship between length of exposure to ESA and safety, so we are unable to find a scientific explanation for these recommendations. ESA therapy has been recognized as a standard of care for myelodysplastic syndrome (MDS) by national guidelines (ASCO, ASH, and NCCN) for years. We were unable to identify any safety concerns in any of the MDS literature. It is not clear to us what justification one would propose to change the standard of care for this disease.

As practicing oncologists, we have all experienced a significant improvement in the quality of life for our cancer patients since the advent of ESAs. Anyone who would deny that there is significant improvement in the quality of life of a patient who has an improvement in their baseline hemoglobin from 10 or 11 to 12 has certainly not cared for patients in the oncology setting. These agents make a significant impact on our patients' lives, and we feel that limiting our patients' access to these life-improving agents would be tragic. As oncologists, we spend our entire careers making risk benefit decisions. Based upon our review of the literature and our greater than 10 years of experience, we feel the benefits greatly outweigh the risks to ESA use for the majority of our patients with anemia. To suggest that CMS is better positioned to judge this risk benefit decision is objectionable to our medical professionals.

We ask that your final NCD be based upon the available scientific evidence and allow us to continue to follow our evidence-based national treatment guidelines.

Sincerely,

A handwritten signature in cursive script that reads "Patrick B. Murphy".

Patrick B. Murphy, MD  
President  
Tennessee Oncology Practice Society

*Philip C. Lynch, M.D., S.C.*

867 W. Harper Avenue  
Decatur, Illinois 62526

Telephone (217) 454-1414

June 4, 2007

Ms. Maria Ciccanti, RN  
Lead Analyst  
Centers for Medicare and Medicaid Services  
7500 Security Boulevard  
Baltimore, MD 21244

Dear Ms. Ciccanti:

It has come to my attention that CMS may not continue to cover the administration of erythropoiesis stimulating agents (ESA's) for non-renal disease. I believe that to discontinue this coverage for patients with MDS would be a serious mistake and would ultimately result in the death of patients whose anemia is being controlled by the administration of ESA's.

Sincerely,

  
Philip C. Lynch, M.D.

*pcl-200706june04-mciccanti.doc*

## Member Address

Steve Phurrough, MD, MPA  
Coverage and Analysis Group  
Centers for Medicare and Medicaid Services  
Department of Health and Human Services  
Mailstop: C1-09-06  
7500 Security Boulevard  
Baltimore, MD 21244

RE: Proposed Coverage Decision Memorandum for the Use of Erythropoiesis Stimulating Agents in Cancer and Related Neoplastic Conditions (CAG-00383N)

Dear Dr. Phurrough:

I am Preston H. Dalglish, Jr. M.D., a Medical Oncologist practicing in Maine. I currently see approximately **230** new patients with cancer each year. Additionally I see many patients with anemias of a variety of types. Many of these patients are currently treated with Erythropoiesis Stimulating Agents (ESAs). I have been in practice for ( ---) years, and have personally seen the benefits of these agents on my ability to administer adequate doses of chemotherapy, on the reduction in the need for transfusions and the improvement in the quality of life of my patients with anemias for which ESAs have been traditionally prescribed.

I am well aware of new clinical data suggesting that treating patients with ESAs to hemoglobins over 12 g/dl or hematocrits over 36% may well be deleterious to my patients' health. Still I believe the proposed National Coverage Determination included in the above Memorandum goes far beyond the bounds of good patient care, available science or the legal restrictions on cancer care as listed in Medicare statute.

The Medicare Statute as amended in 1993 by the so called Rockefeller Levin Bill, section 1861(t)(2) of the Social Security Act (42 U.S.C. §1395x(t)(2)) states that CMS must cover anti-neoplastic drugs including supportive medications for which an indication is approved by the FDA, listed as acceptable by approved compendia, or supported by peer reviewed medical literature. The restrictions for coverage included in the proposals of the above Memorandum far exceed any of indications required by statute.

Treatment of anemia due to myelodysplasia with ESAs is standard clinical practice. It is supported by ASCO/ASH guidelines which are strictly evidence based. Additionally MDS is listed as an "accepted" indication in the USPDI Drug Compendium. MDS should not be an exclusion for coverage by CMS. I have several patients who have become transfusion independent as a result of being on ESA's.

The proposal that treatment with ESAs should not be used in patients with anemia and erythropoietin-type resistance due to neutralizing antibodies is completely unrealistic as this assay is not clinically available. This proposal should be rejected.

The proposal that patients being treated with EGFR or VEGF antibodies are not appropriate candidates for ESA therapy is likewise unsupported by evidence based prospective medical literature. This proposal is also inconsistent with FDA labeling and compendia citations and should be rejected.

The proposal that "ESA treatment is only reasonable and necessary under specified conditions for the treatment of anemias in those types of cancers which the presence of erythropoietin receptors on either normal tissue/cell lines or malignant tissue/cell lines has been reported in the literature" is completely unsupported by evidence based medical literature.

The proposal that ESA therapy should not be initiated unless the hemoglobin/hematocrit is  $< 9$  g/dl or 27% or  $< 10$ g/dl or 30% in those individuals with cardiovascular disease is also contrary to clinical practice and appropriate clinical trials. Further the implication that transfusion of PRBCs is a safer alternative than ESA therapy in this and other clinical situations is an untested hypothesis.

The proposal to limit coverage to 12 weeks per year is completely inconsistent with good clinical practice. Many of my patients are on chemotherapy that goes well beyond 12 weeks. There is clear evidence that these patients require fewer transfusions and have a better quality of life as a result of ESA therapy. Further there is no evidence that ESA use for more than 12 weeks presents a safety risk.

Further the proposal to limit the total four week dose of erythropoietin to 126,000U or darbepoietin to 630 mcG is contrary to FDA labeling as well as ASCO/ASH guidelines. Additionally this proposal does not allow for appropriate dose escalations as recommended in the above cited references.

The statement that "continued use of the drug (ESAs) is not reasonable and necessary if there is evidence of poor drug response (hemoglobin/hematocrit rise  $< 1$  g/dl/ $<3\%$ ) after four weeks of treatment" is again contrary to good clinical practice or evidence based studies. In clinical practice we treat individuals with anemia due to chemotherapy to levels that will avoid the need for transfusion of PRBCs or prevent cardio-respiratory decompensation. Setting artificial standards of an increase in hemoglobin or hematocrit is contrary to proper patient management. Additionally the product labels specifically allow for dose escalations in hypo-responders.

Lastly the proposal that ESAs should only be covered if dispensed in the context of a clinical trial is completely out of bounds. Erythropoietin and darbepoietin are FDA approved drugs and when prescribed in the support of anti-neoplastic therapy or for the treatment of MDS must be covered by CMS according to statute.

In summary, if the current CMS proposal is approved without alteration, I will be forced to support my patients with an increased number of blood transfusions. This change in my practice will be costly to the patients and to the Medicare and Medicaid systems. It will expose patients the potential side-effects of transfusion including iron overload, transfusion reactions, fluid overload and infections. This change in practice will stress an already tenuous national blood supply. Having to travel to get blood transfusions will create a great hardship for patients already burdened with the rigors of chemotherapy and serious diseases. And lastly there is no conclusive evidence that supporting patients with transfusion therapy is better medical care than the current standard of care using ESAs.

Thank you for your attention to my concerns.

Sincerely,

Preston H. Dalglish, Jr., M.D.  
Maine Center for Cancer Medicine  
26 W. Cole Rd.  
Biddeford, ME 04005

Nancy Benoit-Saunders  
Chief Executive Officer

**EXECUTIVE BOARD**

William T. McGraw, PhD  
Executive Past Board President  
Chief Executive Officer  
National Comprehensive Cancer Network

Edward G. Conneise, M.D.  
Board President  
Bayer Research, PA

Christian Downs, MHA, JD  
Board Vice President  
Executive Director  
Association of Community Cancer Centers

Leah Aronoff, RN, MPH, MBA  
Board Secretary  
Nursing Director, University Health Services  
University of Texas at Austin

John L. Blumley  
Board Financial Officer  
Equiscope Capital, LLC

Don Conway, MD  
Board Financial Officer  
Director, The Healthcare Initiative  
Tuck School of Business  
Dartmouth College

Bruce Anny, MD  
Hematology-Oncology Knoxville

Ray A. Beveridge, MD  
Co-Director, Stem Cell Transplant Center  
Inova Fairfax Hospital

Dennda A. Goodman, MD  
Director, Human Cell Therapy Laboratory  
Division of Transfusion Medicine  
and Hematology  
Algo Clinic

Richard D. Carver, M.D.  
Center & Day

The Honorable Phil Hamilton  
Virginia Honor of Delegation  
Sheldon Wechsler, M.D.  
Vascular & Pulmonary

Rene S. Colwell-Daniels, JD, MPH  
Director  
Office of Health Policy and Planning  
Virginia Department of Health

**SCIENTIFIC BOARD**

Lesl Williams, DPH, RN, AOCN  
Chief, Scientific Board of Directors  
University of Texas

MD Anderson Cancer Center  
Houston School of Nursing

Olle W. Wenberg, MD  
Professor, Henry School of Medicine  
Baylor University

David Heston, MD  
Professor

Chief, University Medical System  
Hematology-Oncology Department

Robert M. Willsie, MD, FACP  
Director, Cellular Transplantation  
Rocky Mountain Blood

& Marrow Transplant Program  
Rocky Mountain Cancer Centers

F. Marc Stewart, MD  
Medical Director, SSGA

Professor of Medicine  
University of Washington

Past Hutchinson Cancer Research Center

Richard L. Tweedell, DO, MBA  
Professor of Medicine  
MD Anderson Cancer Center

**EMERGENCY BOARD**

The Honorable Mary T. Christian

John H. Smith, Jr., Co-Secretary  
Chief Development Officer

Paul Hirsch, MD, MPH, EBAN  
Director, Essex House

Paula Vialano-Morgan, BA, MSN, AOCN, EBAN  
Chief Executive Officer  
Oncology Nursing Society

Leo E. Bonds  
Executive Vice President &  
Chief Administrative Officer  
U.S. Oncology

Doris Simonson

April 13, 2007

VIA E-Mail to [CAGinquires@cms.hhs.gov](mailto:CAGinquires@cms.hhs.gov)

Maria Ciccanti, RN  
Centers for Medicare & Medicaid Services  
7500 Security Blvd.  
Mail Stop C1-09-06  
Baltimore, MD 21244-1850

Re: Erythropoiesis Stimulating Agents for Non-Renal Indications: CAG#00383N

Dear Ms. Ciccanti:

Anemia is commonly encountered in malignancies. Anemia may be directly caused by the malignant disease or may be a consequence of the therapy for the disease. Up to 70% of patients with hematologic malignancies may experience anemia and up to 50% of patients with solid tumors may have some degree of anemia after initiation of chemotherapy or combined modality therapy. Anemia may be a direct consequence of the disease or may be due to the toxicities of therapy on the kidneys or bone marrow. Treatments for anemia include transfusion of allogeneic red cells. The risks of transfusion include transmission of diseases but more commonly transfusion reactions including transfusion-related-lung injury (TRALI) and over-transfusion (volume-overload).

Erythropoiesis-stimulating-agents have been available since 1989 and became widely used in the treatment of severe to very mild anemia, first in renal failure and then other conditions. Large, randomized, double-blind cooperative group trials have confirmed the effectiveness of ESAs in reducing transfusion needs and improved quality of life in cancer patients (Witzig, JCO, 2005, 23;2606-17). Recent trials reporting higher mortality in treatment groups with a target hemoglobin level over 12 gm/dL have raised caution concerning the use of erythropoietin and darbepoietin alpha. A recent trial in head and neck cancer patients was stopped early after interim analysis revealed an increased risk of locoregional recurrence. It is important to note the high hemoglobin target and the mean hemoglobin level of 15.4 g/dL in the treatment group after nine weeks of treatment. Much of the recent data remains reported in meetings only or as reports to the FDA so that broad analysis of the data has not been available.

<http://www.fda.gov/medwatch/safety/2007/safety07.htm#Aranesp>

For the many patients experiencing anemia while on chemotherapy for cancer, the benefits of the ESAs remain, and are acknowledged in the FDA alert last updated on 3/9/2007. Access to the ESAs should be preserved for patients undergoing active chemotherapy, and the ability to avoid the largely non-infectious risks of blood transfusions extended. A recent meta-analysis (Ross et al, Clinical Therapeutics, Vol 28, No. 6, p801-831) supported a reduction in transfusions with both erythropoietin alpha and darbepoietin for patients undergoing cancer therapy. In addition to the end-point of number of transfusions, quality of life measures have also demonstrated superiority of intervention with erythropoiesis stimulating agents (Savonijie, The Oncologist, 2006, 11; 206-216).

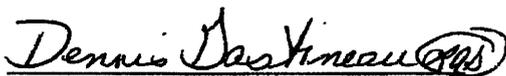
In some disease states, specifically myelodysplastic syndromes, a benefit of ESAs measured by an increase in hemoglobin has been demonstrated (Giraldo et al, Cancer, 2006;107:2807-16). No thrombotic or cardiovascular events were observed in this study

The caution concerning certain uses of erythropoietin is appropriate, although the value to the chemotherapy-treated patient with a hemoglobin less than 12 g/dL remains. More recent trials questioning the benefit of ESAs have had target hemoglobins higher than the original studies ( Henke trial, Lancet 2003; DAHANCA letter, December 1, 2006; FDA Alert 3//9/2007). These trials also addressed the problem of acute chemotherapy induced anemia. The rationale for limiting the target hemoglobin levels to 12 g/dL appears to remain sound.

We find there is compelling evidence of improvement of quality of life and reduction in the need for blood component therapy with the use of ESAs in patients undergoing chemotherapy for malignant diseases. (Bohlius, Cochrane Review, 2007, Issue 1, 1-228). There is additional evidence for the use of ESAs in focused applications such as myelodysplastic syndromes. The efficacy and safety of the the available preparations appear equivalent, and the selection of the agent should be based upon individual circumstances.

We strongly endorse the continued access to these agents by cancer patients as important modalities in treatment of cancer chemotherapy-associated anemia and focused primary bone marrow diseases. Cancer patients and their families should be able to accrue the benefits of these therapies as part of the complex supportive care required for successful cancer treatment.

Respectably submitted:



Dennis A. Gastineau, MD.  
Director, Human Cell therapy Laboratory  
Divisions of Transfusion Medicine & Hematology  
Mayo Clinic  
Rochester, MN

Lori Williams (AS)

Lori Williams, DSN, RN, AOCN  
University of Texas  
MD Anderson Cancer Center  
PAF Scientific Chair  
Houston, TX

F. Marc Stewart (AS)

F. Marc Stewart, MD  
Professor of Medicine, University of Washington  
Fred Hutchinson Cancer Research Center  
Seattle, WA

Roy A. Beveridge (AS)

Roy A. Beveridge, MD  
Co-Director, Stemcell Transplant  
Inova Fairfax Hospital  
Fairfax, VA

Bruce Avery (AS)

Bruce Avery, MD  
Hematology-Oncology Knoxville  
Knoxville, TN

Don Conway (AS)

Don Conway, MD  
Director, The Healthcare Initiative  
Tuck School of Business  
Dartmouth  
Hanover, NH

*Robert M. Rifkin (M.D.)*

Robert M. Rifkin, MD, FACP  
Director, Cellular Therapeutics  
Rocky Mountain Blood & Marrow Transplant Program  
Rocky Mountain Cancer Centers  
Denver, CO

*David Brizel (M.D.)*

Dr. David Brizel, Professor  
Duke University Health System  
Radiation Oncology Department  
Durham, NC

The premier education and advocacy  
organization for the oncology team



Association of Community Cancer Centers

May 31, 2007

**OFFICERS:**

Richard B. Reiling, MD, FACS  
President  
(Charlotte, North Carolina)

Ernest R. Anderson, Jr., MS, RPh  
President-Elect  
(Burlington, Massachusetts)

Luana R. Lamkin, RN, MPH  
Secretary  
(Boise, Idaho)

Al B. Benson III, MD, FACP  
Treasurer  
(Chicago, Illinois)

James C. Chingos, MD, CPE  
Immediate Past President  
(Jacksonville, Florida)

**TRUSTEES:**

Connie T. Bollin MBA, RN  
(Akron, Ohio)

Gabriella Collins, RN, MS, OCN  
(Plattsburgh, New York)

Becky L. DeKay, MBA  
(Shreveport, Louisiana)

Thomas A. Gallo, MS  
(Richmond, Virginia)

Anna M. Hensley, MBA, RT(T)  
(Columbus, Ohio)

George Kovach, MD  
(Davenport, Iowa)

Diane M. Otte, RN, MS, OCN  
(La Crosse, Wisconsin)

Nicholas J. Petrelli, MD  
(Newark, Delaware)

Alan S. Weinstein, MD, FACP  
(Mount Holly, New Jersey)

Thomas L. Whittaker, MD, FACP  
(Indianapolis, Indiana)

**EXECUTIVE DIRECTOR:**

Christian G. Downs, JD, MHA

Steve Phurrough, M.D., MPA  
Coverage and Analysis Group  
Centers for Medicare and Medicaid Services  
Department of Health and Human Services  
Mailstop: C1-13-18  
7500 Security Boulevard  
Baltimore, MD 21244

**RE: Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N)**

Dear Dr. Phurrough:

The Association of Community Cancer Centers (ACCC) appreciates this opportunity to comment on the Centers for Medicare and Medicaid Services' (CMS) proposed decision regarding the Medicare National Coverage Determination for Erythropoiesis Stimulating Agents (ESAs).<sup>1</sup> ACCC is a membership organization whose members include hospitals, physicians, nurses, social workers, and oncology team members who care for millions of patients and families fighting cancer. ACCC's more than 700 member institutions and organizations treat 45% of all U.S. cancer patients.

ACCC is committed to ensuring that cancer patients have access to the entire continuum of quality cancer care, including access to the most appropriate cancer therapies that may improve patients' quality of life while they undergo treatments for this debilitating disease. Therefore, ACCC believes that CMS should not limit access to ESAs for proven FDA indications and compendia listings. Doing so may force them to undergo more lengthy blood transfusions, which may take them out of the community office setting, thus further detracting from their quality of life.

<sup>1</sup> <http://www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?id=203>

104

ACCC does not agree with CMS' decision to enforce clinical limitations on ESA usage, both dosage and time limits, when that decision should be made by both the physicians and the Food and Drug Administration (FDA). When label indications are followed, ESAs can be very beneficial to patients, increasing their quality of life. The FDA has yet to determine what, if any, changes will be made to the label of ESAs after the recommendations of the Oncologic Drug Advisory Committee (ODAC) meeting of May 10, 2007. Because of this, the length of time and hemoglobin levels suggested in the proposal seems arbitrary and without an evidentiary basis.

In addition, we believe CMS has made an error in including anemia of Myelodysplastic Syndrome (MDS) in the non-covered category. MDS is a clonal myeloid disorder which may not evolve into acute leukemia, and it should not be included in this decision.

ACCC recognizes the desire of CMS to control costs in Medicare, which is presumably the reason why limitations on duration patients can be on ESAs was included in the proposal. However, it should be noted that taking a patient off of an ESA treatment in favor of blood transfusions or other treatments may be more costly than leaving patients on the medication.

ESAs can be effective as a maintenance tool, and do not only have to be used to raise hemoglobin levels. Often, ESAs are used to maintain a patients' hemoglobin level at the desired level, and may not raise it the required one gram that CMS has included as a stipulation for continuing treatment. ACCC feels that a better understanding of the disease state is necessary before these actions are taken. The most important aspect of using ESAs for treatment is not to over-rise a patient's hemoglobin level, while at the same time maintaining a level as close to normal as possible. Use of ESAs to accomplish this will thus limit the need for lengthy blood transfusions.

As a result of the proposal by CMS, more patients with MDS and chemotherapy induced anemia will require blood transfusions, which may take them out of the community setting where they are receiving chemotherapy. This will put a serious strain on the nation's blood supply, thus affecting not only cancer and MDS patients, but many other types of patients as well. It will also add an additional strain on hospital resources, with hospitals having to utilize more space and personnel to administer the transfusions.

ACCC feels that the best course of action for CMS to take would be to cover for all indications already on the FDA labels and to also use the guidelines for ESA usage that are already in place from the American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO).

ACCC greatly appreciates this opportunity to comment on the proposed NCD. ACCC supports the proper usage of these drugs and the effects they can have on a patient's quality of life.

We would be pleased to answer any questions regarding these comments. Please contact Matthew Farber at 301-984-9496 ext. 221 if ACCC can be of any assistance as CMS continues to evaluate and develop its approach to coverage of ESAs.

Sincerely,

A handwritten signature in cursive script, appearing to read "Richard B. Reiling".

Richard B. Reiling MD, FACS  
President  
Association of Community Cancer Centers (ACCC)

**Ciccanti, Maria L. (CMS/OCSQ)**

**From:** CMS CAGInquiries  
**Sent:** Tuesday, June 05, 2007 7:29 AM  
**To:** Ciccanti, Maria L. (CMS/OCSQ)  
**Subject:** FW: Public comment

**From:** Richard & Channa [mailto:callcallss@msn.com]  
**Sent:** Tuesday, June 05, 2007 12:22 AM  
**To:** CMS CAGInquiries  
**Subject:** Public comment

Title of NCA/CAL: Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications

Public Comment re: Erythropoiesis Stimulating Agents (ESAs) guidelines

As an employee of Utah Cancer Specialists, and patient care advocate, I am concerned about the proposed erythropoietic stimulating agent (ESA) guidelines under consideration. While I understand the need for proper use of these medications, the proposal falls short of providing the best standard of care recommended by oncology organizations such as NCCN, ASCO and ASH. The current proposals will result in a compromised quality of life for our patients, increased blood transfusion requirements with the associated co-morbidity and risk and, ultimately, prove more costly to society than judicious use of ESAs. Please reconsider these guidelines encouraging physicians to carefully weigh the risk/benefit with patients and allow providers to treat this growing population with the best and most compassionate standard of care.

Chemotherapy-induced anemia is a well-known side effect of myelosuppressive therapy. Furthermore it is quite responsive to ESAs when iron stores, vitamin B12 and folate deficiencies and other underlying processes have been corrected. Holding initiation of ESA until the hemoglobin drops to  $<9\text{mg/dl}$  will delay response and most likely result in transfusion for a greater number of our chemotherapy patients. Most chemotherapy regimens last a minimum of 16 weeks (and many are much longer). Therefore, limiting the covered treatment duration to 12 weeks annually will be inadequate treatment for many of our patients on continued myelosuppressive therapy.

According to the proposed guidelines, the Myelodysplastic Syndrome population will be denied access to any form of ESA under all circumstances. While a portion of the MDS patients will not respond to ESAs, a greater number benefit from these medications; reducing the number of necessary blood transfusions, eliminating the complications of iron overload that results from transfusion, enhanced productivity by limiting time spent in a healthcare facility, and an overall improved quality of life.

We do not dispute the recommendations to discontinue use of the ESAs if the patient is non-responsive to treatment, however:

- The recommended four weeks is an inadequate timeframe in which to evaluate patient responsiveness. Former guidelines allow 12 weeks to determine response. Clearly, four weeks is an irresponsible timeframe.
- The proposed maximum treatment dose is insufficient to provide standard doses within the recommended timeframes. The maximum covered four-week treatment dose is 126,000units of Procrit and 630mcg of Aranesp. At an average dose of 40,000 units of Procrit each week, we would need 160,000 units in four weeks. The average dose of Aranesp is 300mcg per 2 weeks – so the 630mcg would be sufficient.

We encourage you to reconsider the list of specified conditions to include other myeloid and erythroid cancers as well as anemia caused by radiotherapy. Some patients will respond, therefore a trial of an ESA medication seems prudent.

Thank you for your consideration of this request. As a community oncology practice we strive to provide the optimal care to our patients. Please allow us the support we need to continue this practice.

Respectfully,  
 Richard D. Call

EMPLOYEE NAME

06/11/2007

143

# VIRGINIA ASSOCIATION OF HEMATOLOGISTS and ONCOLOGISTS

President:  
Richard Ingram, M.D.  
(Winchester)

June 6, 2007

Vice President/  
Immediate Past President:  
James T. May, III, M.D.  
(Richmond)

Steve Phurrough, M.D., MPA  
Coverage and Analysis Group  
Centers for Medicare and Medicaid Services  
Department of Health and Human Services

Treasurer:  
Attique Samdani, M.D.  
(Richmond)

Mailstop: C1-13-18  
7500 Security Blvd.  
Baltimore, MD 21244

Secretary:  
Patrick J. Byrne, M.D.  
(Fairfax)

RE: Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESA's) for Non-Renal Disease Indications (CAG-00383N)

Board of Trustees:  
David C. Caldwell, M.D.  
(Danville)

Dear Dr. Phurrough:

Robert J. Christie, M.D.  
(Arlington)

The Virginia Association of Hematologists and Oncologists (VAHO) represents over 200 cancer care providers in the Commonwealth of Virginia who are committed to the treatment of cancer and blood-related diseases. VAHO members include hematologist/oncologists who regularly render services to Medicare beneficiaries. The society appreciates this opportunity to provide comments to CMS on the appropriate use of erythropoiesis stimulating agents (ESA's).

Charles L. Maurer, M.D.  
(Fredericksburg)

Of paramount importance to VAHO is to ensure the highest degree of patients' safety and to protect against not only the overuse of these drugs, but their underuse and misuse as well.

Recent research studies reviewed by the oncologic advisory committee of the food and drug administration report and access of serious or life-threatening events associated with the use of ESA's in nonanemic patients in various clinical settings. The food and drug administration has recently issued new warnings regarding the use of ESAS. We would like to comment on the appropriate use of ESA's in light of current scientific evidence.

A recent FDA black box warning cautions clinicians that there is an "increased... risk of death when ESA's are administered to a target hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESA's are not indicated for this population." This statement is mainly based upon an unpublished Amgen study (#20010103) of patients with anemia of cancer (non-myeloid) who were not receiving active anticancer treatment. Few of those patients had hematologic malignancies, and none had myelodysplastic syndrome (MDS).

The present quality of data to extend this FDA warning to patients with hematologic malignancies or MDS does not currently exist. We agree with numerous national organizations including the American Society of Hematology and the American Society of Clinical Oncology that Phase 3 studies need to be initiated to address these issues in patients with both myelodysplastic syndrome and hematologic malignancies.

---

Executive Office: 11600 Nebel Street • Suite 201 • Rockville, MD 20852-2557

PHONE: 301.984.9496 • FAX: 301.770.1949

www.vah-o.org

Below are VAHO's comments concerning appropriate use, treatment targets and duration of use of ESA's for patients with chemotherapy associated anemia and for patients with hematologic malignancies not on chemotherapy.

*Appropriate use of the ESA is for patients with cancer oriented conditions*

**Chemotherapy Associated Anemia**

ESA's may be used as a treatment option for patients with chemotherapy associated anemia. VAHO agrees with several national organizations including the American Society of Hematology's observation that a patient may continue to suffer from anemia for some time following completion of chemotherapy treatment and recommends that coverage of ESA's be continued for treatment of anemia due to chemotherapy for 90 days post chemotherapy. If anemia persists beyond 90 days after completion of chemotherapy, it would be reasonable to reevaluate the anemia to determine if this continues to be a result of the chemotherapy, thereby justifying continuation of ESA treatments, or if another processes is in place.

Maximum treatment duration of 12 weeks per year is grossly inadequate for many patients. Patient receiving chemotherapy with curative intent in the adjuvant setting typically has treatment regimens ranging from 4 to 6 months time. The use of the ESA's both during the time of active chemotherapy and for a period post chemotherapy stretch beyond the recommended maximum treatment duration of 12 weeks per year. In addition, patients with metastatic disease may receive multiple courses of chemotherapy that last for many months.

The proposed exclusion of patients receiving VEGF and EGFR inhibitors is not based on any current clinical evidence. This would preclude treatment with ESAs for many patients with breast, colorectal, and lung cancer without any supporting scientific or clinical data.

**Patients with hematologic malignancies not on chemotherapy**

ESA's may be used as a treatment option for patients with hematologic malignancies who are not on chemotherapy. There is evidence to support the use of the ESA is in patients with anemias associated with low risk myelodysplasia (less than 5% blasts). Myelodysplastic syndromes are a heterogeneous group of hematological malignancies characterized by dysplastic and ineffective hematopoiesis with a variable risk of transformation to acute leukemia. Low risk myelodysplasia with less than 5% blasts can include the following (World Health Organization classification) forms of myelodysplasia:

- Refractory anemia
- Refractory anemia with ring sideroblasts
- Refractory cytopenia with multi-lineage dysplasia
- Refractory cytopenia with multi-lineage dysplasia and ring sideroblasts
- Myelodysplastic syndrome, unclassified
- Myelodysplastic syndrome associated with isolated deletion (5q)

Evidence of effective treatment outcomes is present throughout the medical literature with the use of ESA's in the supportive treatment of patients with myelodysplastic syndromes, specifically those of a low risk score by the IPSS staging system. This evidence is represented in treatment guidelines created by the National Comprehensive Cancer Network (NCCN) which are based on evidence based medical practices.

***Treatment recommendations***

Evidence suggests that transfusion avoidance is better accomplished by early intervention with ESA's. Initiation of therapy at a Hgb level <11g/dL has been shown to be superior to <10 g/dL by every measure in 6 different randomized studies. The use of a Hgb level of <9g/dl as a treatment initiation point is inadequate and not based on current data derived guidelines of therapy. Current data show many of the patients who receive ESA's after Hgb falls below <9g/dl will require transfusions that are otherwise avoidable because their Hgb will continue to fall for several weeks after ESA use is initiated.

The therapeutic goal of therapy should be a level of no higher than 12 g/dL and the dose of the ESA should be modified in accordance with the recent FDA black box warning when the hemoglobin level approaches 12 g/dL.

A "stopping rule" at 4 weeks if a 1g/dl rise in Hgb is not achieved is not consistent with the clinical trial data.

The clinical trials with both ESA agents demonstrate that up to 8 weeks may be required to achieve a 1 g/dl rise.

Dose escalation has been a critical element of most of the clinical trials. A significant number of patients who failed to respond to initial ESA use will respond after administering a single dose 50% higher than the initial dose. Therefore, dose escalation has become part of the accepted standard of care.

VAHO agrees with the current data that ESA's should not be continued after 8 weeks of therapy in the absence of response, assuming the appropriate dose increase has been attempted in the low responders. A response is a rise in hemoglobin of 1 g/dL or greater.

VAHO agrees with concerns that the American Society of Hematology, American Society of Clinical Oncology, and other national oncology groups have concerning the impact on the nations blood supply that CMS's proposal will have due to the increase in transfusions that will be necessary in these patient populations. Therefore, the impact on the blood supply should be taken into account when determining changes in the use of these products.

Of paramount importance to practicing hematologists and oncologists such as me, is to ensure the highest degree of patients' safety while offering sound the medical care that is founded in clinical research and clinical experience.

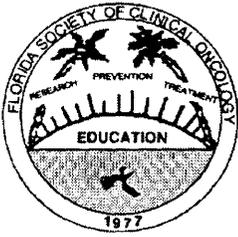
Steve Phurrough, M.D., MPA  
June 6, 2007  
Page 4

On behalf of VAHO, I greatly appreciate this opportunity to comment on the proposed NCD. I humbly urge CMS to listen to practicing physicians such as myself and to work with state societies such as VAHO along with the national organizations of practicing hematologists and oncologists to form working groups that can properly analyze available data and effectively apply this to our patient population. This will ensure data-driven high quality medical practice for our Medicare beneficiaries.

Sincerely,

A handwritten signature in black ink, appearing to read "Richard M. Ingram". The signature is stylized, with a large, looped "R" and a distinct "A" at the end.

Richard M. Ingram, M.D.  
President  
Virginia Association of Hematologists and Oncologists



May 21, 2007

Steve Phurrough, MD, MPA  
Director, Coverage and Analysis Group  
Centers for Medicare and Medicaid Services

[CAGinquiries@cms.hhs.gov](mailto:CAGinquiries@cms.hhs.gov).

**RE: Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N).**

On behalf of the 400 members of the Florida Society of Clinical Oncology, I am writing to convey our comments and concerns regarding the Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for Non-Renal Disease Indications (CAG-00383N).

We recognize that there are safety concerns regarding the use of ESAs. However, we feel that the proposed coverage decision inappropriately restricts use of ESAs because a number of the proposals are not supported by scientific data, rely on poor quality data, or are in conflict with expert scientific analysis. In particular, the proposed policy does not take into consideration recommendations made by FDA's Oncology Drug Advisory Committee during a May 10th meeting.

We are especially concerned about the exclusion of use of ESAs for treatment of anemia due to myelodysplasia (MDS). There is evidence to support the use of ESAs in a significant number of patients with anemia associated with MDS to decrease the need for blood transfusions. Unfortunately, there are few effective treatment options for MDS. Denial of coverage for ESAs will deprive patients with MDS of an effective therapy for their illness, one on which many of them already depend.

We are also dismayed by other aspects of the coverage decision which are arbitrary, premature, and not based on scientific data. These include the maximum covered treatment duration of 12 weeks per year, which is not adequate either for patients who are undergoing cancer chemotherapy or for those with anemia due to MDS. Likewise, the maximum four week dosage limits are inadequate, as is the limit of four weeks of treatment while awaiting response.

The State of Florida has a very large population of Medicare beneficiaries. Coverage decisions like this one affect a very significant portion of our patients. Our State Society is committed to ensuring that cancer patients have access to the entire continuum of quality cancer care, including access to the most appropriate cancer therapies in the most appropriate settings. We believe that underuse of appropriate therapies is as detrimental as overuse. We feel that it is vitally important for coverage decisions like this one to be guided by the best available scientific evidence to ensure the highest degree of patient access and safety, and not to be based solely on economic considerations.

Sincerely,

Robert Cassell, MD, FLASCO President

FLORIDA SOCIETY OF CLINICAL ONCOLOGY  
3709 W. Jetton Ave – Tampa, FL 33629  
Tel: 813.253.0541 – Fax: 813.254.5857

**MartiNelsonCancerFoundation**

1520 East Covell Blvd. B5#103  
Davis, California 95616

June 12, 2007

Steve Phurrough, MD, MPA  
Director, Coverage and Analysis Group  
Centers for Medicare & Medicaid Services  
Mail Stop C1-09-06  
7500 Security Boulevard  
Baltimore, MD 21244

RE: National Coverage Analysis for Erythropoiesis Stimulating Agents (ESAs) for  
Non-Renal Disease Indications (CAG-00383N)

Dear Dr. Phurrough:

The Marti Nelson Cancer Foundation is a nonprofit, 501(c)3, cancer patient advocacy organization founded in 1994. Our work focuses on the needs of individual cancer patients seeking effective treatment and also on broader issues related to clinical trials, experimental medicine and the drug approval process. Our work is performed free of charge by unpaid volunteers, and we have no financial or professional ties to the companies that manufacture or market erythropoiesis stimulating agents (ESAs). We are submitting this letter in response to your request for public comments on your proposed decision memorandum, CAG-00383N.

First, we would like to offer some general observations and recommendations for your consideration, and then provide you with additional specific questions and comments.

**Safety and Context Considerations in ESA Use**

Although consumers expect pharmaceutical products prescribed by their physicians to be both safe and effective, the unfortunate reality is that drugs frequently do not provide the benefit expected. For the most part, it is not technologically possible at this time to determine in advance which patients will benefit and which will not benefit from any given drug. Adjustments to complex treatment regimens, or cycling from a first drug to a second upon futility of the first, are generally empirical decisions based on physician judgment and patient experience.

All drugs involve some risk, and each day physicians and patients must make decisions about the probability of benefit versus the risk of harm. A fully informed decision to use or not to use a particular drug can only be made when all available information is objectively presented to physicians and patients for consideration within the context of a patient's individual situation. The choices that may be made about risk tolerance may vary significantly from one individual to another depending on circumstances and priorities of the persons involved. One person may be willing to take a known risk in

64

## **MartiNelsonCancerFoundation**

exchange for the possibility of an improvement in the quality or quantity of life while another person may find any new risk to be intolerable.

As we have helped cancer patients select and enroll in clinical trials, or gain access to experimental medicine via compassionate access or expanded access programs, we have met many people willing to risk early death for a possibility of extended life. We have also met many people who place far greater value on the quality of their remaining period of life than they do on its absolute length. However, it is incorrect to assume that a person in poor health, or given a diagnosis such as metastatic cancer, will necessarily be willing to tolerate significantly more risk from a pharmaceutical product than a person who is in relatively good health. The varying values and priorities of different individuals are difficult to quantitatively describe through academic research, but their reality should be considered and respected by CMS as it finalizes its coverage decisions.

Our recommendation is that CMS consider the variety of individual patient perspectives in its assessment of the reasonable and necessary uses of ESAs, including the following:

- Safety is not an absolute value but is a relative value. The risk of harm may be quantified with respect to a given statistical sample, but current knowledge does not allow prediction of absolute risk, nor absolute benefit, for an individual person.
- Patients benefit from a medical system that enables exercise of judgment by individual physicians and patients.
- Clinical practice is best guided by the circumstances and values of each patient and the judgment of each treating physician rather than by reimbursement policy, as long as sufficient and objective data is available for fully informed decision making.

### **Over-Promotion Should Not Be Followed by Under-Utilization**

At the May 10, 2007 meeting of the FDA's Oncologic Drugs Advisory Committee, many aspects of ESA use were analyzed and discussed, including briefly the issue of direct-to-consumer advertising and its impact on the perception of these products by both physicians and patients. Many believe that inappropriate advertising drove some of the demand for these products in the past, and may have provided a false impression of their safety and effectiveness in certain applications; however, this history must not influence the objectivity of the essential, current analysis of the optimal use of these important biologics.

The FDA is now investigating the circumstances under which certain particularly aggressive advertisements were allowed to run. The May 18, 2007 issue of *The Cancer Letter* quoted Richard Pazdur, MD., FDA's Director of the Office of Oncology Drug Products, "We are looking into this whole issue of why these ads were allowed to go on, and I think that the FDA is responsible for giving the American public as well as the

## **MartiNelsonCancerFoundation**

review staff that sits here the reasons why these ads were allowed to go on.” Because the problem of over-promotion of drugs through inappropriate pharmaceutical product advertising is broader than the ESA category, we have requested additional information about past and current FDA practices regarding drug advertising. We look forward to receiving the requested information and to learning more in the near future about the status of the current internal FDA review.

Balancing our concern about over-promotion of ESAs in the past is our equally strong concern about a potential over-correction leading to inappropriately restrictive reimbursement policies that will deny patients the benefit of products that are safe and effective for their needs and circumstances. Objective analyses of data from well-designed, controlled clinical trials have demonstrated the safety and efficacy of ESAs for cancer patients in a wide variety of clinical circumstances.

Despite the newer safety signals, and *in vitro* or animal data that raise theoretical concerns, ESA use clearly obviates some of the risks of red blood cell transfusion for many patients and reduces demand on hospital facilities and finite blood supplies. Additional benefits are clearly documented by years of clinical evaluation and widespread use in a heterogeneous population. Patients will not be well served if these benefits of treatment are denied them in an aggressive attempt to limit unrelated, inappropriate use of ESAs.

We are also concerned about the impact that overly conservative CMS policies may have on the for-profit health insurance industry. We recommend that CMS take the following into consideration:

- Despite significant differences in the population characteristics of their customer bases versus the populations covered by CMS, many health insurance companies are likely to view the CMS final decision memorandum as an opportunity to excessively reduce coverage for ESA use, thereby improving their overall corporate financial performance. When financial stakes are high, even well-intentioned professionals can make the wrong decisions. Thus, we believe it is important for CMS to document the evidentiary basis for, and limitations of, each reduction in coverage it makes from its recent historical policies.

### **FDA Mandate Versus CMS Mandate**

We acknowledge the differences between the mandate of FDA to make marketing approval decisions based on the safety and efficacy of a drug in a specified indication, and the mandate of CMS to establish coverage policy based on a determination of reasonable and necessary use of a drug in the CMS-covered population. Thus, it may be logical that objective analysis of all available data may lead to the establishment of coverage parameters by CMS that are not congruent with the FDA-approved label of a given drug.

## **MartiNelsonCancerFoundation**

However, the final parameters determined by CMS may be significantly influenced by which of two alternative starting assumptions guide its analysis. One can begin with the assumption that an ESA safety signal in a given patient population, treated in accordance with a specific regimen, should be extrapolated to all other uses of ESAs until and unless the drugs are proven safe for each indication and regimen. Alternatively, one can begin with the assumption that ESAs are safe when used as approved for use by the FDA, in the absence of clinical evidence to the contrary, for each indication, regimen, or patient population of potential concern.

We recommend that CMS coordinate its analysis very closely with the FDA's ongoing assessment of ESA safety and consider this issue in three parts.

- First, we recommend that CMS continue to provide coverage for use of ESAs within the parameters of the FDA approved label until and unless data confirm safety problems arising from ESA use in any indication, regimen or patient subpopulation currently within the parameters of the FDA-approved label.
- Second, for indications, regimens or subpopulations that are outside the FDA-approved label parameters and within which clear safety signals have arisen, we recommend that CMS withdraw coverage until and unless safety is established through controlled clinical trials.
- The more difficult third category are those indications, regimens and subpopulations currently outside the parameters of the FDA label but within which significant safety signals have not been seen. Our recommendation in these cases, an example of which is myelodysplastic syndrome, is that CMS weigh the preponderance of the evidence and continue to provide coverage where clinical data demonstrate patient benefit and simultaneously establish incentives and mechanisms whereby new clinical data can be gathered on both the safety and efficacy of ESAs in these applications.

### **Specific Questions and Comments**

Quality of Life Issues. Despite the difficulty in objectively proving quality of life benefits from ESA use, large numbers of patients and physicians believe that such benefits are objectively real. Some might argue that many years of advertising have led people to expect a subjective benefit, and therefore the placebo effect is a significant factor in this perception. On the other hand, it is an objective fact that ESA use raises hemoglobin levels for most patients; the symptoms of anemia correlate with lower hemoglobin levels; and subjective experiences such as fatigue are correlated with other clinical signs of anemia.

CMS may be able to provide incentives to accelerate the accumulation of sufficient objective data to define the specific circumstances, if any, under which ESA use provides quality of life benefits in its beneficiary population.

## **MartiNelsonCancerFoundation**

Concomitant Factors. CMS Proposes that ESA treatment is not reasonable and necessary for beneficiaries with any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis. Obviously, the specified conditions may occur in a patient who is also receiving chemotherapy. In such a situation, it may not be practical to reach firm conclusion about cause and effect relationships among clinical findings, treatment regimens, and anemia. Does CMS intend to provide a mechanism for coverage of ESA use by patients undergoing chemotherapy whose clinical condition and anemia results from a combination of causes including the chemotherapy treatment?

Myelodysplasia. We are aware that CMS has received many comments on the value of ESA use by these patient populations. Others can provide arguments stronger than ours on this topic, but we add our voice to the suggestions that CMS reconsider denying coverage for ESA use in this indication. Use in myelodysplasia appears to be one of the more compelling off-label uses for ESAs and we do not believe patients should be denied access to the potential benefit of these agents while waiting for the accumulation of additional data to substantiate or contradict a presumption of safety and efficacy.

Patients in Transition. We encourage CMS to consider in more detail the determination of the clinical point of transition between chemotherapy-induced anemia and anemia of cancer. Our view is that this is a good example of a situation that requires reliance on the judgment of a physician treating an individual patient. There is a risk that the current proposal would deny patients beneficial access to ESAs who have completed a chemotherapy regimen but have not yet recovered from chemotherapy-induced anemia.

ESA Use with Antibodies. We are not aware of clinical data to support a theory that risks of ESA are increased in patients undergoing treatment with anti-angiogenesis agents such as bevacizumab, or antibodies directed against the EGF receptors such as cetuximab. Since most patients who receive these therapies are also treated with chemotherapy, elimination of coverage for these regimens is a surprising component of the CMS proposal that should not be implemented lightly.

We encourage CMS to coordinate its work with FDA to seek unpublished data from each of the companies that manufactures or markets antiangiogenesis or EGF receptor-targeted agents (both biologics and drugs). We recommend revision of your proposal to eliminate reference to these agents as a basis for denying coverage for ESA use until and unless specific safety signals emerge.

Unresolved Biological Questions. We encourage you, perhaps in collaboration with FDA and NCI, to offer incentives to more rapidly and completely address the remaining preclinical, biological questions regarding ESA receptors, possible mechanisms of tumor promotion, and a potential role for ESAs in stimulation of angiogenesis. Much of the available information is not of sufficient quality for a regulatory process. If the existing data support exaggeration of the potential risks of ESAs, then patients are harmed by under-use in certain circumstances. If the existing data incompletely address a real and serious risk to certain patients undergoing certain treatment regimens, then continued

## **MartiNelsonCancerFoundation**

ambiguity can only harm those patients. Conducting relevant experiments, with high-quality, validated reagents, to thoroughly address these fundamental questions should be a priority for everyone involved in the production, marketing, use and regulation of ESAs.

Initiation of Dosing. Do clinical data support the contention that ESAs would be effective in raising hemoglobin concentration to a level sufficient to avoid the need for red blood cell transfusion, if initiation of dosing is delayed until hemoglobin concentrations drop to the levels specified by the CMS proposal (<9 g/dl or <10g/dl)?

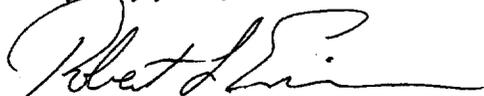
Duration of Treatment. What clinical data were used to determine the maximum proposed covered treatment duration of 12 weeks/year? Would this maximum be applied to a patient who must initiate two chemotherapy regimens within the same calendar year? What clinical data were used to determine the proposed maximum covered 4 week treatment doses? We suggest that any specification of a maximum covered dose should provide the treating physician with the latitude to adjust the dose based on the weight of the patient and other relevant patient characteristics.

### **Additional Data and Clinical Trials**

Gaps in knowledge and inadequate clinical data limit objective understanding of some important biological and clinical consequences of ESA use in the complex variety of disease types, stages, and patient populations in which they historically have been used. Additionally, a range of conflicting conclusions about relative risk and benefit of ESA use in various indications can be supported by reference to conflicting clinical trial results and by extrapolation of results from specific clinical trial settings to other, different clinical situations. Clearly more information would be beneficial, and for individual physicians and patients to make optimal decisions, access to complete and objectively obtained and analyzed data is essential.

We question the practicality of requiring that all future use of ESAs by CMS beneficiaries occur in the context of clinical trials. The additional cost and administrative burdens of designing, enrolling and administering clinical trials for such a large number of participants would probably result in insurmountable treatment access barriers for many patients who would otherwise benefit from using ESAs. However, we encourage CMS to work with the FDA, the NCI and the companies that manufacture and market ESAs to identify the highest priority, addressable clinical questions, and establish the necessary incentives to accelerate the pace of data development.

Very truly yours,



Robert L. Erwin  
President  
Marti Nelson Cancer Foundation

*Robert Long*



June 12, 2007

Steve Phurrough, MD, MPA, CPE  
Director, Coverage and Analysis Group  
Office of Clinical Standards and Quality  
Centers for Medicare and Medicaid Services  
Department of Health and Human Services  
Mail Stop: C1-09-06  
7500 Security Boulevard  
Baltimore, Maryland 21244

Dear Dr. Phurrough:

Several months ago a group of expert physicians, academic researchers, and advocates developed an independent report on the future of drug safety. The principles asserted in the resulting document “Drug Safety and Drug Efficacy: Two Sides of the Same Coin” ([www.focr.org/drugsafetyreport.htm](http://www.focr.org/drugsafetyreport.htm)) are very relevant to current concerns surrounding erythropoietin stimulating agents (ESAs).

At the level of medical practice, safety and efficacy are always considered together by the treatment professional in the context of a patient’s specific circumstances and preferences. The regulatory process should reflect this essential balance that is fundamental to all medical decision-making.

Just as this committee concluded that drug safety decisions must be driven by scientific and clinical evidence, so too should coverage decisions made by the Centers for Medicare and Medicaid Services (CMS). While we agree that caution must be taken with the use of ESAs, we are concerned with the lack of clinical evidence to support several conditions of the CMS Proposed Decision Memorandum for ESAs (CAG-00383N). Areas of particular concern include:

- The use of ESAs in conjunction with anemia of myelodysplasia would be non-covered
- Maximum covered treatment duration would be 12 weeks/year

- Hemoglobin/hematocrit levels immediately prior to initiation of dosing for the month should be <9 g/dl/27% in patients without known cardiovascular disease and <10 g/dl/30% in patients with documented symptomatic ischemic disease that cannot be treated with blood transfusion.
- The hypothesis that ESA interaction with erythropoietin receptors drives tumor growth
- The use of ESAs with certain treatment programs that include chemotherapy and biological agents would be non-covered

In all treatment decisions medical professionals and patients must weigh both the benefits and risks associated with a particular treatment. Clinical evidence supports the use of ESAs in the treatment of anemia of MDS. Numerous clinical studies have been conducted demonstrating the benefit of ESA treatment for MDS patients in reducing blood transfusions.<sup>1</sup> Furthermore, a long-term study of MDS patients treated with ESAs and granulocyte-colony stimulating factor revealed no difference in overall survival or risk of AML development in ESA-treated patients compared to data from untreated patients.<sup>2</sup> In addition, the evidence for continued coverage of ESAs in MDS patients was supported at a May 10, 2007 FDA Oncology Drugs Advisory Committee meeting when OODP Director, Dr. Richard Pazdur, stated, “Those are two different things. I do not want them [MDS patients] to get swept away with this. We will discuss this with our colleagues at CMS to make sure that does not occur.”<sup>3</sup>

Due to the fact that the duration of chemotherapy treatment often exceeds 12 weeks, the clinical rationale for this proposed coverage decision is not clear. Medical societies have recognized this in stating that the duration of ESA therapy may need to be up to 90 days post-chemotherapy with potentially longer durations based on individual circumstance.<sup>4</sup>

While ESA should not be used to achieve high hemoglobin levels, the proposal to restrict coverage to patients with levels less than 9.0 g/dL (in patients without known cardiovascular disease) is not clearly supported by clinical evidence. The goal of treatment with ESAs is to prevent the need for blood transfusions in anemic patients. Not only is the proposed coverage restriction not consistent with the approved FDA label and guidelines from major professional societies,<sup>5</sup> but it could negate the treatment goal

---

<sup>1</sup> Balducci, L. Transfusion independence in patients with myelodysplastic syndromes: impact on outcomes and quality of life. *Cancer* 106(10); May 15, 2006: 2087-94

<sup>2</sup> Jadersten M, et. al. Long-term outcome of treatment of anemia in MDS with erythropoietin and G-CSF. *Blood* 106(3); Aug 1, 2005: 803-11

<sup>3</sup> Pazdur, R. Comments from United States Food and Drug Administration Oncology Drugs Advisory Committee on May 10, 2007

<sup>4</sup> American Society of Hematology. ASH Statement on Medicare Proposed National Coverage Policy on Erythropoiesis-Stimulating Agents (ESAs). Available at: <http://www.hematology.org/policy/news/05182007.cfm>. Accessed June 7, 2007.

<sup>5</sup> Rizzo, J.D. et. al. Use of Epoetin in Patients With Cancer: Evidence-Based Clinical Practice Guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *J Clin Oncol* 20(19) Oct 1, 2002: 4083-4107

giving many patients no other options than to receive higher risk transfusions for treatment of chemotherapy associated anemia.

It appears that some of the proposed CMS coverage decision relies heavily on the hypothesis that erythropoietin receptor (EPO-R) activation by ESAs drives tumor growth. There is little scientific and clinical evidence for this hypothesis. Further examination of the role of EPO-R in malignant human cells is warranted at this point, but the role of EPO-R in human tumor growth remains speculative at this time.<sup>6</sup>

There is no medical evidence that supports restricting the use of ESAs in combination with certain chemotherapy regimens. Epidermal growth factor receptor (EGFR) inhibitors and anti-angiogenic agents are often used in combination with myelosuppressive therapy, which is well known to result in anemia. Studies that specifically demonstrate ESA interference with EGFR signaling are not available. In addition, preclinical and clinical data regarding the direct contribution of exogenous erythropoietin to angiogenesis is purely speculative.<sup>7</sup>

We appreciate the opportunity to share our concerns with you. As a group of physicians and advocates, we have focused our attention on the need for a rigorous, scientific foundation on which to base benefit-risk decisions. We ask that CMS do the same and wait to consider the FDA final decisions before completing the National Coverage Decision for the use of ESAs.

Sincerely,

**Robert C. Young, M.D.** (*Drug Safety Committee Chair*) President, Fox Chase Cancer Center, Philadelphia, PA

**Edward J. Benz, Jr., M.D.** President, Dana-Farber Cancer Institute, Boston, MA

**William P. Bro,** President and Chief Executive Officer, Kidney Cancer Association, Evanston, IL

**Michael A. Caligiuri, M.D.** Director, Comprehensive Cancer Center The Ohio State University James Cancer Hospital & Solove Research Institute, Columbus, OH

**Bruce A. Chabner, M.D.** Clinical Director, Massachusetts General Hospital Cancer Center, Boston, MA

**William S. Dalton, Ph.D., M.D.,** President, Chief Executive Officer and Center Director, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

---

<sup>6</sup> Osterborg A, et. al. Preclinical studies of erythropoietin receptor expression in tumor cells: Impact on clinical use of erythropoietic proteins to correct cancer-related anemia. *Eur J Cancer*. 2007;43:510-519

<sup>7</sup> Ribatti, D. et. al. Erythropoietin/erythropoietin receptor system is involved in angiogenesis in human neuroblastoma. *Histopathology*. 50(5); Apr 2007: 636-41.

**G. Denman Hammond, M.D.** Founder & Trustee, National Childhood Cancer Foundation,  
Arcadia, CA

**Paul J. Limburg, M.D., M.P.H.** Associate Professor of Medicine, Division of Gastroenterology  
and Hepatology, Mayo Clinic College of Medicine, Rochester, MN

**H. Kim Lyerly, M.D.** Director, Duke Comprehensive Cancer Center, Durham, NC

**Richard L. Schilsky, M.D.** Associate Dean for Clinical Research, University of Chicago  
Pritzker School of Medicine, Chicago, IL

**Ellen V. Sigal, Ph.D.** Chairperson and Founder, Friends of Cancer Research, Washington, DC

**Jerome W. Yates, M.D., M.P.H.** National Vice President for Research, American Cancer  
Society, Atlanta, GA

June 13, 2007

***BY ELECTRONIC DELIVERY***

Steve Phurrough, MD, MPA  
Coverage and Analysis Group  
Centers for Medicare and Medicaid Services  
Department of Health and Human Services  
Mailstop: C1-12-28  
7500 Security Blvd.  
Baltimore, MD 21244

**Re: Proposed Decision Memorandum for Erythropoiesis Stimulating Agents (ESAs) for Non-Renal Disease Indications (CAG-00383N)**

Dear Dr. Phurrough:

The Biotechnology Industry Organization (BIO) appreciates this opportunity to comment on the Centers for Medicare and Medicaid Services' (CMS) Proposed Coverage Decision Memorandum for the Use of ESAs in Cancer and Related Neoplastic Conditions (hereinafter "Proposed NCD"). BIO is the largest trade organization to serve and represent the biotechnology industry in the United States and around the globe. BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers, and related organizations in the United States. BIO members are involved in the research and development of health care, agricultural, industrial, and environmental biotechnology products. In particular, many of our members are involved in the research and development of cancer therapies and play a critical role in delivering treatments that both prolong life and reduce the burden of disease for cancer patients worldwide.

In the Proposed NCD, CMS proposes a series of broad coverage restrictions on both the Food and Drug Administration (FDA) approved uses and off-label uses of ESAs in cancer-related anemia. BIO has a strong interest in this matter because CMS' proposal could establish a precedent that affects Medicare patient access to a wide range of innovative drug and biological therapies on a national basis. Such a policy approach, if more broadly adopted by CMS, could have far-reaching implications for other patient populations and treatments of other serious and life-threatening diseases.

Given the extensive comments submitted by practicing oncologists and other relevant stakeholders, BIO is concerned that the Proposed NCD could curtail legitimate, medically appropriate uses of FDA-approved ESA therapy that are supported by the scientific evidence and widely accepted clinical practice guidelines. Specifically,



PRINTED ON  
RECYCLED PAPER

18

clinical experts in the oncology community have questioned the completeness and rigor of CMS' review of the scientific evidence upon which the agency's coverage proposals are based. As a general principle, BIO strongly urges CMS to strictly follow sound principles of evidence-based medicine in formulating coverage policies and ensure that any coverage limitations on ESAs are firmly grounded in the available clinical evidence. BIO is also concerned that, based upon CMS' review of the evidence, the agency appears to be substituting its own conclusions regarding the safety and effectiveness of approved uses of ESAs for those of FDA. BIO urges CMS to acknowledge the important role of the FDA and its experts in evaluating the safety and effectiveness of approved indications of drugs and biologicals. Therefore, CMS should delay finalizing the Proposed NCD until after the FDA has completed its current clinical review of the safety and effectiveness of ESA therapy. Finally, BIO requests that CMS ensure that its coverage policies do not interfere with the ability of practitioners to make patient-centered treatment decisions, especially in oncology, and that CMS abide by the statutory protections for anti-cancer therapy.

**I. Medicare Coverage Decisions on Drugs and Biologicals Should Be Firmly Supported by the Scientific Evidence.**

BIO recognizes CMS' statutory authority to provide Medicare coverage only for those health care items and services that the agency determines are reasonable and necessary for the diagnosis or treatment of illness or injury.<sup>1</sup> However, it is imperative that CMS rely on a strong evidentiary foundation when making national coverage determinations that affect Medicare beneficiary access to care, particularly when such determinations result in coverage restrictions. BIO is a strong supporter of evidence-based medicine, and believes that clinical decisions made by physicians and patients should be based on the best available scientific evidence. Evidenced-based medicine "de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision-making and stresses the examination of evidence from clinical research."<sup>2</sup> The Proposed NCD seems to conflict with the evidence-based coverage standards that CMS has endeavored to uphold by not evaluating the totality of the scientific evidence, and reaching conclusions that contradict the medical judgment of experienced clinical oncologists. Indeed, Dr. S. Gail Eckhardt, Chair of FDA's Oncology Drugs Advisory Committee (ODAC) recently commented, "I was shocked to see how the CMS restrictions go way beyond the scientific evidence that indicates what's actually proven beneficial or not beneficial..."<sup>3</sup> CMS appears to be proposing coverage restrictions on ESAs based on an unproven theoretical premise regarding the safety of the products in certain instances, and placing the burden on the manufacturers to prove this premise wrong. BIO is concerned by the potential precedent of this approach to Medicare coverage because it lacks firm

---

<sup>1</sup> Social Security Act § 1862(a)(1)(A).

<sup>2</sup> Dr. Steve Phurrough, "Medicare Coverage Decisions: Balancing Competing Demands." National Health Policy Conference Presentation, February 2, 2005, available at: <http://www.academyhealth.org/nhpc/2005/phurrough.pdf>.

<sup>3</sup> *The Cancer Letter*, May 18, 2007, Vol. 33 No. 19

grounding in the available scientific evidence. BIO urges CMS to strictly adhere to the principles of evidence-based medicine when making coverage decisions that affect Medicare beneficiary access to ESAs, as well as other drug and biological therapies.

BIO is concerned that the specific coverage restrictions on ESAs in the Proposed NCD lack clear support in the scientific evidence, and contradict the established standard of care. Several of the proposed restrictions are inconsistent with widely accepted clinical practice guidelines, and have been questioned by members of the practicing oncology community who have submitted comments to the Proposed NCD. For example, many clinical experts in oncology disagree that the scientific evidence supports CMS' proposed non-coverage for the use of ESAs in chemotherapy regimens that include certain drug and biological therapies. Clinical experts also disagree that the evidence supports restrictions on the coverage of ESAs to only patients with hemoglobin levels of  $< 9$  g/dl immediately prior to initiation of dosing for the month in patients without known cardiovascular disease. In light of these concerns, BIO strongly urges CMS to ensure that the final NCD is well-supported by the full body of scientific evidence, and that any coverage restrictions do not inappropriately limit medically accepted uses and further restrict the FDA labeled indications.

## **II. CMS Should Acknowledge the Role of the FDA in Evaluating the Safety and Effectiveness of Approved Uses of Drugs and Biologicals.**

As a payer of health care services, CMS has the authority to provide Medicare reimbursement for health care items and services that the agency determines are reasonable and necessary. FDA's mission is to promote and protect the public health, which includes the approval of drugs and biologicals based upon demonstration of safety and effectiveness for the conditions of use prescribed in the labeling.<sup>4</sup> FDA has approved two ESAs for oncology indications and continues to monitor and assess the safety and effectiveness of these products. FDA worked with the manufacturers to change the full prescribing information for the products earlier this year, and the ODAC recently recommended that: FDA consider additional labeling changes; that additional safety studies be conducted; and that the committee reconvene to consider additional issues and recommendations to FDA.

In light of the pending FDA review and action, implementation of the coverage restrictions outlined in this Proposed NCD is premature. Disregarding the FDA's safety and effectiveness review of ESAs would essentially result in CMS creating a second set of prescribing guidelines in addition to FDA, and would result in the inability of Medicare patients to access the approved treatment to the full extent of the labeling. The four corners of the approved labeling—as agreed upon by experts in oncology and other related areas of medicine, both within and outside of FDA, and as implemented to meet a particular patient's needs—would become less relevant in light of

---

<sup>4</sup> FDA Modernization Act of 1997 (P.L. 105-115); Section 505(d) of the Federal Food, Drug and Cosmetic Act.

these Medicare coverage realities. Thus, CMS should delay finalizing this NCD until FDA has considered the results of the May 10, 2007 ODAC and completed its reevaluation of the ESA labels. In addition, CMS should take into account the results of the FDA's review prior to implementing any Medicare coverage restrictions.

Also of significant concern to BIO is the statement in the Proposed NCD that CMS is interested in public comments addressing whether access to ESAs should be limited to patients who are enrolled in clinical research trials with informed consent and safety monitoring. BIO strongly disagrees with any efforts to limit coverage of all uses of an approved drug or biological solely to patients enrolled in clinical research trials. Such an unprecedented action would be inconsistent with the status of ESAs as approved by FDA to provide safe and effective treatment for anemia in cancer patients, and with recent actions and recommendations by FDA and ODAC. It would also significantly interfere with the ability of physicians to provide proper care and treatment to their cancer patients. Limiting coverage of ESAs only to those in clinical trials would discriminate against Medicare beneficiaries who are unable to enroll in such trials due to factors beyond their control (e.g., proximity to an approved study site). Not all community oncologists are clinical investigators, and this restriction would place an undue burden on providers who would be required to administer the research protocol. Additionally, making coverage available only to beneficiaries enrolled in clinical trials could be considered coercion. Medicare patients should not be pressured into signing informed consent forms and participating in clinical trials in order to access ESAs or any other FDA-approved therapies. Given the aforementioned concerns, BIO urges CMS not to implement such unprecedented restrictions in cancer care.

### **III. CMS Should Not Interfere with Physician Judgment in Medical Decision-Making, Especially in Oncology.**

BIO is also deeply concerned that CMS' proposal would interfere with the ability of clinicians to make appropriate treatment decisions based on the unique clinical circumstances and preferences of each patient, and could effectively limit beneficiary access to medically appropriate therapies. Patients respond differently to the same treatment interventions based on a variety of clinical factors. This is especially true in the case of innovative drug and biological therapies, which often target specific mechanisms of action that allow particular therapies to work in specific patient populations. In order to achieve the best possible health outcomes, practitioners must have the flexibility to tailor the appropriate course of treatment for each patient based on individual clinical circumstances. In addition, many new uses of drugs and biologicals are found to be effective in very small, unique patient populations for whom FDA-approved labeling is difficult to obtain. Imposing coverage requirements that fail to adequately allow for practitioner flexibility and variations among patients can interfere with the ability of providers to deliver the most appropriate care, and could lead to suboptimal health outcomes.

The ability of clinicians to make patient-centered treatment decisions based on the scientific evidence is particularly important in oncology. In oncology, the standard of care advances approximately every six months, if not sooner, as clinical research discovers effective new treatment regimens. Many of these treatment options involve drugs and biologicals for indications not initially approved by the FDA. Congress recognized the critical role of protecting Medicare beneficiary access to medically appropriate uses of drug and biological therapies in fighting cancer when it enacted the Medicare statute's requirement to cover off-label indications of drugs used in anticancer regimens when listed in the recognized compendia.<sup>5</sup> Medicare contractors are also granted the discretion to ensure beneficiary access to important drugs and biologicals if they determine that the use is supported by peer-reviewed medical literature or that the use is "medically accepted generally as safe and effective for the particular use."<sup>6</sup>

The Proposed NCD would eliminate Medicare coverage for certain unapproved uses of ESAs in oncology, including anemia of myelodysplasia (MDS) and anemia of myeloid cancers. This would severely limit the treatment options available to cancer patients and their doctors, and undermine the Congressional protections for anti-cancer therapy to the extent that the uses are medically accepted in the recognized compendia and established in the medical literature. By eliminating coverage for many off-label uses of ESAs, many cancer patients who would benefit from such treatment could be effectively denied it. Further, many cancer patients currently rely on ESAs to tolerate the side effects of other chemotherapy agents. By restricting coverage for ESAs, CMS could, by default, also limit access for other effective anti-cancer therapies used as part of a chemotherapy regimen. In finalizing the NCD, CMS should consider these consequences, and recognize the critical role of the physician in determining and delivering the most appropriate care for each Medicare patient.

#### **IV. CMS Should Remain Consistent with Current Statutory Protections for Anti-Cancer Therapy and Adhere to the FDA Label.**

Due to the existing statutory protections for Medicare beneficiary access to anti-cancer therapies, CMS should adhere to the approved indications of ESAs until further action by the FDA. Doing so is not only necessary to ensure that Medicare patients maintain access to medically appropriate cancer treatments, but also is consistent with the laws that govern Medicare coverage policies. In 1993, Congress enacted legislation that was intended to resolve questions about the discretion of Medicare officials and contractors to limit coverage of medically appropriate cancer therapies. Accordingly, in §1861(t)(2) of the Social Security Act (42 U.S.C. §1395x(t)(2)), the term "drugs" is specifically defined to include "any drugs or biologicals used in an anticancer chemotherapeutic regimen for a medically accepted indication," which is further defined to include "any use which has been approved by the Food and Drug Administration" as

---

<sup>5</sup> Social Security Act § 1861(t)(2)(B)(i)(I).

<sup>6</sup> Social Security Act § 1861(t)(2)(B)(i)(II); Medicare Benefit Policy Manual (CMS Pub. 100-2), ch. 15, § 50.4.5.

Dr. Phurrough  
June 13, 2007  
Page 6

well as any compendia-supported use that has not been found by the Secretary to be medically inappropriate.

In enacting this legislation, Congress clearly intended for Medicare beneficiaries to have access to on-label and off-label uses of medically appropriate cancer therapies. BIO believes that CMS is acting contrary to this Congressional intent and is doing so without an evidentiary basis with regard to the coverage limitations applicable to on-label uses of ESAs. In addition, the statute provides that if off-label coverage is to be restricted in a manner that conflicts with compendia references, there must be a specific determination by the Secretary that the restricted uses are medically inappropriate. There is no evidence supporting such a determination.

**V. Conclusion**

In conclusion, BIO sincerely hopes that CMS will give thoughtful consideration to our comments and concerns prior to finalizing this NCD. If you have any questions regarding our comments, please contact John Siracusa at 202-312-9281. Thank you for your attention to this very important matter.

Respectfully submitted,

/s/

Sandra J.P. Dennis  
Deputy General Counsel for Health  
Care Regulatory Affairs

/s/

John A. Siracusa  
Manager, Medicare Reimbursement  
and Economic Policy

cc: Louis Jacques, MD  
Maria Ciccanti, RN  
Tara Turner, PharmD  
Elizabeth Koller, MD, FACE  
Shamiram Feinglass, MD, MPH

## Physicians

### *Hematology & Oncology*

Thomas A. Alberico, M.D.  
Burton F. Alexander, III, M.D.  
Daniel M. Atienza, M.D.  
Bruce W. Booth, M.D.  
Robert L. Burger, M.D., F.A.C.P.  
Paul R. Conkling, M.D.  
Scott J. Cross, M.D.  
Elke K. Friedman, M.D.  
Edward R. George, M.D., F.A.C.P.  
Elizabeth A. Harden, M.D., F.A.C.P.  
John R. Howard, Jr., D.O.  
John F. Kessler, M.D., F.A.C.P.  
Scott Kruger, M.D., F.A.C.P.  
Michael E. Lee, M.D.  
John Q. A. Mattern II, D.O.  
Dean S. McGaughey, III, M.D.  
John C. Paschold, M.D.  
David M. Powell, M.D.  
Christina W. Prillaman, M.D.  
John J. Regan, M.D.  
Ronald J. Ruzkowski, M.D.  
Joseph J. Schulz, M.D.  
Michael S. Steinberg, M.D., F.A.C.P.  
Alexander K. Su, M.D.  
Valiant D. Tan, M.D.

### *Gynecologic Oncology*

Munir F. Nasr, M.D., F.A.C.O.G.  
Stacey J. Rogers, M.D., F.A.C.O.G.  
Robert C. Squatrito, M.D., F.A.C.O.G.

## Office Locations

### *Southside*

5900 Lake Wright Drive  
Norfolk, VA 23502  
(757) 466-8683  
FAX (757) 466-8892

1012 First Colonial Rd., Suite 102  
Va. Beach, VA 23454  
(757) 481-6120  
FAX (757) 496-3738

5818 Harbour View Blvd., Suite 230  
Suffolk, VA 23435  
(757) 686-1042  
FAX (757) 686-1055

102 Fairview Dr., Suite E  
Franklin, VA 23851  
(757) 569-9709  
FAX (757) 569-6102

300 Medical Parkway, Suite 314  
Chesapeake, VA 23320  
(757) 549-4403  
Fax (757) 549-4332

150 Burnett's Way, Suite 310  
Suffolk, VA 23434  
(757) 539-0670  
Fax (757) 539-1062

### *Peninsula*

895 Middle Ground Blvd., Bldg. 200  
Newport News, VA 23606  
(757) 873-9400  
FAX (757) 873-9420

3000 Coliseum Dr., Suite 104  
Hampton, VA 23666  
(757) 827-9400  
FAX (757) 827-9320

3901 Treyburn Dr., Suite 2A  
Williamsburg, VA 23185  
(757) 229-2236  
FAX (757) 221-0409

6870 Main Street  
Gloucester, VA 23061  
(804) 693-3232  
FAX (804) 693-3342

### *North Carolina*

110 Medical Dr., Suite 7  
Elizabeth City, NC 27909  
(252) 331-2044  
FAX (252) 331-1909

5565 Croatan Hwy.  
Kitty Hawk, NC 27949  
(252) 261-5800  
FAX (252) 261-5301

### *Central Business Office*

5900 Lake Wright Dr., Suite 300  
Norfolk, VA 23502  
(757) 213-5700  
FAX (757) 213-5701  
TOLL FREE 1-800-998-3450

## Web Address

www.virginiacancer.com



6/4/2007

Stephen Phurrough, MD,MPA

Elizabeth Koller, MD,F.A.C.E.

Marsha Ciccanti, RN

Coverage Analysis Group/Office of Clinical Standards

Quality Center for Medicare and Medicaid Services

Baltimore, Maryland 21244-1849

Scott Kruger MD

3000 Coliseum Drive #104

Hampton, Virginia 23666

Re: ESA Guidelines

Dear Committee:

Thank you for your hard work in addressing this issue. As a practicing medical hematologist and oncologist, I am very concerned about the ramification some of the new proposals would have on my patients. I have used erythropoietins for more than 10years. I believe, like any drug a physician needs to use them carefully for appropriate reasons and weight the risks and benefits of treatment. Having had a patient develop hepatitis C from blood transfusions and die of liver failure keeps the risk of transfusion in the front of my mind. While the blood system is safer today, this risk is real. Aids and other diseases can cause unnecessary mortality and morbidity. The erythropoietin's do decrease the need for RBC transfusions and when used appropriately a safer alternative. In my community, we do not have a place where we could handle the increased number of transfusions that the current proposal would result in. As a certificate of public needs state our inpatient beds are limited. We will not be able to meet our patient's needs for transfusion therapy. Outpatient space is also limited and there will not be enough blood available to meet the need. I feel that appropriate use of erythropoietins is warranted.

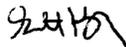
the drug is initiated. As you are aware, clinical studies show that a 1 g/dl rise in Hgb can take 6 – 8 weeks once drug therapy is initiated. Avoidance of transfusions is better accomplished by an earlier intervention at a HGB of <11. This has been shown in at least 6 different randomized studies.

The current proposal to limit the maximum treatment at 12 weeks per year does not take into account the advances we are making with cancer patients with metastasis disease. Many patients are working and maintaining their quality of life by staying on treatment. It is not uncommon to see a terminal colon cancer or breast cancer patient stay on treatment for months and even years for palliation. Many of my patients have been on many treatment regimens and continue to work and care for their families. The ESA have been instrumental in helping them to maintain a productive quality of life. The exclusion of EGFR and VEGF inhibitors is not based on any safety or clinical study. A patient receiving chemotherapy in combination with these newer agents should not be prevented from receiving the benefits of the ESA drugs.

As a practicing hematologist, I am particularly concerned about my patients with myelodysplasia and multiple myeloma. There are many randomized trials that show efficacy of these drugs in these conditions. I have seen first hand, how these drugs improve the quality of life of patients with these diseases.

While I do not envy your task, I do feel that there are safe and reasonable guidelines that can maximize the safety to our patients and not compromise clinical efficacy. Physician groups have used the medical literature effectively and written guidelines for these medications (ASCO, NCCN, US Oncology). I ask that we take an evidence medicine based approach in this decision making process. I encourage you to ask the pharmaceutical industry to fund clinical trials to answer further questions. Please, let's not ignore the benefits of these medications. The ESA have benefited cancer patients and allowed them to live, work and function in society. Years ago, patients stayed in hospitals or remained homebound because they were too weak and sick to function. Please, let us not take a step backwards. I would rather see us go forward and use the current medical literature that supports rational guidelines for the use of these agents.

Sincerely,



Scott Kruger MD



**FRED S. MARCUS, MD, AND ASSOCIATES**

A PROFESSIONAL CORPORATION

***Internal Medicine, Hematology, and Medical Oncology***

Fred S. Marcus, MD  
Shane P. Dormady, MD, PhD  
John A. Hayward, MD  
Debra D. St. Claire, MD  
Peggy Ross, RNP, MS

2940 Whipple Avenue, Suite B • Redwood City, California 94062  
(650) 216-8300 Telephone (650) 216-8401 Facsimile

Sherri Garoutte, RN, OCN  
Diana Goodenough, RN, OCN  
Theresa Koettters, RN, MS

June 5, 2007

Steve Phurrough, MD, MPA

Elizabeth Koller, MD, FACE

Maria Ciccanti, RN

Coverage Analysis Group

Office of Clinical Standards and Quality

Centers for Medicare and Medicaid Services

Mail Stop C1-12-28

7500 Baltimore, MD 21244-1849

Re: Comment Regarding Changes in Medicare Policy re: Erythropoiesis Stimulating Agents (ESAs) for  
Non-renal Disease Indications (CAG-00383N)

Thank you for inviting comment regarding your proposed changes in Medicare policy re: ESAs. I have been in the practice of Hematology and Medical Oncology in the Community and University settings in North Carolina and California for over six years, treating patients with a broad spectrum of malignancies and blood disorders. I agree that growth factors have made a huge (positive) difference in our treatments and I agree that there is a need for national coverage standards as well as a rational, evidence-based response to FDA warnings about ESAs (and all drugs).

It is my experience that both darbepoetin alfa and epoetin alfa have equal efficacy in treating selected forms of anemia and I believe that CMS should therefore establish the same list of indications to support medical necessity for both. This list should include all indications where evidence shows that ESAs are safe and effective.

I believe that Quality of Life, reduced morbidity and side effects secondary to our antineoplastic therapies, and transfusion avoidance are relevant, important endpoints for patients living with cancer. Transfusions carry both expense (cost of blood, blood bank personnel time, nursing time, transfusion bed time, and the patient's time) and considerable risk (of reactions, HIV, and Hepatitis).

I disagree with discontinuing ESAs for failure to achieve a 1 g/dl Hemoglobin increase in four weeks; I do not believe that this is evidence-based. Clinical studies consistently show that the optimal response takes 2 – 12 weeks to occur.

Neither darbepoetin alfa nor epoetin alfa reliably achieves and increase of 1 g/dl in 4 weeks at standard doses. Standard doses usually require 5 – 7 weeks for 1 g/dl response.

I believe that there must be a provision for dose escalation in non-responders – it has been the standard of care of ten years to dose escalate in non-responders at 6 – 8 weeks. There has been no evidence showing a safety risk associated with dose escalation.

I agree with restricting the use of ESAs in most people who have a hemoglobin level of > 12 g/dl. Trials that pushed hemoglobin above the limit (in the hopes of improving patients' response rates to treatment) showed an increased risk of thrombotic events, clearly not in the patients' best interest. However, in patients who are currently undergoing chemotherapy, who have a hemoglobin level of 12.0 or 12.1 and who will be receiving myelosuppressive treatments within the next week, should receive ESAs with the goal of keeping the hemoglobin at the 12.0 g/dl level.

I disagree with your suggested change to not cover multiple myeloma, MDS, and chronic anemia of cancer. Transfusion avoidance is as important for people who are currently not receiving chemotherapy (such as people multiple myeloma, myelodysplastic syndromes, or metastatic cancers) as for those who are receiving chemotherapy. Studies that showed significant and life-threatening events in certain patients who have taken ESAs for non-renal diseases, do not appear to have included any patients with bone marrow failure (such as MDS). Most patients with MDS are elderly; many have comorbidities that make alternative treatments such as chronic transfusions and aggressive chemotherapy, very risky. ESAs have been found to be safe and beneficial (therapeutic as well as supportive) in all subtypes of MDS.

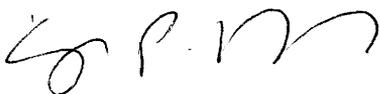
I disagree with a 12 week maximum allowance for ESA usage. When the original studies that formed the basis for FDA approval of ESAs in chemo-related anemia were done, they were done with a 12 week course of chemotherapy. In the last 20 years, the duration of antineoplastic therapies has increased due to the availability of supportive agents as well as the number of active agents available. For patients undergoing first, second, and third line regimens lasting even 6 -12 months in a given year, the 12 week maximum allowance is grossly inadequate. Also, there is no evidence suggesting that the use of ESAs for more than 12 weeks is associated with more safety issues (as there is with greatly elevated hemoglobin levels).

I disagree with your proposed non-coverage ESAs in patients receiving VEGF or EGFR inhibitors. These agents are known to induce anemia and are often given with other anemia-inducing regimens. There is no evidence that ESA usage antagonizes the therapeutic effect of VEGF/EGFR inhibitors.

In summary, I believe that the benefits of ESAs have been demonstrated in the literature in over 2000 patients, correcting anemia and reducing transfusion rates. While cancer patients' quality of life, functionality, and general well-being are greatly improved by maintaining hemoglobin concentrations near 12 g/dl, there is no evidence that transfusions are safer or more effective than ESA use in patients with Hemoglobin levels between 9 – 11. Your proposed changes could increase the blood demand by 20% and could risk depletion of the national blood supply.

**I strongly recommend that you approve use of ESAs:** 1) to be started at Hgb < 11 g/dl, 2) that dose escalation be allowed, 3) that treatment be held with Hgb > 12 and treatment be restarted as soon as Hgb subsequently drops below 12, 4) include coverage for MDS and Multiple Myeloma, 5) maintain coverage for patients receiving VEGF and EGFR inhibitors, and 6) coverage be continued for as long as chemo-induced anemia continues up to 12 weeks after chemotherapy is concluded. Thank you for inviting my comments.

Sincerely,



Shane P. Dormady, MD, PhD

SPD:sdg



**FRED S. MARCUS, MD, AND ASSOCIATES**

A PROFESSIONAL CORPORATION

***Internal Medicine, Hematology, and Medical Oncology***

Fred S. Marcus, MD  
Shane P. Dormady, MD, PhD  
John A. Hayward, MD  
Debra D. St. Claire, MD  
Peggy Ross, RNP, MS

2940 Whipple Avenue, Suite B • Redwood City, California 94062  
(650) 216-8300 Telephone (650) 216-8401 Facsimile

Sherri Garoutte, RN, OCN  
Diana Goodenough, RN, OCN  
Theresa Koettters, RN, MS

June 5, 2007

Steve Phurrough, MD, MPA

Elizabeth Koller, MD, FACE

Maria Ciccanti, RN

Coverage Analysis Group  
Office of Clinical Standards and Quality  
Centers for Medicare and Medicaid Services  
Mail Stop C1-12-28  
7500 Baltimore, MD 21244-1849

Re: Comment Regarding Changes in Medicare Policy re: Erythropoiesis Stimulating Agents (ESAs) for  
Non-renal Disease Indications (CAG-00383N)

Thank you for inviting comment regarding your proposed changes in Medicare policy re: ESAs. I am an Oncology Nurse Clinician, treating patients with a broad spectrum of malignancies and blood disorders in the Community setting for twenty years. I agree that growth factors have made a huge (positive) difference in our treatments and I agree that there is a need for national coverage standards as well as a rational, evidence-based response to FDA warnings about ESAs (and all drugs).

It is my experience that both darbepoetin alfa and epoetin alfa have equal efficacy in treating selected forms of anemia and I believe that CMS should therefore establish the same list of indications to support medical necessity for both. **This list should include all indications where evidence shows that ESAs are safe and effective.**

I believe that Quality of Life, reduced morbidity and side effects secondary to our antineoplastic therapies, and transfusion avoidance are relevant, important endpoints for patients living with cancer. Transfusions carry both expense (cost of blood, blood bank personnel time, nursing time, transfusion bed time, and the patient's time) and considerable risk (of reactions, HIV, and Hepatitis).

I disagree with discontinuing ESAs for failure to achieve a 1 g/dl Hemoglobin increase in four weeks; I do not believe that this is evidence-based. Clinical studies consistently show that the optimal response takes 2 – 12 weeks to occur.

Neither darbepoetin alfa nor epoetin alfa reliably achieves and increase of 1 g/dl in 4 weeks at standard doses. Standard doses usually require 5 – 7 weeks for 1 g/dl response.

I believe that there must be a provision for dose escalation in non-responders – it has been the standard of care of ten years to dose escalate in non-responders at 6 – 8 weeks. There has been no evidence showing a safety risk associated with dose escalation.

I agree with restricting the use of ESAs in most people who have a hemoglobin level of > 12 g/dl. Trials that pushed hemoglobin above the limit (in the hopes of improving patients' response rates to treatment) showed an increased risk of thrombotic events, clearly not in the patients' best interest. However, in patients who are currently undergoing chemotherapy, who have a hemoglobin level of 12.0 or 12.1 and who will be receiving myelosuppressive treatments within the next week, should receive ESAs with the goal of keeping the hemoglobin at the 12.0 g/dl level.

I disagree with your suggested change to not cover multiple myeloma, MDS, and chronic anemia of cancer. Transfusion avoidance is as important for people who are currently not receiving chemotherapy (such as people multiple myeloma, myelodysplastic syndromes, or metastatic cancers) as for those who are receiving chemotherapy. Studies that showed significant and life-threatening events in certain patients who have taken ESAs for non-renal diseases, do not appear to have included any patients with bone marrow failure (such as MDS). Most patients with MDS are elderly; many have comorbidities that make alternative treatments such as chronic transfusions and aggressive chemotherapy, very risky. ESAs have been found to be safe and beneficial (therapeutic as well as supportive) in all subtypes of MDS.

I disagree with a 12 week maximum allowance for ESA usage. When the original studies that formed the basis for FDA approval of ESAs in chemo-related anemia were done, they were done with a 12 week course of chemotherapy. In the last 20 years, the duration of antineoplastic therapies has increased due to the availability of supportive agents as well as the number of active agents available. For patients undergoing first, second, and third line regimens lasting even 6 -12 months in a given year, the 12 week maximum allowance is grossly inadequate. Also, there is no evidence suggesting that the use of ESAs for more than 12 weeks is associated with more safety issues (as there is with greatly elevated hemoglobin levels).

I disagree with your proposed non-coverage ESAs in patients receiving VEGF or EGFR inhibitors. These agents are known to induce anemia and are often given with other anemia-inducing regimens. There is no evidence that ESA usage antagonizes the therapeutic effect of VEGF/EGFR inhibitors.

In summary, I believe that the benefits of ESAs have been demonstrated in the literature in over 2000 patients, correcting anemia and reducing transfusion rates. While cancer patients' quality of life, functionality, and general well-being are greatly improved by maintaining hemoglobin concentrations near 12 g/dl, there is no evidence that transfusions are safer or more effective than ESA use in patients with Hemoglobin levels between 9 – 11. Your proposed changes could increase the blood demand by 20% and could risk depletion of the national blood supply.

**I strongly recommend that you approve use of ESAs:** 1) to be started at Hgb < 11 g/dl, 2) that dose escalation be allowed, 3) that treatment be held with Hgb > 12 and treatment be restarted as soon as Hgb subsequently drops below 12, 4) include coverage for MDS and Multiple Myeloma, 5) maintain coverage for patients receiving VEGF and EGFR inhibitors, and 6) coverage be continued for as long as chemo-induced anemia continues up to 12 weeks after chemotherapy is concluded. Thank you for inviting my comments.

Sincerely,



Sherri D. Garoutte, RN, OCN

SDG:mp

**[ASH Comments to the Centers for Medicare and Medicaid Services on coverage for Erythropoiesis Stimulating Agents (ESAs) filed electronically on April 12, 2007]**

April 12, 2007

The American Society of Hematology (ASH) represents over 11,000 hematologists in the United States who are committed to the treatment of blood and blood-related diseases. ASH members include hematologists and hematologist/oncologists who regularly render services to Medicare beneficiaries. The Society appreciates this opportunity to comment on the use of Erythropoiesis Stimulating Agents (ESAs) for conditions other than end-stage renal disease as Medicare begins developing a National Coverage Determination (NCD).

New research studies report an excess of serious and life-threatening events associated with the use of ESAs in non-anemic patients in various clinical settings, and the Food and Drug Administration (FDA) has recently issued new warnings regarding the use of ESAs. Thus, ASH believes it is important for Medicare to carefully review all policies related to the administration of ESAs and, in particular, the scientific evidence, to determine the appropriate use of ESAs for multiple clinical indications.

Of paramount importance to ASH is to ensure the highest degree of patient safety and to protect against not only the overuse of these drugs, but their underuse and misuse as well. Consequently, ASH notes that ESAs help to reduce the need for transfusions and thereby alleviate strain on the nation's blood supply. Therefore, the impact on the blood supply should be taken into account when determining changes in the use of these products. In addition, while ASH accepts the relevance of four recently completed cancer trials that evaluated new dosing regimens and new patient populations, we recognize that additional high quality clinical trials are needed to better understand the impact of ESAs on patients with hematologic malignancies.

Below are ASH's comments concerning use of ESAs for patients with conditions other than end-stage renal disease, including recommendations about treatment targets and duration. Because all ESAs have the same mechanism of action, ASH, like the FDA, believes these comments apply to all ESAs (marketed as Procrit, Epogen, and Aranesp). While some local carriers have separated policies for darbepoetin alfa (Aranesp) and epoetin alfa (Epogen and Procrit), ASH believes there should be a single national coverage policy because the products are basically interchangeable and use of one is essentially equal to the use of the other.

*Coverage of ESAs for Patients with Conditions Other than End-Stage Renal Disease*

• **Chemotherapy associated anemia (285.22)**

ESAs may be used as a treatment option for patients with chemotherapy-associated anemia. ASH notes that a patient may continue to suffer from anemia for some time following completion of chemotherapy treatment and recommends that coverage of ESAs be continued for treatment of anemia for 90 days post chemotherapy. If anemia

persists beyond 90 days after completion of chemotherapy, it would be reasonable to re-evaluate the anemia to determine if this continues to be a result of the chemotherapy, thereby justifying continuation of ESA treatment, or if another process is in place. ASH believes most patients should recover in this time period, but notes evidence from randomized clinical trials concerning this issue is not available and recommends prospective studies concerning this topic.

- **Anemia of chronic disease (Anemia of chronic inflammation) (285.29)**  
ESAs may be used as a treatment option for patients with anemia of chronic inflammation. ASH notes that the anemia of cancer is not included and is distinct from this category. Anemia of inflammation is a common consequence of chronic infections and noninfectious generalized inflammatory disorders. The diagnosis is usually exclusionary; meaning other causes of the anemia have been ruled out. Common features include: low or normal serum iron, low or normal iron-binding capacity levels, and elevated iron in reticuloendothelial cells in bone marrow; however, there may be variation. ASH recommends that Medicare cover the use of ESAs for the anemia of chronic disease when the following conditions are met: the pretreatment Hct level is 30 percent or less and/or if the patient has been transfusion dependent; the pretreatment erythropoietin level is 100MU/ml or less; and at least one of the following applies: low or normal serum iron, low or normal iron binding capacity, normal or elevated serum ferritin, iron is present in the bone marrow (requires bone marrow aspiration and/or biopsy).
  
- **Patients with hematologic malignancies not on chemotherapy**  
ESAs may be used as a treatment option for patients with hematologic malignancies but who are not on chemotherapy. There is evidence to support the use of ESAs in patients with anemia associated with low-risk myelodysplasia (less than five percent blasts). Myelodysplastic syndromes (MDS) are a heterogeneous group of hematological malignancies characterized by dysplastic and ineffective hematopoiesis and a variable risk of transformation to acute leukemia. Low risk myelodysplasia with less than five percent blasts can include the following (World Health Organization classification) forms of myelodysplasia:
  - Refractory anemia (RA) (238.72)
  - Refractory anemia with ringed sideroblasts (RARS) (238.72)
  - Refractory cytopenia with multilineage dysplasia (RCMD) (238.72)
  - Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS) (238.72)
  - Myelodysplastic syndrome, unclassified (MDS-U) (238.75)
  - MDS associated with isolated del(5q) (238.74)Refractory anemia can be defined as erythropoietic insufficiencies that cannot be assigned to a specific vitamin or mineral deficiency. ASH recommends that Medicare cover treatment with ESAs in patients with MDS who meet the following criteria:
  1. Hemoglobin (Hgb) of 10 g/dl or Hematocrit (Hct) of 30% or less
  2. Patients who have a reasonable expectancy of longer survival
  3. Patients who need or are anticipated to need frequent transfusions

#### 4. Treatment with ESAs will end or reduce the need for transfusions.

Experts in hematology have used ESAs to treat anemic patients with multiple myeloma, non-Hodgkin lymphoma and chronic lymphocytic leukemia (CLL) in the absence of chemotherapy where the ESAs have proven effective. ASH acknowledges, however, that there are no randomized clinical trials to support use of ESAs in these hematologic malignancies, and strongly recommends this to be an area for further study and evaluation. ASH notes that the large seminal studies used by FDA to support public safety warnings do not include adequate numbers of patients with hematologic malignancies not undergoing chemotherapy to allow appropriate analysis. In the absence of randomized clinical trial data, coverage for these patients should be on a case by case basis.

#### *Treatment Recommendations*

- **Starting and ending targets**

ASH recommends that ESAs be started in appropriate clinical settings at a hemoglobin level at or below 10 g/dl. (ASH notes that this can be considered the same as an Hct of 30%, but uses hemoglobin because it is directly measurable and used in the literature.) ASH notes, however, that there may be extenuating circumstances when treating patients with co-morbidities, such as cardiac or pulmonary disease, (which should be documented) that could justify use of ESAs before the hemoglobin has decreased to 10 g/dl.

ASH believes the therapeutic goal should be a hemoglobin level of no higher than 12 g/dl and recommends that the dose of ESA be modified in accordance with the recent FDA black box warning when the hemoglobin approaches 12 g/dl. It is important to encourage doctors to be vigilant in monitoring patient blood counts when treating with ESAs, and iron levels in non-responders.

- **Non-response**

ESAs should not be continued after eight weeks in the absence of response, assuming the appropriate dose increase has been attempted in low-responders. A response is a rise in hemoglobin of 1 g/dl or greater.

- **Hematologic malignancy patients treated with chemotherapy**

Chemotherapy associated anemia in patients with hematologic malignancies (Myeloma and other plasma cell dyscrasias, Hodgkins and non-Hodgkins lymphoma, low grade myelodysplasias, and CLL) should be treated according to the parameters recommended above.

- **Anti-tumor therapy**

Current data do not support the use of ESAs solely to potentiate the effectiveness of anti-tumor therapy.

Again, thank you for this opportunity to share ASH's recommendations concerning use of ESAs for conditions other than ESRD. ASH is currently updating our evidence-based

practice guidelines concerning use of Epoetin to include other ESAs and is willing to share this information as the draft becomes available later this summer. We would welcome a meeting with Medicare medical officers and analysts to discuss our recommendations with more specificity and hope to maintain an ongoing dialog with CMS over the issue of ESA usage, particularly as additional information becomes available and ASH's ESA guidelines are finalized. In the meantime, if you need additional information or have any questions, please contact Mila Becker of the ASH staff at 202-776-0544 or [mbecker@hematology.org](mailto:mbecker@hematology.org).

Sincerely,



Samuel Silver, MD, PhD  
Chair, ASH Reimbursement Subcommittee  
Councilor, ASH Executive Committee

References follow

## Reference List

Bohlius J, Wilson J, Seidenfeld J, et al: Recombinant human erythropoietins and cancer patients: Updated meta-analysis of 57 studies including 9353 patients. *J Natl Cancer Inst.* 98: 708-714, 2006

Goldberg P: Study finds more deaths on Aranesp arm in cancer anemia study, no benefit seen [newsletter]. *The Cancer Letter* 33:1, 2007

Demetri GD, Kris M, Wade J, et al: Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: Results from a prospective community oncology study – Procrit Study Group. *J Clin Oncol* 16: 3412-3425, 1998

Gabrilove JL, Gleeland CS, Livingston RB, et al: Clinical evaluation of one-weekly dosing of epoetin alfa in chemotherapy patients: Improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. *J Clin Oncol* 19: 2875-2882, 2001

Littlewood TJ, Bajotla E, Nortier JW, et al: Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving non-platinum chemotherapy: Results of a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 19:2865-2874, 2001

Leyland-Jones B, BEST Investigators and Study Group: Breast cancer trial with erythropoietin terminated unexpectedly. *Lancet Oncol* 4: 459-460, 2003

Henko M, Loszig R, Rube C, et al: Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: Randomised, double-blind, placebo-controlled trial. *Lancet* 362: 1255-1260, 2003

Witzig TE, Silberstein PT, Loprinzi CL, et al: A phase III randomized double-blind study of epoetin alfa versus placebo in anemic patients with cancer undergoing chemotherapy. *J Clin Oncol* 23: 2606-2617, 2005

Rizzo DJ, Lichtin AE, Woolf SH, et al: Use of epoetin in patients with cancer: Evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *J Clin Oncol* 20:4083-4107, 2002

Leyland-Jones B, Semiglazov V, Pawlicki M, et al: Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: A survival study. *J Clin Oncol* 23: 5960-5972, 2005

# CONNECTICUT ONCOLOGY ASSOCIATION

June 11, 2007

Steve E. Phurrough, MD, MPA  
Director, Coverage and Analysis Group  
Centers for Medicare & Medicaid Services  
Mail Stop C1-09-06  
7500 Security Boulevard  
Baltimore, MD 21244

RE: Proposed Decision Memorandum for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N)

Dear Dr. Phurrough:

On behalf of the Connecticut Oncology Association, representing medical oncologists and community oncology in the state of Connecticut, we would like to present our comments regarding the above-referenced proposed National Coverage Determination (NCD) use of erythropoiesis-stimulating agents (ESAs) in the management of anemia due to conditions other than chronic renal insufficiency.

## Introduction

Anemia is a major problem in cancer patients, with significant adverse effects on quality of life and overall health. Estimates of the proportion of cancer patients with anemia are as high as 100% in some populations. Adverse effects of anemia include fatigue, weakness, congestive heart failure, worsening dementia and risk of falls. Prior to the availability of ESAs such as epoetin alfa (Procrit, Epogen) and darbepoetin alfa (Aranesp), anemia in cancer patients was generally treated only with transfusions of packed red blood cells, adding a significant additional burden to cancer patients' difficult treatment regimens and exposing patients to the many adverse effects of transfusions.

The availability of ESAs has revolutionized the treatment of anemia in cancer patients, decreasing the frequency of transfusions and their attendant adverse effects, improving the tolerability of chemotherapy and other difficult cancer treatments, and improving patient quality of life. Since the initial FDA approval of epoetin alfa in 1989, ESAs have had a long history of safe and effective use when used appropriately.

## Results of recent trials

Recent studies have reported adverse outcomes in patients receiving ESAs for various indications. These studies generally used unapproved or experimental doses and schedules of ESAs that do not reflect the current standard of care for ESA use in contemporary community oncology or current evidence-based guidelines published by national groups. In general, the experimental regimens involved higher hemoglobin (Hgb)/hematocrit (Hct) targets than are used in practice and/or inadequate monitoring of response to treatment. As noted below, some of these studies have not been published. The results of the published studies are briefly reviewed here.

### DAHANCA 10 (Danish Head and Neck Cancer Study Group)

In this trial,<sup>1</sup> patients receiving radiation therapy for advanced head and neck cancer were randomized to receive (1) darbepoetin to maintain a hemoglobin of 14.0-15.5 g/dL, or (2) no darbepoetin. The darbepoetin group had poorer three-year locoregional control and a trend toward poorer survival ( $p=0.08$ ). The trial was terminated early.

The target hemoglobin range in the treated group in this study would be considered inappropriately high by today's standards. The current standard of care generally includes beginning treatment with an ESA when the hematocrit is less than 33% (roughly equivalent to a hemoglobin of less than 11 g/dL) and withholding treatment if the hematocrit is 36% or greater (hemoglobin 12 g/dL or greater).

### Amgen trial

Amgen<sup>2</sup> reported preliminary results of a randomized controlled trial in which 989 anemic cancer patients not receiving chemotherapy were randomized to receive (1) darbepoetin with a target hemoglobin of 12 g/dL, or (2) placebo. The treated arm did not have a lower need for PRBC transfusions and had increased mortality (hazard ratio 1.25, 95% confidence interval 1.04-1.51). The results of this study were discussed in a "Dear Health Care Professional" letter sent by Amgen, but the study has not been published.

These findings are concerning because the target hemoglobin range appears similar to that used in practice today, but further details of the trial have not been released and thus multiple questions remain unanswered. Were other causes of anemia excluded or treated appropriately? Was appropriate iron supplementation given? Were the patients terminally ill, or did they have a particularly poor prognosis? What were the "cutoff" rules for administering Aranesp? What was the effect of treatment on quality of life? It is difficult to assess the relevance of this trial without answers to these questions.

### Ortho Biotech study

Wright *et al.*<sup>3</sup> reported the results of a randomized controlled trial in which anemic non-small-cell lung cancer patients not receiving chemotherapy were randomized to receive (1) epoetin alfa with a target hemoglobin of 12-14 g/dL, or (2) placebo. The study was closed early because of higher mortality in the treated arm ( $p=0.04$ ). Patients in the treated arm did not have fewer PRBC transfusions or improved quality of life.

Again, the target hemoglobin range in the treated group in this study would be considered inappropriately high by today's standards. Epoetin alfa was only withheld if the hemoglobin exceeded 14 gm/dL, and was then resumed with a 25% dose-reduction when the hemoglobin fell below 12 gm/dL. A 25% dose-reduction was also instituted if the hemoglobin increased by 2 mg/dL or more during any four-week period. The standard of care in the community is to withhold treatment with ESAs if the hematocrit is 36% or greater (roughly equivalent to a hemoglobin of 12 gm/dL or greater).

### Hoffman-La Roche study

Hoffman-La Roche<sup>4</sup> suspended a trial of a pegylated epoetin beta product in February 2007 because of "a numerical imbalance in the number of deaths across the four arms of the study." No other information on this trial is available. Pegylated epoetin beta is not approved for use in the United States and thus the applicability of

these results is unclear. In addition, the unanswered questions regarding the Amgen trial above apply for this study as well.

#### N93-004 trial

Grote *et al.*<sup>18</sup> reported the results of a randomized, double-blind, placebo-controlled trial in which patients receiving chemotherapy for small-cell lung cancer and hemoglobin less than or equal to 14.5 g/dL were randomized to receive either epoetin alfa 150 U/kg three times weekly or placebo until three weeks after the completion of chemotherapy. The trial was terminated early “because of slow improvement and suboptimal enrollment,” not because of adverse events. In this trial, despite a hemoglobin starting level higher than that used in the community, no differences in overall survival or mortality were observed.

#### Leyland-Jones trial

Leyland-Jones *et al.*<sup>19</sup> reported the results of a randomized, double-blind, placebo-controlled trial in which patients receiving chemotherapy for metastatic breast cancer with a hemoglobin of less than 13 g/dL were randomized to receive either epoetin alfa 40,000 units weekly, with a hemoglobin target range of 12-14 g/dL, or placebo. The hemoglobin was monitored weekly for the first four weeks of therapy and every three to four weeks thereafter. The trial was terminated early because of inferior survival in the epoetin alfa group.

The higher target hemoglobin range in this study does not reflect the standard of care in the community. In fact, many of the patients in this study would not even have been started on an ESA in most oncology practices today, since ESAs are usually not started until the hematocrit is less than 33% (roughly equivalent to a hemoglobin of less than 11 g/dL). In addition, monitoring of hemoglobin response was performed inappropriately infrequently during the trial. In most oncology practices, the hemoglobin and hematocrit are checked prior to each ESA dose.

#### Rosenzweig trial

Rosenzweig *et al.*<sup>20</sup> reported the results of a randomized, unblinded trial in which patients receiving chemotherapy for metastatic breast cancer with a hemoglobin of less than 12 g/dL were randomized to receive either epoetin alfa 40,000 units weekly or placebo. The trial was terminated early because of an excess of thrombotic complications in the epoetin group. Four of 14 patients on the epoetin alfa arm developed thrombotic complications, whereas none of 13 patients on the observation arm developed thrombotic complications. The hemoglobin levels in patients with thrombotic complications were 12.0, 11.2, 14.5 and 11.4 g/dL. The authors noted that “[t]he thrombotic event incidence was non-significant between groups.”

The results of this trial, as the authors indicate, do not show a statistically significant increase in thrombotic complications in patients receiving epoetin alfa. In addition, no information is reported on how the response to epoetin alfa was monitored, what (if any) stopping rules were used, or whether there was any difference in survival between groups.

#### Henke trial

Henke *et al.*<sup>21</sup> reported the results of a randomized, double-blind, placebo-controlled trial in which patients with head and neck cancer who had a hemoglobin of less than 12 g/dL (women) or 13 g/dL (men) and who were receiving radiotherapy with curative intent were randomized to receive epoetin beta 300 U/kg three times weekly or placebo. 82% of patients receiving epoetin beta achieved a hemoglobin of greater than 14 g/dL (for women) or 15 g/dL (for men). In follow-up correspondence on this study published in the same journal,<sup>22</sup> Henke noted that “the mean haemoglobin concentration during radiotherapy was 143 g/L [14.3 g/dL] for patients on erythropoietin.” The study demonstrated inferior progression-free survival in the epoetin beta arm.

The higher hemoglobin starting level and very high observed hemoglobin outcome in this study does not reflect the standard of care in the community. In fact, many of the patients in this study would not even have been started on an ESA in most oncology practices today, since ESAs are usually not started until the hematocrit is less than 33% (roughly equivalent to a hemoglobin of less than 11 g/dL). In addition, epoetin beta is not approved for use in the United States and thus the applicability of these results is unclear.

#### Elective spinal surgery study

A study of preoperative epoetin alfa in patients undergoing elective spinal surgery<sup>5</sup> reportedly showed an increased frequency of deep venous thrombosis in patients treated with epoetin alfa (4.7% vs. 2.1%, “more than twice” the frequency in untreated patients). No other information on this trial is available, and it is thus difficult to comment on the relevance of these results. In particular, it is not known how the drug was given, under what circumstances doses were withheld, or whether the difference in frequency of deep venous thrombosis was statistically significant.

#### CREATE trial

Drueke *et al.*<sup>6</sup> reported the results of the CREATE trial, in which 603 patients with moderate renal insufficiency (GFR 15-35 mL/min) and “mild-to-moderate anemia” (Hgb 11.0-12.5 g/dL) were all treated with epoetin beta; they were randomized to a target hemoglobin of 13.0-15.0 g/dL or 10.5-11.5 g/dL. Epoetin beta was administered weekly, but dose adjustments were only made every four weeks; the dose was increased by “25 to 50%” if the hemoglobin rose by less than 0.5 g/dL, and the dose was decreased by “25 to 50%” if the hemoglobin rose by more than 1 g/dL. It is not stated whether or under what circumstances epoetin beta was withheld. The patients were seen every two weeks for the first three months, and every three months thereafter. Iron supplementation was left to the discretion of the investigators, although they were “encouraged to follow clinical guidelines.” The observed hemoglobin results in the two treatment arms were reported in graph format and not numerically, but the graph appears to indicate that the hemoglobin in the high-target patients was nearly always greater than 12, often greater than 13 and sometimes greater than 14 g/dL.

The higher target range in this study was higher than the standard of care in the community, as was the observed outcome in terms of hemoglobin. In fact, most of the patients in this study would not even have been started on an ESA in most oncology practices today, since ESAs are usually not started until the hematocrit is less than 33% (roughly equivalent to a hemoglobin of less than 11 g/dL). The patients were also monitored much less frequently than is the standard of care in the community; in most oncology practices, the hemoglobin and hematocrit are checked prior to each ESA dose. In addition, since epoetin beta is not available in the United States, the applicability of these results is unclear.

#### CHOIR trial

Singh *et al.*<sup>7</sup> reported the results of the CHOIR trial, in which 1432 patients with chronic renal insufficiency (GFR 15-50) and anemia (Hgb < 11.0 g/dL) were all treated with epoetin alfa; they were randomized to a target hemoglobin of 13.5 or 11.3 g/dL. An appendix to the report states that epoetin alfa was administered “based on a pre-specified dosing algorithm to achieve the randomized [hemoglobin] target,” but the algorithm is not specified. In particular, “cutoff” rules are not reported. The patients in the higher-target group had a poorer outcome in terms of a composite endpoint of death and cardiovascular events, although the difference in outcome for individual events comprising the composite endpoint (death, CHF requiring hospitalization, non-fatal MI and non-fatal stroke) was not statistically significant. Again, the observed hemoglobin results in the two treatment arms were reported in graph format and not numerically, but the graph appears to show that the hemoglobin was in the range of 12.5 to 13.0 g/dL (and sometimes higher) for the high-target group and in the range of 11.3-11.8 g/dL for the low-target group.

Again, the higher hemoglobin target range and the observed hemoglobin outcome in this study were higher than the standard of care in the community and higher than recommended by commonly-used guidelines.

### CMS recommendations for NCD

The proposed NCD contains extensive recommendations for limiting the use of ESAs for the treatment of multiple conditions. These recommendations go far beyond the safety concerns raised by the trials described above and would result in greatly curtailed use of ESAs for Medicare patients. Several specific recommendations for noncoverage of ESAs are addressed below.

1. “... any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis.”

Oncologists do not treat anemia due to these conditions with ESAs, and we do not disagree with this recommendation. However, anemia in cancer patients is often multifactorial, and these conditions may often supervene in patients with anemia due to chemotherapy. In particular, patients receiving ESAs often develop functional iron deficiency which requires parenteral iron supplementation in order for ESA therapy to continue to be effective. Patients receiving ESAs for an approved indication who also have or develop one of the conditions described above should not have further ESA therapy denied.

**2. "... the anemia of myelodysplasia."**

A large body of evidence and years of clinical experience has established the safety and efficacy of the use of ESAs to treat the anemia associated with myelodysplastic syndromes.<sup>23-28</sup> No evidence has been put forward to support the noncoverage of ESAs for these patients. Patients requiring ESAs for the treatment of anemia due to myelodysplastic syndromes generally have chronic anemia and would be at particular risk for harm if this treatment option were withdrawn. In addition, patients with myelodysplastic syndromes are at particularly increased risk for transfusion-related secondary iron overload, the incidence of which would greatly increase if ESAs were unavailable to them.

**5. "... the anemia of cancer not related to cancer treatment."**

As noted above, the studies presented to date on this group of patients are flawed in that:

- they have not yet been published and thus cannot be adequately evaluated;
- they used experimental ESA doses and/or schedules that included starting inappropriate patients on ESAs and/or using inappropriately high Hgb/Hct targets; and/or
- they used inadequate monitoring of patients' response to treatment.

The studies presented to date do not support a categorical denial of coverage for ESAs for cancer patients not receiving chemotherapy. Furthermore, anemic cancer patients with anemia who are not receiving specific treatment for their malignancy are generally seriously ill and are likely to be seriously affected by their anemia. In such patients, a careful analysis of the risks and benefits of treatment options such as ESAs becomes particularly important. This analysis must be made by the patient and their physician (see Conclusion below).

**7. "... prophylactic use to prevent chemotherapy-induced anemia."**

Oncologists do not use ESAs for this indication outside of clinical trials, and we do not disagree with this recommendation.

**8. "... prophylactic use to reduce tumor hypoxia."**

Oncologists do not use ESAs for this indication outside of clinical trials, and we do not disagree with this recommendation.

**10. "... patients with treatment regimens including anti-angiogenic drugs such as bevacizumab."**

Bevacizumab and other anti-angiogenic drugs are an important part of many chemotherapy regimens for cancer patients, and patients receiving these agents often become anemic. No evidence has been put forward to support the noncoverage of ESAs for these patients.

**11. "... patients with treatment regimens including monoclonal/polyclonal antibodies directed against the epidermal growth factor (EGF) receptor."**

Anti-EGFR agents are an important part of many chemotherapy regimens for cancer patients, and patients receiving these agents often become anemic. No evidence has been put forward to support the noncoverage of ESAs for these patients.

**13. "... patients with thrombotic episodes related to malignancy."**

The studies showing increased risk of thrombotic events in patients receiving ESAs have uniformly used excessively high doses of ESAs or excessively high Hgb/Hct targets. The finding that patients treated excessively with ESAs have an increased risk of thrombotic events is not a valid reason to deny coverage for ESAs for all patients experiencing thrombosis, even at lower Hgb/Hct levels.

The proposed NCD also suggests “that ESA treatment is only reasonable and necessary under specified conditions for the treatment of anemia in those types of cancer in which the presence of erythropoietin receptors on either normal tissue/cell lines or malignant tissue/cell lines has been reported in the literature.” (A list of 18 selected malignancies is given.) No evidence has been presented to show that benefit from treatment with ESAs is limited to patients with these tumor types (which, incidentally, amount to approximately 78.7% of cancer cases in the United States in 2007)<sup>15</sup>, or that patients with other tumor types have less benefit or no benefit.

The proposed NCD gives specific parameters for which use of ESAs is or is not proposed to be reasonable and necessary. The following proposed requirements are discussed below:

1. **“the hemoglobin/hematocrit levels immediately prior to initiation of dosing for the month should be <9 g/dl/27% in patients without known cardiovascular disease and <10 g/dl/30% in patients with documented symptomatic ischemic disease that cannot be treated with blood transfusion (The latter patients should be alerted to the increased potential for thrombosis and sequelae.) (We suggest that patients, especially those in the latter category, be alerted to the increased potential for thrombosis and sequelae.) “**

Many clinical studies, evidence-based guidelines and years of experience support the initiation of ESAs when the hemoglobin falls below 11 g/dL or the hematocrit falls below 33%. No evidence has been presented to support this more restrictive guideline.

2. **“the maximum covered treatment duration is 12 weeks/year; “**

The duration of anemia in patients requiring ESAs is dependent on their underlying medical condition. In particular, patients with chronic medical conditions such as myelodysplastic syndromes have chronic anemia and require ongoing treatment with ESAs if this treatment is elected. No evidence has been presented to support cutting off coverage for ESAs after twelve weeks of treatment. This restriction would have particularly devastating effects on patients with chronic ESA-responsive anemias.

3. **“the maximum covered 4 week treatment dose is 126,000 units for erythropoietin and 630 µg for darbepoietin (*sic*); “**

These limits equate to an average dose of 31,500 units per week for erythropoietin and 157.5 mcg for darbepoietin. The standard of care for patients receiving ESAs includes doses of erythropoietin from 10,000 to 60,000 units per week and doses of darbepoietin from 100 to 200 mcg per week. No evidence has been presented to support these dose-restrictions.

4. **“continued use of the drug is not reasonable and necessary if there is evidence of poor drug response (hemoglobin/hematocrit rise <1 g/dl/<3%) after 4 weeks of treatment; “**

(See Item 6.)

5. **“continued administration of the drug is not reasonable and necessary if there is an increase in fluid retention or weight (5 kg) after 2 weeks of treatment ... “**

Patients may have rapid weight gain for various reasons, not solely due to ESA use. The judgment as to whether a particular adverse event such as fluid retention is due to ESA use must be left to the clinician and should not be the subject of a blanket requirement to stop the ESA.

6. "continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin/hematocrit >1 g/dl/>3% after 2 weeks of treatment. "

An excessively rapid rise in the hemoglobin or hematocrit is grounds for decreasing the dose of the ESA or interrupting its use temporarily. It is not grounds for declaring the ESA not reasonable and necessary and prohibiting its use entirely. It should be noted that Items 4 and 6 together require that the hemoglobin must rise less than 1 g/dL after two weeks of treatment, but more than 1 g/dL after four weeks of treatment in order to continue ESA treatment. It would be frankly impracticable to attempt to maintain the hemoglobin within this extremely narrow range during the first four weeks of treatment.

### Risks of blood transfusions

The proposed NCD suggests blood transfusions as an alternative to treatment with ESAs. It should be noted that ESAs were originally developed to lessen the dependence of patients with end-stage renal disease on blood products. Blood transfusion therapy is not harmless and comes with its own risks and benefits. An estimated 20% of blood transfusions result in an adverse effect, and an estimated 0.5% of blood transfusions result in serious harm.<sup>17</sup> Possible adverse effects of blood transfusions include:

- hemolytic transfusion reactions due to incompatibility;
- febrile transfusion reactions;
- transfusion-related acute lung injury (TRALI);
- allergic or anaphylactic reactions;
- infectious disease transmission, including human immunodeficiency virus (HIV), viral hepatitis, cytomegalovirus, human T-lymphotropic virus type 1 (HTLV-1), Epstein-Barr virus, and bacterial sepsis;
- alloimmunization resulting in increased refractoriness to transfusion therapy (1% of patients);
- congestive heart failure due to volume overload; and
- secondary iron overload, particularly in patients with myelodysplastic syndromes.

Widely-used guidelines for blood product use require the presence of severe anemia (usually hemoglobin < 7-8 g/dL for asymptomatic patients, 8-10 g/dL for symptomatic or other selected patients, and rarely or never for patients with hemoglobin > 10 g/dL) before transfusions of packed red blood cells are given. Allowing cancer patients to develop anemia of this severity before any effective treatment can be given often results in complications such as angina pectoris, myocardial infarction, congestive heart failure, and worsening pulmonary status, particularly in patients with pre-existing cardiac or pulmonary disease. This seriously jeopardizes their overall health and impedes effective treatment for their malignancy.

### FDA review process

The Oncology Drugs Advisory Committee (ODAC) of the Food and Drug Administration (FDA) met in May 2007 to review the issue of ESA safety. Among their findings and recommendations were the following:

- ODAC recommended that additional trials using ESAs be done to clarify safety issues; however, it did not recommend that patients be required to enroll in a trial in order to receive ESAs.
- ODAC recommended that a hemoglobin level be defined at which ESA treatment should be initiated; however, it did not recommend that ESA dosing be adjusted solely with the goal of avoiding blood transfusions.
- ODAC agreed that ESAs are a valuable component of supportive care and that their use reduces the risks associated with blood transfusions.
- ODAC noted that excessive restrictions on ESA use could increase the frequency of blood transfusion and increase the burden on the blood supply.

FDA has not yet acted on the ODAC recommendations and should be given an opportunity to do so.

### Conclusion

The use of erythropoiesis-stimulating agents (ESAs) has been of enormous benefit to patients with anemia, and in particular to patients with cancer—those who are receiving chemotherapy as well as those who are not receiving chemotherapy. Numerous previous studies have clearly demonstrated that treatment with ESAs results in improved quality of life as well as decreased need for packed red blood cell transfusions. The long-term safety and efficacy of ESAs, when used in accordance with the current standard of care and under currently accepted, evidence-based guidelines, is well-established.

Recent studies raising safety concerns regarding the use of ESAs, without exception, either involved administering ESAs in ways that would be considered inappropriate by today's standards (i.e., using an unreasonably high hemoglobin/hematocrit target or not monitoring treatment adequately), or have not been reported in their entirety and thus cannot be commented on adequately. These studies should constitute a warning not to use ESAs inappropriately. They do not change the established fact that ESAs are safe and effective when used correctly, and they should not lead to unreasonable restrictions on the use of ESAs, particularly in cancer patients.

We are particularly alarmed about CMS's suggestion that "coverage for ESA therapy for Medicare beneficiaries with cancer should occur only within appropriately designed clinical research studies where informed consent and safety monitoring can be assured." Making patients' ability to receive a safe, effective, FDA-approved drug contingent upon their participation in a clinical trial is an unreasonably coercive and—to our knowledge—unprecedented restriction, and appears to violate the Nuremberg Code's requirement that participants in medical research be afforded "free power of choice, without the intervention of any element of ... constraint or coercion."<sup>16</sup>

Cancer patients, including those who have discontinued chemotherapy or whose condition does not permit treatment with chemotherapy, are faced with severe, life-threatening medical problems, and improving quality of life in these patients is of the utmost importance. Previous studies of ESAs have consistently demonstrated improved quality of life using validated and reproducible QOL measures in patients with cancer.<sup>8-14</sup> The benefits of ESAs in cancer patients are significant and should not be discarded lightly. New study results that raise the possibility of adverse effects should be taken seriously and should be subjected to peer review and open discussion; however,

they should not be the basis for denying patients safe and effective treatment. Guidelines for the use of ESAs should be evidence-based and not arbitrary.

Cancer patients routinely receive FDA-approved chemotherapy drugs with significant, even life-threatening toxicities (usually far greater than those being attributed to ESAs), because the benefits of such treatment are sometimes found to outweigh the risks. Weighing these risks and benefits must be done by the patient and their physician, taking into account the patient's individual medical condition and wishes. This careful analysis may result in a recommendation by the physician, and a decision by the patient, in favor of a treatment with the potential for adverse effects if the benefits are felt to outweigh the risk in that patient's particular case. The decision to use an ESA in a particular patient should be made by the patient and their physician after a frank discussion of the risks, benefits and alternatives of ESA therapy.

On behalf of the Connecticut Oncology Association and patients with cancer and blood disorders in Connecticut, we urge you not to adopt the proposed NCD restricting the use of erythropoiesis-stimulating agents (ESAs).

Thank you very much for your consideration.

Sincerely,

---

Stephen C. Lattanzi, M.D.  
Vice President, Connecticut Oncology Association

Joseph A. O'Connell, M.D.  
President, Connecticut Oncology Association

## References

1. DAHANCA 10 study referenced in FDA alert of 11/16/2006, updated 2/16/2007 and 3/9/2007; trial not published
2. Amgen study referenced in FDA alert of 11/16/2006, updated 2/16/2007 and 3/9/2007; trial not published
3. Wright JR *et al.* Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. *J Clin Oncol* 2007 Mar 20; 25(9)—epub ahead of print)
4. Hoffman-La Roche study referenced in FDA alert of 11/16/2006, updated 2/16/2007 and 3/9/2007; trial not published
5. Ortho Biotech study referenced in FDA alert of 11/16/2006, updated 2/16/2007 and 3/9/2007; trial not published
6. Druke TB *et al.* Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006; 355: 2071-84.
7. Singh AK *et al.* Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; 355: 2085-98.
8. Cella D *et al.* The longitudinal relationship of hemoglobin, fatigue and quality of life in anemic cancer patients: results from five randomized clinical trials. *Ann Oncol* 2004; 15: 979-86.
9. Littlewood TJ *et al.* Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2001; 19: 2865-74.
10. Glaspy J *et al.* Darbepoetin alfa given every 1 or 2 weeks alleviates anaemia associated with cancer chemotherapy. *Br J Cancer* 2002; 87: 268-76.
11. Cella D *et al.* Control of cancer-related anemia with erythropoietic agents: a review of evidence for improved quality of life and clinical outcomes. *Ann Onc* 2003; 14: 511-9.
12. Glaspy J *et al.* A randomized, active-control, pilot trial of front-loaded dosing regimens of darbepoetin-alfa for the treatment of patients with anemia during chemotherapy for malignant disease. *Cancer* 2003; 97: 1312-20.
13. Vansteenkiste J *et al.* Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. *J Natl Cancer Inst* 2002; 94: 1211-20.
14. Hedenus M *et al.* Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: a randomized, double-blind, placebo-controlled study. *Br J Haematol* 2003; 122: 394-403.
15. Jemal A *et al.* Cancer statistics, 2007. *CA Cancer J Clin* 2007; 57: 43-66.
16. Directives for human experimentation (Nuremberg Code). From: *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Vol. 2, pp. 181-182.* Washington, D.C.: U.S. Government Printing Office, 1949
17. Complications of transfusion. In: McCullough J. *Transfusion medicine.* New York: McGraw-Hill, 1998. 337-359.
18. Grote T *et al.* Efficacy and safety analysis of epoetin alfa in patients with small-cell lung cancer: a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2005 Dec 20;23(36):9377-86.
19. Leyland-Jones B *et al.* Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *J Clin Oncol* 2005 Sep 1;23(25):5960-72.
20. Rosenzweig MQ *et al.* The decision to prematurely terminate a trial of R-HuEPO due to thrombotic events. *Pain Symptom Manage* 2004 Feb;27(2):185-90.
21. Henke M *et al.* Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet* 2003 Oct 18;362(9392):1255-60.
22. Henke M and Pajonk F. Erythropoietin to treat anaemia in patients with head and neck cancer. *Lancet* 2004; 363: 993.
23. A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes. Italian Cooperative Study Group for rHuEpo in Myelodysplastic Syndromes. *Br J Haematol* 1998; 103:1070-4,
24. Giraldo P *et al.* Darbepoetin alpha for the treatment of anemia in patients with myelodysplastic syndromes. *Cancer* 2006; 107: 2807-16.
25. Mannone L *et al.* High-dose darbepoetin alpha in the treatment of anaemia of lower risk myelodysplastic syndrome: results of a phase II study. *Br J Haematol* 2006; 133: 513-9.
26. Musto P *et al.* Darbepoetin alpha for the treatment of anaemia in low-intermediate risk myelodysplastic syndromes. *Br J Haematol* 2005; 128: 204-9.

27. Spiriti MA et al. Impact of a new dosing regimen of epoetin alfa on quality of life and anemia in patients with low-risk myelodysplastic syndrome. *Ann Hematol* 2005; 84: 167-76.
28. Stasi R et al. Darbepoetin alfa for the treatment of anemic patients with low- and intermediate-1-risk myelodysplastic syndromes. *Ann Oncol* 2005; 16: 1921-7.

# Hematology-Oncology Associates Of Boca Raton, P.A.

Sunil Patel, M.D. Samarth Reddy, M.D.  
9980 Central Park Blvd., Suite 216, Boca Raton, FL 33428  
Telephone: (561) 482-6611  
Fax: (561) 482-3056

June 1, 2007

We are a Hematology-Oncology Practice located in Palm Beach County serving predominantly elderly population. Our patients are quite concerned and have voiced a strong desire about recently purposed changes in the erythropoietin stimulating agents availability.

CMS has purposed non-coverage for many of the conditions which predominantly affect this elderly group of the patients who also suffer from underlying extensive angina, heart problem, emphysema, and peripheral vascular disease. Many of these patients require high degree of hemoglobin to be fully functional and avoid the symptoms related to emphysema, angina, and poor circulation.

Non-coverage related to the myelodysplasia, anemia of a malignancy, related to the radiation therapy and related to the chemotherapy would lead to significant interruption in these patients planned therapy. There also is a significant shortage of blood products available in the country.

None of the area hospitals are currently fully equipped to handle additional inflow of the patients for blood transfusion. In addition, blood transfusion is certainly associated with significant risk of transfusion reactions including life-threatening TRALI syndrome, fluid overload, and infectious complications. This would certainly cause lot of emotional and mental distress to this elderly population.

Accordingly, we strongly urge CMS that current indication for erythropoietin stimulating agents be maintained with some strict criteria. We certainly support the idea of discontinuing the erythropoietin therapy at hemoglobin of 12.

We urge CMS on behalf of myself, my associate Dr. Samarth Reddy, my office staff, and our patients that current indication for erythropoietin therapy be maintained.

---

**Sunil Patel, M.D.**

SP/AS/GS

***Dictated but not verified, subject to dictation/transcription variance.***

**Ciccanti, Maria L. (CMS/OCSQ)**

---

**From:** Dr. Beeker [Dr.Beeker@southerncancercenter.com]

**Sent:** Thursday, June 14, 2007 1:22 PM

**To:** Ciccanti, Maria L. (CMS/OCSQ)

**Subject:** ESA's for nonrenal indications.

Dear Ms. Ciccanti,

I am writing to you in regards to the use of erythropoietins for non renal induced anemia. There has been some concern that medicare will not cover erythropoietin for diseases such as myelodysplasia (MDS). Numerous studies have shown that patients with MDS can obtain significant improvement in their peripheral counts (wbc, rbc and platelets) with the use of growth factor stimulants such as erythropoietin. With the U.S. population getting older the number of MDS patients will continue to increase and not allowing the use of erythropoietin in their care will have dramatic effects on health care. We will be denying a treatment which has shown a response rate of 20-30% in patients with few options. Some people have advocated supporting patients with MDS with transfusions. This is not feasible. Blood products such as packed red blood cells and platelets are in high demand and in short supply. Blood banks across the country are barely able to cover the current needs for blood products due to emergency surgery, elective surgery, and for other disease processes such as leukemia, lymphoma, and multiple myeloma. The blood banks will not be able to keep up with this dramatic increase in demand for products such as packed red blood cells. The national blood supply is already diminishing, straining to keep up with the current need across the U.S. and abroad to support our troops injured in the service of their country. Without the ability to use erythropoietin in the treatment of patients with MDS you will be placing all patients who require transfusion support at risk due to the lack of a valuable biologic commodity, blood. Decisions made in regards to the use of erythropoietin for MDS will have more reaching consequences other than the cost savings from using blood transfusions instead of erythropoietin.

Thank you for your consideration.

Thaddeus A. Beeker M.D. Medical Oncologist

06/18/2007





June 11, 2007

Steve Phurrough, M. D., MHA  
Director

Maria Ciccanti, RN  
Lead Analyst

Shamiram Feinglass, MD. MPH  
Lead Medical Officer

Coverage and Analysis Group  
Centers for Medicare and Medicaid Services  
7500 Security Blvd  
Baltimore, MD 21244-18850

Re: NCD: NCA for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N)

Dear Drs. Phurrough and Feinglass and Ms. Ciccanti,

On behalf of the Mississippi Society of Oncology, I would like to submit the following comments regarding the proposed NDC for ESAs. The Mississippi Society of Oncology is the statewide organization representing hematologists and oncologists in Mississippi. Our patients receive services in both institutional and community based settings.

We have been very active in working with our Part B carrier especially in the area of ESAs. We do support the use of policies that are necessary for guidance. However, these proposed changes go beyond the scope of reimbursement issues and will restrict the access of Medicare beneficiaries to this therapy.

The FDA effectively has handled the safety concerns with the summary statement of the FDA black box warning for ESAs and is a reasonable warning that provides appropriate guidance for physicians. Per CMS regulations drugs and biologics that are FDA approved that are medically reasonable are reimbursable. ESAs are FDA approved and are effective treatment in relieving symptoms of anemia in cancer patients receiving chemotherapy and in preventing transfusions and have been considered medically reasonable. The potential risks and safety issues for certain patients is a treatment decision that should be made by the physician and the patient. Therefore, this should not be an issue for CMS regarding reimbursement. We understand the need for policy but any policy should reflect not only

available clinical evidence but also respect for physician discretion in making patient-specific decisions that are appropriate for each individual patient. Under this restrictive policy the Medicare beneficiary would not be allowed access to reasonable treatment and would in effect be discriminated against as opposed to a non Medicare patient in being able to receive appropriate therapy.

The benefits of ESAs have been documented over the last 20 years and have dramatically changed the delivery of care to the cancer patient. The drugs are safe and the benefits to the patients when administered in accordance with doses and approved by the FDA greatly exceeds the risks to patients with Myelodysplastic Syndromes, Multiple Myeloma, and anemia associated with chemotherapy.

Clinical trials provide data and as community oncologists we see the “real” data as once these drugs were utilized the quality of life of cancer patients changed dramatically. ESAs improved the quality of life and well-being of these patients. ESA administration obviously has proven benefits in the avoidance of transfusions and this is a significant outcome. Avoiding transfusions and the complications that can result has allowed patients and caregivers to be able to continue in meaningful employment thereby continuing to contribute. Transfusions management is not the equivalent of hemoglobin maintenance achieved by ESA therapy. Patient access to appropriate facilities, patient inconvenience and demand for the resources of the blood banks are of concern as well.

The safety concerns that prompted the review are based on trials with hemoglobin targets that are higher than what is standard and exceeded target hemoglobin of 12 g/dl. We don't believe these studies reflect the standard of care. The published evidence supports favorable risk-to-benefit ratio for the use of ESAs in patients with Multiple Myeloma, and anemia associated with cancer therapy. It will be an injustice to Myelodysplastic syndrome patients to be required to have multiple transfusions and iron overload and subsequent organ failure as a result of restriction by CMS to medically reasonable treatment.

Use of a hemoglobin of <9 g/dL as a treatment initiation point is inadequate and was overturned in policy revision years ago. There are no trials that support this restriction. NCCN information supports the initiation of ESAs at hemoglobin levels less than 11 g/dL. ESA therapy should be provided at a hgb level of 11 g/dL and should be continued to a target of 12 g/dL which is our current local policy.

The clinical trials of ESAs demonstrate that 6 – 8 weeks may be required to achieve a 1 g/dL rise and therefore the proposed rule to stop at 4 weeks if a rise is not achieved is not consistent with data.

Dose escalation has been effective in patients that fail to initially respond and has become part of the standard of care.

Maximum treatment duration of 12 weeks per year is totally inadequate for many patients. We cannot determine any clinical justification for this proposed restriction.

Exclusion of patients receiving anti-angiogenic therapy is not based on clinical evidence and would further restrict reasonable care for these patients.

There will be no cost savings to the program as cost shifting will result from multiple transfusions and hospitalizations and potential tax paying employees that have to stop employment due to fatigue or

(patients and caregivers) lose their jobs due to time away from work for long transfusions or hospitalizations.

On behalf of the Mississippi Society of Oncology I would urge CMS to reevaluate the proposals. These changes have potentially life-altering consequences. This is one area where the usefulness and effectiveness of the therapy has been clearly demonstrated by the patients by making a significant difference in the quality of their daily life and their ability to continue to receive treatment for their diseases.

Sincerely,

A handwritten signature in black ink, appearing to read "Van L. Lackey". The signature is fluid and cursive, with a large initial "V" and "L".

Van L. Lackey, M. D., President  
MS Society of Oncology

Cc: Dr. Jim Strong  
Senator Trent Lott  
Senator Thad Cochran  
Congressman Chip Pickering

213



W. T. Bruns, MD, FAAP, FACCP  
9160 SW 192<sup>nd</sup> Court Rd  
Dunnellon, FL 34432

31 May 2007

Center for Medicare & Medicaid Services  
**Oncology Drug Advisory Committee**  
7500 Security Boulevard  
Baltimore, MD 21244

Re: **Procrit & Aranesp**

Dear Center for Medicare and Medicaid Services,

I wish to voice my strong objections to the planned changes in the rules for the administration of anemia correcting medications (Procrit and Aranesp).

These injections are not just ameliorating substances but truly life saving drugs for many patients.

1. While their use for individuals with normal or high normal hemoglobin values should be stopped, it is also medically unconscionable to set the cut-off level at 9 gm of hemoglobin, at which point many patients incur difficulties in performing moderate physical work.
2. To artificially limit the treatment with these substances to only 12 weeks per year defies any therapeutic logic.
3. The reimbursement to the treating physicians should be realistic and not to be pushed to a low point, where it will become a financially losing therapy and undoubtedly leave many anemic patient to a poorly or even untreated fate. Switching the treatment to hospital clinics because of their discounted ESA prices would increase the hardship for most patients because of notoriously much longer waiting times and a farther traveling distance.

I have no remunerating personal interest in this. I am a retired physician who has contact with anemic individuals receiving above medications. But I feel distressed reading about the contemplated changes in this program which most certainly will lead to sicker patients and potentially deaths.

I urge you to give your plans a more humane and logical approach, which will avoid a waste of Medicare funds, but still achieve the goals for which Medicare had been started.

Sincerely yours . .

**Ciccanti, Maria L. (CMS/OCSQ)**

**From:** CMS CAGInquiries  
**Sent:** Tuesday, June 05, 2007 7:30 AM  
**To:** Ciccanti, Maria L. (CMS/OCSQ)  
**Subject:** FW:

**From:** Walt Moyer [mailto:Wmoyer@utahcancer.com]  
**Sent:** Monday, June 04, 2007 5:30 PM  
**To:** CMS CAGInquiries  
**Subject:**

Title of NCA/CAL: Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications

Public Comment re: Erythropoiesis Stimulating Agents (ESAs) guidelines

As an employee of Utah Cancer Specialists, and patient care advocate, I am concerned about the proposed erythropoietic stimulating agent (ESA) guidelines under consideration. While I understand the need for proper use of these medications, the proposal falls short of providing the best standard of care recommended by oncology organizations such as NCCN, ASCO and ASH. The current proposals will result in a compromised quality of life for our patients, increased blood transfusion requirements with the associated co-morbidity and risk and, ultimately, prove more costly to society than judicious use of ESAs. Please reconsider these guidelines encouraging physicians to carefully weigh the risk/benefit with patients and allow providers to treat this growing population with the best and most compassionate standard of care.

Chemotherapy-induced anemia is a well-known side effect of myelosuppressive therapy. Furthermore it is quite responsive to ESAs when iron stores, vitamin B12 and folate deficiencies and other underlying processes have been corrected. Holding initiation of ESA until the hemoglobin drops to  $<9\text{mg/dl}$  will delay response and most likely result in transfusion for a greater number of our chemotherapy patients. Most chemotherapy regimens last a minimum of 16 weeks (and many are much longer). Therefore, limiting the covered treatment duration to 12 weeks annually will be inadequate treatment for many of our patients on continued myelosuppressive therapy.

According to the proposed guidelines, the Myelodysplastic Syndrome population will be denied access to any form of ESA under all circumstances. While a portion of the MDS patients will not respond to ESAs, a greater number benefit from these medications; reducing the number of necessary blood transfusions, eliminating the complications of iron overload that results from transfusion, enhanced productivity by limiting time spent in a healthcare facility, and an overall improved quality of life.

We do not dispute the recommendations to discontinue use of the ESAs if the patient is non-responsive to treatment, however:

- The recommended four weeks is an inadequate timeframe in which to evaluate patient responsiveness. Former guidelines allow 12 weeks to determine response. Clearly, four weeks is an irresponsible timeframe.
- The proposed maximum treatment dose is insufficient to provide standard doses within the recommended timeframes. The maximum covered four-week treatment dose is 126,000units of Procrit and 630mcg of Aranesp. At an average dose of 40,000 units of Procrit each week, we would need 160,000 units in four weeks. The average dose of Aranesp is 300mcg per 2 weeks – so the 630mcg would be sufficient.

We encourage you to reconsider the list of specified conditions to include other myeloid and erythroid cancers as well as anemia caused by radiotherapy. Some patients will respond, therefore a trial of an ESA medication seems prudent.

Thank you for your consideration of this request. As a community oncology practice we strive to provide the optimal care to our patients. Please allow us the support we need to continue this practice.

Respectfully,

Walter A. Moyer  
 CEO  
 Utah Cancer Specialists P.C.

06/11/2007

170



National  
Comprehensive  
Cancer  
Network®

500 Old York Road  
Suite 250  
Jenkintown, PA 19046  
215.690.0300  
Fax: 215.690.0280  
www.nccn.org

William T. McGivney, PhD  
Chief Executive Officer  
mcgivney@nccn.org

June 12, 2007

Steve E. Phurrough, MD, MPA  
Director, Coverage and Analysis Group  
Centers for Medicare & Medicaid Services  
Mail Stop C1-09-06  
7500 Security Boulevard  
Baltimore, MD 21244

Dear Dr. Phurrough:

The National Comprehensive Cancer Network (NCCN) is pleased to provide comments in response to the Proposed Decision Memo (CAG 00383N) for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications. The NCCN shares the commitment of our colleagues at CMS to base decisions on the best available scientific evidence in order to assure safe and effective care for the patients whom we serve. NCCN limits our comments to those issues relating to the management of patients with cancer.

On March 9, 2007, the FDA announced alerts and strengthened safety warnings for the use of Erythropoiesis-Stimulating Agents (ESAs). They noted that increased mortality, possible tumor promotion, and thromboembolic events have been observed in patients receiving ESAs when dosing has targeted hemoglobin levels >12 g/dL in several patient subsets: chronic kidney failure, head and neck cancer receiving XRT, in cancer patients not receiving chemotherapy, in orthopedic surgery patients. The recommended labeled target hemoglobin in current product labeling is 12 g/dl: (<http://www.fda.gov/cder/drug/advisory/RHE2007.htm>). Following the FDA announcement, relevant NCCN panels met to discuss how this new information should be incorporated into their recommendations regarding use of these agents.

As a result of the FDA statements, the Centers for Medicare and Medicaid Services (CMS) have issued a Proposed Coverage Decision Memorandum for the Use of Erythropoiesis Stimulating Agents in Cancer and Related Neoplastic Conditions. Although the prompt response of CMS to the FDA issued warning is commendable as it works toward protecting patients, the broad-based language of the proposed coverage decision memorandum is inconsistent with both published data and FDA package inserts for epoetin alfa and darbepoetin. NCCN appreciates the opportunity to comment on the Proposed Decision Memo.

- City of Hope
- Dana-Farber/Brigham and Women's Cancer Center  
Massachusetts General Hospital  
Cancer Center
- Duke Comprehensive  
Cancer Center
- Fox Chase Cancer Center
- Huntsman Cancer Institute  
at the University of Utah
- Fred Hutchinson Cancer  
Research Center/  
Seattle Cancer Care Alliance
- Arthur G. James Cancer  
Hospital & Richard J. Solove  
Research Institute at  
The Ohio State University
- The Sidney Kimmel  
Comprehensive Cancer Center  
at Johns Hopkins
- Robert H. Lurie Comprehensive  
Cancer Center of Northwestern  
University
- Memorial Sloan-Kettering  
Cancer Center
- H. Lee Moffitt Cancer Center  
& Research Institute at the  
University of South Florida
- Roswell Park Cancer Institute
- Siteman Cancer Center at  
Barnes-Jewish Hospital and  
Washington University  
School of Medicine
- St. Jude Children's  
Research Hospital/  
University of Tennessee  
Cancer Institute
- Stanford Comprehensive  
Cancer Center
- University of Alabama  
at Birmingham Comprehensive  
Cancer Center
- UCSF Comprehensive  
Cancer Center
- University of Michigan  
Comprehensive  
Cancer Center
- UNMC Eppley Cancer  
Center at The Nebraska  
Medical Center
- The University of Texas  
M. D. Anderson Cancer Center
- Vanderbilt-Ingram  
Cancer Center

50

<b>CMS Restriction by Disease State</b>	<b>NCCN Comment</b>
<p>1. Any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis</p>	<p>NCCN guidelines are consistent with the restriction.</p>
<p>2. The anemia of myelodysplasia</p>	<p>NCCN Guidelines recommend the use of ESAs in symptomatic MDS patients. ESAs have been used safely in large numbers of adult MDS patients and have become important for symptomatic improvement of those affected by the anemia caused by this disease often with a decrease in RBC transfusion requirements. Published data on the safe and effective use of ESAs in MDS patients that span more than a decade are available. (NCCN MDS Practice Guidelines v.1.2007, especially see algorithm on MDS-6, <a href="http://www.nccn.org">www.nccn.org</a>).</p> <p>Studies assessing the long term use of erythropoietin with or without GCSF in MDS patients compared to either randomized controls<sup>1</sup> or historical controls<sup>2,3,4</sup> have shown no negative impact on survival or AML evolution of such treatment. In addition, reference 3 indicates improved survival in low risk MDS patients with low transfusion need treated with these agents. Reference 4 indicates improved survival and decreased AML progression of International Prognostic Scoring System (IPSS) Low/Int-1 patients treated with erythropoietin /GCSF compared to the historical control International MDS Risk Analysis Workshop (IMRAW) database patients (IPSS and IMRAW database<sup>5</sup>). Thus, these data do not indicate a negative impact of these drugs for treatment of MDS and indicate potentially improved survival.</p> <p>In addition to the positive impact on survival and transformation to AML, accumulating data in MDS indicate that debilitating fatigue and transfusion dependence significantly negatively impact patients' quality of life<sup>6</sup>. Symptomatic relief from anemia with ESAs should remain a therapeutic option for those MDS patients who have been shown to benefit from such treatment.</p>

	<p>A major aim in management of MDS patients having symptomatic anemia is to decrease the need for RBC transfusions. The potential negative consequences of recurrent RBC transfusions are well recognized---iron overload, viral infections, transfusion reactions, isosensitization to platelets, negative impact on quality of life. This is in addition to the potential negative impact on national blood supply resources.</p> <p>The NCCN MDS Practice Guidelines Committee met recently and endorsed and re-iterated its prior recommendations for ESA use in the management of symptomatic anemia in MDS patients (NCCN MDS Practice Guidelines v.1.2007), albeit with a change in the target hemoglobin—i.e., to aim for a target hemoglobin of up to 12g/dl (v.1.2008). The NCCN guidelines recommend that MDS patients with symptomatic anemia and with serum epo levels <math>\leq 500</math>, who are iron replete and have no other causes for their anemia (e.g., B12 or folate deficiency, hemolysis, blood loss) would be candidates for ESA therapy.</p>
<p>3. The anemia of myeloid cancers</p>	<p>Recommendations: NCCN has not made recommendations regarding the use of ESAs in hematologic malignancies excluding myelodysplastic syndromes.</p> <p>NCCN supports further research in evaluation of the effect of ESA on quality of life, disease response/progression, and survival.</p> <p>The use of ESAs in hematological malignancies has been studied in a number of clinical trials. An analysis of these trials indicates the following benefits and harms:</p> <p>Potential Benefits: High quality randomized evidence indicate that ESA increases hemoglobin level and reduce transfusion risk in hematological malignancies, primarily Non-Hodgkin’s lymphoma, multiple myeloma, and MDS. It is also likely that ESAs improve quality of life.</p> <p>Potential Harms: ESA increases risk of thromboembolic events (TE) and probably hypertension. The effect of ESA on tumor growth and overall survival appears to be neutral.</p>

<p>4. The anemia associated with the treatment of myeloid cancers or erythroid cancers</p>	<p>Recommendations: NCCN has not made recommendations regarding the use of ESAs in treatment of treatment-related anemia in hematologic malignancies.</p> <p>NCCN supports further research in evaluation of the effect of ESA on quality of life, disease response/progression, and survival.</p> <p>The use of ESAs in hematological malignancies has been studied in a number of clinical trials. An analysis of these trials indicates the following benefits and harms:</p> <p>Potential Benefits: High quality randomized evidence indicate that ESA increases hemoglobin level and reduces transfusion risk in hematological malignancies. It is also likely that ESA improve quality of life.</p> <p>Potential Harms: ESA increases risk of thromboembolic events (TE) and probably hypertension. The effect of ESA on tumor growth and overall survival appears to be neutral.</p>
<p>5. The anemia of cancer not related to cancer treatment</p>	<p>NCCN guidelines are consistent with the restriction and NCCN supports further research of the effect of ESAs on quality of life, disease response/progression and survival.</p>
<p>6. Any anemia associated with radiotherapy</p>	<p>This issue is not directly addressed by NCCN guidelines. When radiotherapy is used with chemotherapy (excluding head and neck cancer patients), it may be reasonable to use ESAs provided the patient meets other criteria for their use; this is consistent with the recently revised FDA label.</p>
<p>7. Prophylactic use to prevent chemotherapy-induced anemia</p>	<p>NCCN guidelines are consistent with the restriction.</p>
<p>8. Prophylactic use to reduce tumor hypoxia</p>	<p>NCCN guidelines are consistent with the restriction.</p>

9. Patients with erythropoietin-type resistance due to neutralizing antibodies	NCCN do not address the restriction
10. Patients with treatment regimens including anti-angiogenic drugs such as bevacizumab	There are insufficient data to support or disagree with recommendation. NCCN supports further study of this issue.
11. Patients with treatment regimens including monoclonal/polyclonal antibodies directed against the epidermal growth factor (EGF) receptor	There are insufficient data to support or disagree with recommendation. NCCN supports further study of this issue..
12. Anemia due to cancer treatment if patients have uncontrolled hypertension	NCCN guidelines are consistent with the restriction for uncontrolled hypertension.
13. Patients with thrombotic episodes related to malignancy	NCCN guidelines do not directly address this issue, though a high index of suspicion for thrombosis is encouraged in patients with signs and symptoms of thrombosis who are being treated with ESAs.

CMS Proposed Restriction on ESA Use	NCCN Comments
<p>1. The hemoglobin/hematocrit levels immediately prior to initiation of dosing for the month should be &lt;9 g/dl/27% in patients without known cardiovascular disease and &lt;10 g/dl/30% in patients with documented symptomatic ischemic disease that cannot be treated with blood transfusion. (The latter patients should be alerted to the increased potential for thrombosis and sequelae.)</p>	<p><b>Hemoglobin levels at initiation:</b> NCCN guidelines recommend consideration of ESAs with a hemoglobin &lt; 11 g/dL. Numerous studies have documented the efficacy of ESAs in reducing red cell transfusion requirements and improving quality of life parameters in cancer patients receiving chemotherapy<sup>7, 8, 9</sup>. A 2006 meta-analysis analyzed data from 57 trials and 9353 cancer patients and demonstrated that ESAs significantly reduced the probability of a patient needing of red cell transfusions<sup>10</sup>. Guidelines recommendations from ASCO/ASH<sup>11</sup> and NCCN<sup>12</sup> which are based on results of clinical trials all recommend initiating ESA therapy at a hemoglobin level <math>\leq 10</math> g/dL with treatment continued as long as the patient is receiving therapy and remains anemic.</p> <p>The proposed CMS policy changes recommend starting ESAs at a lower hemoglobin level, and limiting the ESA dose and treatment period. These changes could result in patients being subjected to more severe anemia for longer periods of time. When ESAs are used in the approved fashion, there are insufficient data to support CMS restrictions.</p> <p><b>Transfusion:</b> NCCN guidelines recommend ESA use as an option to reduce the requirement for transfusions. This is consistent with FDA package inserts. The CMS Coverage Decision Memorandum indicates a preference for transfusion over ESA therapy. Following this CMS directive, transfusion requirements for patients would increase and patients requiring chronic red cell transfusions could develop iron overload (requiring iron chelation therapy), in addition to being exposed to other risks of blood transfusion (transfusion reactions, viral transmission). These risks are not described in</p>

	<p>the discussion of risk and benefit to be initiated with patients described by the Proposed Medicare Coverage Decision Memo. As such, the recommendation is unbalanced.</p> <p>Most medical centers have a limited blood supply; a significant reduction in appropriate ESA use would lead to an even tighter blood supply and the likelihood that many patients would experience delays in transfusion. We are concerned that the proposed policy changes would result in poorer patient outcome.</p>
<p>2. The maximum covered treatment duration is 12 weeks/year</p>	<p>NCCN guidelines do not recommend a specific duration of treatment, but rather, base this decision on medical necessity and response to ESA therapy. Given the duration of treatment for some malignancies, treatment with ESAs may be required for many months to maintain adequate hemoglobin levels.</p> <p>The proposed CMS policy changes recommend limiting the ESA dose and treatment period. These changes would result in patients being subjected to more severe anemia for longer periods of time. When ESAs are used in the approved fashion, there are insufficient data to support CMS restrictions.</p>
<p>3. The maximum covered 4 week treatment dose is 126,000 units for erythropoietin and 630 µg for darbepoetin</p>	<p>The NCCN guidelines recommend dosing consistent with FDA package insert. The proposed CMS policy changes recommend limiting the ESA dose and treatment period. These changes would result in patients being subjected to more severe anemia for longer periods of time. When ESAs are used in the approved fashion, there are insufficient data to support CMS restrictions.</p> <p>FDA package insert specifies up to 60,000 Units SC weekly for erythropoietin for patients who did not respond initially and had their dosage escalated. At this level, 240,000 Units could be required in a 4-week period. With</p>

	<p>respect to darbepoetin, the package insert specifies a once every three week dose of 500mcg as a SC injection. The second dose at the beginning of the second three week period would result in exceeding the 630 mcg dose specified by CMS.</p>
<p>4. Continued use of the drug is not reasonable and necessary if there is evidence of poor drug response (hemoglobin/hematocrit rise &lt;1 g/dl/&lt;3%) after 4 weeks of treatment</p>	<p>The NCCN guidelines specify a dose increase at 4 weeks if there was no response and titration to maintain hemoglobin between 11 and 12 g/dL. If there is no response at 9-12 weeks, NCCN recommends discontinuation. The Epoetin alfa FDA package insert indicates that dose should be increased if “response is not satisfactory (no reduction in transfusion requirements or rise in hemoglobin) after 8 weeks to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL.”</p> <p>The proposed CMS Coverage Decision Memo is not consistent with the labeled dosing or with the more conservative NCCN dosing recommendations which were based on clinical trials data. The CMS Coverage Decision Memo will result in patients who could benefit from the agent being denied it.</p> <p>With respect to darbepoetin, NCCN guidelines specify a dose increase at 6 weeks if there was no response and titration to maintain hemoglobin between 11 and 12 g/dL. If there is no response at 9-12 weeks, NCCN recommends discontinuation. The FDA package insert specifies that the “dose should be adjusted for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL. Increases should not be made more frequently than once a month, but “further increases may be made at 4-week intervals until the specified hemoglobin is obtained” with no specified</p>

	<p>temporal end point.</p> <p>Again, the proposed CMS Coverage Decision Memo is not consistent with the labeled dosing or the more conservative NCCN dosing recommendations which were based on clinical trials data. The CMS Coverage Decision Memo will result in patients who could benefit from the agent being denied it.</p>
<p>5. Continued administration of the drug is not reasonable and necessary if there is an increase in fluid retention or weight (5 kg) after 2 weeks of treatment</p>	<p>No comment</p>
<p>6. Continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin/hematocrit &gt;1 g/dl/&gt;3% after 2 weeks of treatment</p>	<p>NCCN guidelines are consistent with the FDA package inserts for both agents which address rapidly rising hemoglobin with instruction to reduce the dose by 25% for epoetin alfa and 40% for darbepoetin if hemoglobin approaches 12 g/dL or increases by &gt; 1 g/dL in any two weeks or withhold dose if the hemoglobin exceeds 12 g/dL until the hemoglobin falls below 11 g/dL and restart dose at 25% for epoetin alfa and 40% for darbepoetin below the previous dose. The proposed CMS Coverage Decision memo is inconsistent with these recommendations which were based on clinical trials data. The CMS Coverage Decision Memo will result in patients who could benefit from the agent being denied it.</p>

Again, NCCN applauds CMS for its interest in ensuring patients' safe and effective care. NCCN guidelines are in agreement with the CMS Coverage Decision Memo in the areas where there are data to support restriction such as prophylactic ESA use. We are in disagreement where there is inconsistency with evidence-based conclusions of the FDA, NCCN, and ASCO, and there are insufficient data to support CMS changes. We would be pleased to assist CMS in any way we can with evaluation of evidence and appreciate this opportunity to comment on the Proposed Coverage Decision Memo.

Sincerely,



William T. McGivney, PhD  
Chief Executive Officer

References:

1. Miller KB, Kim HT, Greenberg P, et al, Blood 104 (No. 11): 24a, 2004.
2. Jadersten M, Montgomery SM, Dybedal I, et al: Blood. 2005;106(3):803-11
3. Jädersten, Malcovati, Dybedal, et al. Blood 108 (#11), 158a (#521), 2006.
4. Park S, Grabar S, Kelaidi C, et al., Leukemia Res 31 (Suppl 1): #P135, S113, May, 2007.
5. Balducci L. Cancer. 2006;106:2087-2094.
6. Littlewood TJ, Bajetta E, Nortier JW, et al. J Clin Oncol. 2001;19:2865–2874.
7. Glaspy J. Best Pract Res Clin Haematol. 2005;18:407–416.
8. Hedenus M, Adriansson M, San Miguel J, et al. Br J Haematol. 2003;122:394–403.
9. Vansteenkiste J, Pirker R, Massuti B, et al. J Natl Cancer Inst. 2002;94:1211–1220
10. Bohlius J, Weingart O, Trelle S, et al. Nat Clin Pract Oncol. 2006;3:152–164.
11. Rizzo JD, Lichtin AE, Woolf SH, et al. Blood. 2002;100:2303–2320.
12. Rodgers GM, Cella D, Chanan-Khan A, et al. J Natl Compr Canc Netw. 2005;3:772–789.

**Ciccanti, Maria L. (CMS/OCSQ)**

**From:** CMS CAGInquiries  
**Sent:** Tuesday, June 19, 2007 9:29 AM  
**To:** Ciccanti, Maria L. (CMS/OCSQ)  
**Subject:** FW:

**From:** William Nibley [mailto:wnibley@utahcancer.com]  
**Sent:** Wednesday, June 13, 2007 12:19 PM  
**To:** CMS CAGInquiries  
**Subject:**

Title of NCA/CAL: Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications

Public Comment re: Erythropoiesis Stimulating Agents (ESAs) guidelines

As practicing medical oncologist, and an advocate for compassionate and responsible cancer care, I am deeply concerned about the proposed erythropoietic stimulating agent (ESA) guidelines under consideration.

I understand the need for proper use of these medications; however the proposal falls short of providing the best standard of care recommended by oncology organizations such as NCCN, ASCO and ASH. The current proposals will result in a compromised quality of life for cancer patients, increased blood transfusion requirements with the associated co-morbidity and risk and, ultimately, prove more costly to society than judicious use of ESAs. Please reconsider these guidelines and allow skilled practitioners to treat this growing population with the utmost standard of care.

Chemotherapy-induced anemia is a well-known side effect of myelosuppressive therapy. Furthermore it is quite responsive to ESAs when iron stores, vitamin B12 and folate deficiencies and other underlying processes have been corrected. Holding initiation of ESA until the hemoglobin drops to <9mg/dl will delay response and most likely result in transfusion for a greater number of our chemotherapy patients. Most chemotherapy regimens last a minimum of 16 weeks (and many are much longer). Therefore, limiting the covered treatment duration to 12 weeks annually will be inadequate treatment for many patients requiring continued myelosuppressive therapy.

According to the proposed guidelines, the Myelodysplastic Syndrome population will be denied access to any form of ESA under all circumstances. While a portion of the MDS patients will not respond to ESAs, a greater number benefit from these medications; reducing the number of necessary blood transfusions, eliminating the complications of iron overload that results from transfusion, enhanced productivity by limiting time spent in a healthcare facility, and an overall improved quality of life.

I do not dispute the recommendations to discontinue use of the ESAs if the patient is non-responsive to treatment, however:

- The recommended four weeks is an inadequate timeframe in which to evaluate patient responsiveness. Former guidelines allow 12 weeks to determine response. Clearly, four weeks is an irresponsible timeframe.
- The proposed maximum treatment dose is insufficient to provide standard doses within the recommended timeframes. The maximum covered four-week treatment dose is 126,000units of Procrit and 630mcg of Aranesp. At an average dose of 40,000 units of Procrit each week, we would need 160,000 units in four weeks. The average dose of Aranesp is 300mcg per 2 weeks – so the 630mcg would be sufficient.

It is critical that you reconsider the list of specified conditions to include other myeloid and erythroid cancers as well as anemia caused by radiotherapy. Some patients will respond, therefore a trial of an ESA medication seems prudent.

Thank you for your consideration and responsible action on this request.

Respectfully,

William Nibley, MD  
 Utah Cancer Specialists  
 President, Society of Utah Medical Oncologists

**DUKE UNIVERSITY HEALTH SYSTEM**

William J. Fulkerson, M.D. —  
Professor of Medicine  
Chief Executive Officer, Duke University Hospital  
Vice President, Duke University Health System

June 13, 2007

Facsimile Transmission  
Six Pages  
410 786-9286

Steve E. Phurrough, MD, MPA  
Director, Coverage and Analysis Group  
Centers for Medicare & Medicaid Services  
Mail Stop C1-09-06  
7500 Security Boulevard  
Baltimore, MD 21244

RE: National Coverage Analysis for Erythropoiesis Stimulating Agents (ESAs) for  
Non-Renal Disease Indications (CAG-00383N)

Dear Dr. Phurrough:

Since the opening of our School of Medicine and Hospital in 1930 and School of Nursing in 1931, the physicians, staff, and volunteers at Duke University Health System have striven to advance the quality and span of human life through innovation in clinical care and research, educate tomorrow's leaders in health care, meet the needs of the different communities we serve, and provide compassionate care to the poor and underserved. As part of our responsibility for leading the improvement of human health, we are compelled to comment upon and share our significant concerns regarding the recent proposed decision memorandum regarding coverage of erythropoiesis stimulating agents (ESAs) in non-renal disease indications (CAG-00383N).

As you well know, the use of ESAs in cancer patients is being challenged by the Centers for Medicare & Medicaid Services. CMS' proposal is being advanced without the recommendation from the Food and Drug Administration (FDA), the federal agency entrusted by Congress with the authority to make science-based recommendations on the usage of drugs and biologics. Such a precedent is disturbing at best, detrimental to providing quality patient care at worst. Scientists and clinicians at Duke stand united against the move to make CMS coverage decisions independent of the legal authority instilled in the FDA and unsupported by the best available clinical evidence.

There is more than sufficient clinical data to support the use of ESAs in the treatment of cancer patients. The American Society of Clinical Oncology (ASCO), the leading medical society for physicians involved in cancer treatment and research, has outlined in detail the scientific evidence supporting the use of ESA in their letter to you of June 8, 2007 (copy enclosed.) This letter articulates clearly the CMS coverage proposals and the direct contradiction or lack of scientific foundation for such payment restrictions. We stand in full support of ASCO, the National Comprehensive Cancer Network, and oncology scientific leaders nationwide in their opposition

Steve Phurrough, MD, MPA  
Centers for Medicare & Medicaid Services  
June 13, 2007

Page Two

to this challenge. We too urge the proposed decision memorandum be withdrawn and coverage restrictions be held in abeyance pending FDA review and decisions. We too urge that CMS coverage decisions with respect to ESAs be based on the approvals granted by the FDA rulings.

Duke University Health System is dedicated to providing the best possible care in the most welcoming environment with the optimal outcomes. Accomplishing this requires following evidence-based clinical guidelines and constantly striving to advance the science of medicine. We will be severely constrained in our ability to do this if CMS begins making clinical care coverage decisions independent of the legal and scientific authorities responsible for recommending the appropriate usage of drugs and biologics.

Sincerely,



William J. Fulkerson, MD, MBA

Enclosure

cc w/enclosure: Honorable Elizabeth Dole  
Fax 202 228-2787  
Honorable David Price  
Fax 202 225-2014



**SOUTHEASTERN  
GYNECOLOGIC ONCOLOGY, LLC**

June 12, 2007

Steve Phurrough, MD, MPA, CPE  
Director, Coverage and Analysis Group  
Office of Clinical Standards and Quality  
Centers for Medicare and Medicaid Services  
Department of Health and Human Services  
Mail Stop: C1-09-06  
7500 Security Boulevard  
Baltimore, Maryland 21244

**RE: Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N)**

Dear Dr. Phurrough,

We are writing in response to the solicitation for comments about the ESA proposed decision memo. As the largest private practice Gynecologic Oncology group in the country, we are quite concerned about the deleterious effects of the proposed changes. Individually, each criterion is flawed; taken together they may set back much of the progress made in oncology care over the 15 years. **Specifically, we are concerned that the proposed changes will:**

- Impede patients' ability to safely complete the chemotherapy treatment indicated for their disease
- Significantly reduce the patient's quality of life while doing so
- Prevent us from providing quality care for patients, due to the inflexibility and overly stringent restrictions of the protocol.

In addition to the impact on oncology patients, instituting these changes as proposed will lead to a significant increase in transfusions, potentially straining the blood supply and impacting the entire population. In our practice, we have not noticed a significant increase in the rates of thrombotic events or reduced progression free survival. Instituting these changes in the face of small numbers of complications and the widespread negative effects of withholding ESAs is simply overkill.

The table below summarizes the proposed changes and our current practice standards as well as our recommended changes.

<b>Proposed</b>	<b>Our Current Protocol/Recommended Change</b>
Initiate at < 9g/dl	Initiate < 11 g/dl
Max treatment duration 12 w/yr	As long as necessary to maintain hgb > 12 g/dl
Max covered dose of Procrit 126,000 units/4 weeks	At least 160,000 units/4 weeks (40,000 – 60,000 units/wk)
Max covered dose of Aranesp 630 ug/4 weeks	At least 1000 ug/4 weeks (250 ug/wk)
Continued use not covered if hgb rise < 1 g/dl	No limit until evidence shows otherwise.

**In our view, the most problematic of the criteria include the level at which ESAs may be initiated, the treatment duration limitation, the dosage limitations, the period of time to determine response, the elimination of ESAs during radiotherapy, and restricting the use of ESAs to research trials.**

First, prohibiting patients without known cardiac disease from receiving ESAs until their hemoglobin drops below 9 g/dl will likely result in patients becoming more anemic (and symptomatic) than they would if we started ESAs when the hemoglobin is less than 11 g/dl as is our practice's current protocol. For example, if a patient begins chemotherapy with hemoglobin greater than 9 and less than 10, it is likely that they will become significantly more anemic after therapy. Current NCCN Guidelines support the use of ESAs in asymptomatic patients with hemoglobin less than 11 g/dl, and risk factors for developing symptomatic anemia, including the use of myelosuppressive chemotherapy.<sup>1</sup> These patients are more likely to become symptomatic, requiring transfusions. Symptomatic anemia is not only uncomfortable, but may be dangerous, especially if occult cardiovascular disease is present (as is often the case in our patient population).

Patients who start with hemoglobin less than 9 g/dl are also more likely to respond slowly to ESA therapy, especially under the proposed dosage constraints. These patients are also more likely to require transfusion. In our practice, the vast majority of our patients receive carboplatin and paclitaxel. This regimen results in Grade 1 anemia (hemoglobin between 10 and 12 g/dl) in 35% of patients, Grade 2 anemia (hemoglobin between 8 and 10 g/dl) in 31% of patients, Grade 3 anemia (hemoglobin between 6.5 and 8 g/dl) in 18% of patients and Grade 4 anemia (hemoglobin less than 6.5 g/dl) in 1% of patients.<sup>2</sup> Most of our other frequently used regimens also carry significant risk of anemia. Clearly, nearly all of our chemotherapy patients are at *significant* risk of anemia.

**A more appropriate limit for beginning treatment with ESAs would be hemoglobin less than 11 g/dl or symptomatic anemia.**

Second, limiting the treatment duration to 12 weeks per year is simply inadequate. In our practice, patients who are being treated with chemotherapy are almost never treated for less than 18 weeks for their initial chemotherapy regimen. Most of these patients go on to receive 12 months of consolidation chemotherapy; many of these continue to require growth factor support to safely complete consolidation which contributes both to cure and progression-free survival.

---

<sup>1</sup> "Cancer- and Treatment-Related Anemia." NCCN Practice Guidelines in Oncology. v. 3.2007.

[http://www.nccn.org/professionals/physician\\_gls/PDF/anemia.pdf](http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf) Accessed 6/8/07.

<sup>2</sup> Bolis G, Scarfone, G, Polverino G et al. Paclitaxel 175 or 225 mg per Metes Squared with Carboplatin in Advanced Ovarian Cancer: A Randomized Trial. *J Clin Oncol*. 2004; 22:686-90.

As patients are treated for recurrence or progression, they are often treated with drugs that have more severe bone marrow toxicity while having a reduced capacity to produce erythrocytes without assistance (i.e., more patients require longer treatment with ESAs in order to maintain a tolerable hemoglobin level). With disease progression, patients are often treated without interruption for several months or even years, requiring ESA support throughout that timeframe.

**A more appropriate limit would be limiting treatment duration based upon hemoglobin response (i.e., reduce ESA dosages as hemoglobin levels improve and stop ESA use when hemoglobin rises above 12 g/dl) rather than a fixed period of time that cannot be generically applied to all oncology patients.**

Thirdly, limiting erythropoietin use to less than 126,000 units per four week period, especially when combined with a rule reducing the hemoglobin level at which ESA treatment can begin, will increase our use of blood transfusions. Limiting darbepoietin to 630 g per four week period prevents our use of this drug. In our patient population, this dosage is simply not effective.

**A more appropriate limit would be allowing the use of FDA-approved and typically effective dosages for these drugs: a minimum of 160,000 units to a maximum of 240,000 units of erythropoietin per four week period (weekly dose: 40,000 – 60,000 units) and a minimum of 1000 ug of darbopoetin per four week period (weekly dose: 250 ug) to treat patients who are slower responders or who start ESA use at a lower hemoglobin level (i.e., less than 9 g/dl).**

Fourth, while many patients receiving first line chemotherapy respond well to ESAs and will have at least 1 g/dl rise in hemoglobin after four weeks, some require up to 6 weeks for elevation of hemoglobin levels. In fact, the prescribing information for Procrit reads, "Because of the length of time required for erythropoiesis – several days for erythroid progenitors to mature and be released into the circulation – a clinically significant increase in hematocrit is usually not observed in less than 2 weeks and may require up to 6 weeks in some patients."<sup>3</sup> No studies have been done to show the length of time to response in slow responders or after what period of time a patient should be classified as a non-responder and ESA use stopped. Until there is good evidence, CMS should not make an arbitrary rule on this subject.

---

<sup>3</sup> Ortho Biotech. Procrit Full Prescribing Information.  
[http://www.orthobiotech.com/common/prescribing\\_information/PROCRIT/PDF/ProcritBooklet.pdf](http://www.orthobiotech.com/common/prescribing_information/PROCRIT/PDF/ProcritBooklet.pdf)  
Accessed 6/8/07.

Many or even most patients receiving second, third, fourth or fifth line therapy will take more than four weeks to respond to ESA treatment. Since these patients have accumulated bone marrow toxicity, they often required increased dosages and longer treatment times to respond. This limit, especially in combination with the dosage limit, will further increase our transfusion rate.

**A more appropriate limit would be to allow escalating doses over at least 8 weeks for maximal benefit to most patients until there is adequate evidence supporting a change.**

Fifth, the elimination of ESAs during radiotherapy may lead to an inability to complete radiotherapy, leading to significantly worse rates of cure and progression free survival. Multiple studies note the association between lower hemoglobin levels and worse outcomes.<sup>4-5</sup> One study found that the incidence of anemia for patients with cervical cancer was 67% at baseline and 82% during treatment.<sup>6</sup>

**It is inappropriate to exclude anemia resulting from radiotherapy from treatment with ESAs.**

Finally, restricting the use of ESAs to clinical research trials is not the only way to ensure informed consent and safety monitoring. Practices can establish databases of patients receiving ESAs to track this information. Physicians routinely obtain informed consent for the use of medical and surgical therapies. **This proposed restriction is inappropriate.**

***We do support the appropriate use of ESAs and agree with CMS' desire to prevent overutilization and the attendant risks. However, the proposed rules limit appropriate use of these drugs and the large benefits patients incur from them.***

While the blood supply is as safe as it has ever been, this is not the only consideration for preferring transfusion to ESA use in the anemia expected in cancer and its treatment. Though many of the studies referenced do not show a quality of life improvement for patients on ESAs, the studies are unable to quantify at least one aspect: a patient is much more able to maintain normal daily activities when they receive a quick injection weekly, rather than experiencing significant symptomatic anemia while waiting to receive a transfusion that requires 2 to 10 or more hours of infusion time. It is our current experience that many symptomatic, but not life-threateningly anemic patients must wait 24 to 72 hours for their transfusion. Some patients refuse blood (either for religious reasons

---

<sup>4</sup> Kumar P. Tumor hypoxia and anemia: impact on the efficacy of radiation therapy. *Semin Hematol.* 2000 Oct; 37(4 Suppl 6):4-8.

<sup>5</sup> Munstedt K. Hemoglobin levels during radiation therapy and their influence on local control and survival of patients with endometrial carcinoma. *Oncol Rep.* 11: 711-717, 2004.

<sup>6</sup> Kumar P. Adverse Effects of Anemia on Radiation Therapy and Quality of Life. *Medscape Today.* [http://www.medscape.com/viewarticle/416408\\_3](http://www.medscape.com/viewarticle/416408_3) Accessed 6/8/07

June 12, 2007

5 of 5

or fear of disease), but will accept ESAs. Finally, overuse of transfusions reduces the bone marrow's ability to form new erythrocytes.

Cure is, of course, the primary goal of cancer treatment; an important secondary goal is for patients to continue to live as normally as possible and to limit the effects of cancer treatment on the patient's daily activities. ESAs have radically altered the course of cancer treatment since they have been available. While the risks are real, they may be reduced with thoughtful, appropriate use that is not as crippling as the proposed limitations.

Respectfully,

The Physicians of Southeastern Gynecologic Oncology

Benedict B. Benigno, MD

Matthew O. Burrell, MD

Gerald A. Feuer, MD

Jeffrey F. Hines, MD

Stephen S. Salmieri, DO

Joseph F. Boveri, MD

O.W. Stephanie Yap, MD

RE: CAG 000383N – The use of Erythropoiesis Stimulating Agents in Cancer and Related Neoplastic Conditions

Dear Sir or Madam:

I am writing to respond to the recent draft proposal for coverage of erythropoietic stimulating agents (ESAs) in oncology. This represents a significant departure in policy regarding the coverage of agents and doses that have been approved by the FDA based on clinical trial data or for indications that are recognized by drug compendia. I would urge caution, as I believe the majority of these proposals represent a step backward in the treatment of patients with cancer and lack sound scientific evidence to back them up.

1. The proposal to eliminate coverage for myelodysplastic syndrome (MDS) is totally without merit. For patients with low to intermediate-1 grade MDS, the use of ESAs represent their only alternative to repeated blood transfusion. To my knowledge, there has never been a trial published that hinted at a negative outcome with ESAs in MDS. In fact, it has been shown that increased transfusion leads to poorer overall survival in MDS. Additionally, patients with iron overload that can come from transfusion have shown poorer outcome as well. MDS should not ever have been considered as a limitation.
2. Myeloid cancers have long been a theoretical restriction on the use of ESA because of the possibility of stimulating cells of myeloid lineage. Exclusion of erythro-leukemia is certainly valid, but I would question other myeloid cancers. The use of imatinib has been revolutionary in the treatment of CML and some AML patients. One of the well-known side effects of this drug is anemia. Very small clinical trails have been conducted using ESAs in this patient population successfully. I believe additional studies are certainly needed, but coverage should be an option left to the judgment of the treating physician to discuss with each patient.
3. I am not aware of any trails showing negative outcomes using these agents concomitantly with VEGF or EGFR inhibitors. With the lack of negative data, what is this proposal based on?
4. Many investigators have claimed to have detected the presence of the erythropoietin receptor (EPO-R) on multiple tumor types which you have listed in your proposal. There are two main questions regarding the EPO-R which these studies have never adequately addressed: is it really the EPO-R and if so, is it functional? The vast majority of the studies on this subject have utilized either a non-specific antibody against the intracellular portion of the EPO-R that also binds other proteins including HSP-70 or they have used a PCR method to detect RNA associated with EPO-R transcription. What none of them has done is actually detect a functional EPO-R on the surface of a tumor cell. In vitro studies of tumors have used concentrations of the drugs which far exceed anything possible to achieve

in patients to elicit even a miniscule response. I would strongly recommend you consult with an expert on this topic perhaps at the National Academy of Science prior to limiting therapy based on the "evidence" at hand.

5. The limitations for treatment are not well thought out with regard to quality of patient care, currently published treatment guidelines, or the potential impact these limitations will have on our Nation's blood supply.
  - a. By waiting for patient's hemoglobins to decline to very low levels prior to beginning therapy, you are decreasing the percentage of patients that have the potential for a meaningful response and virtually guaranteeing that all patients will receive at least one transfusion. Clinical studies have shown that response to therapy with these agents is greater when initiated at a hemoglobin greater than 10 gm/dL compared to less than. Also, the increase in hemoglobin is not instantaneous. There is a lag of several weeks after administration before hemoglobin begins to increase. This is related to the intrinsic mechanism of these agents and the physiology of red blood cell expansion. For this reason, clinical trials that have shown the advantage in transfusion reduction with both Procrit and Aranesp typically do not include the first 4 weeks of therapy in their analysis. In other words, if we wait for a hemoglobin of 9 gm/dL before beginning therapy, that patient will likely never have their hemoglobin increase by a gram or more. If an initiation hemoglobin level is required, I would recommend following currently published guidelines and allowing a hemoglobin of less than or equal to 11 gm/dL.
  - b. The risk of thrombosis is well described and has been a part of the package insert since these drugs were originally approved. The recent addition of the 'black box' highlights this adequately. Additional restrictions based on this are not necessary.
  - c. The restriction of only 12 weeks of therapy per year is also not based on scientific evidence. Many chemotherapy regimens exceed 12 weeks in length and patients often receive more than one course per year. This is especially true of patients with metastatic disease or receiving palliative care. This would potentially eliminate the utility of these agents for those patients that need them most. I also would recommend the allowance of therapy for some period beyond the end of chemotherapy as chemotherapy induced anemia does not go away the moment chemotherapy stops. The insult to the marrow takes time to recover. The length of time needed is very patient specific as there are many factors that will effect how long it takes to regain adequate marrow function including number of previous therapies and age.
  - d. Limiting erythropoietin to only 126,000 units per 4 week period is less than the current FDA approved dose of 40,000 units weekly

(40,000 X 4 = 160,000 units in a 4 week period). This recommendation would limit Procrit's use to three times weekly dosing resulting in either greater charge to CMS for administration or pushing all use of ESAs to darbepoietin. The limitation of darbepoietin's dose is less drastic but still fails to take into account patients greater than 70 kg if the FDA approved weight based dose is used to come about this limitation of 630 mcg per week (2.25 mcg/kg X 75kg X 4 = 675 mcg). Of interest to me is the dose conversion ratio proposed here as well. The first CMS dose conversion ratio for erythropoietin vs. darbepoietin was 260:1, which was revised the following year to 330:1. Amgen has proposed a 400:1 conversion and Ortho Biotech usually has spoken of a 260:1 or less. This current proposal recommends 200:1. Is CMS basing these recommendations on scientific evidence or is it based on something else? Furthermore, this maximal 4-week dose does not allow for patients to be dose escalated for less than optimal response. If maximal doses are included, they should represent the approved labeling of the drugs at equivalent dose ratios.

- e. Failure to achieve a rise in hemoglobin of 1 gm/dL or greater by a set time point (week four for Procrit and week 6 for Aranesp) results the need for a dose increase, not discontinuation. Erythropoietin has the greatest data published showing hemoglobin increase over time. More than half of patients actually achieve a 1 g or greater rise by week 4 with a starting dose of 40,000 unit weekly, but a much higher percentage of patients actually achieve a hemoglobin of 12 g/dL or a 2 gram increase over baseline by end of study. Darbepoietin studies have typically expressed their results as percentage of patients achieving a target hemoglobin between 11 and 12 g/dL. They typically report a need for dose increase comparable to that seen with erythropoietin. Clearly, this demonstrates that patients will receive benefit from these agents, either in achieving a target hemoglobin or avoiding transfusion even if they fail to get a 1 gram rise by week four. Does a patient who achieves a 0.9 g/dL rise in hemoglobin after 4 weeks of therapy deserve to be considered a non-responder and sentenced to possible transfusion as a result? Additionally, I would refer back to section a) in this letter and point out once again that by starting at a lower hemoglobin, fewer patients will likely actually get this 1 g/dL rise by week four, setting patients up for failure and certain transfusion. This should be eliminated from the proposal as the approved label for these products describes appropriate evidence based recommendations. To suggest that anything less than a 1 g/dL increase in hemoglobin is not worthy of further dosing is without merit and not supported data.

- f. I'm not sure how an increase in weight can be attributed to ESAs and what clinical significance it may have for requiring their termination. I am not aware of good scientific evidence for this and it therefore should be eliminated from the proposal.

Finally, the question of whether these drugs should be available only to patients on clinical trials is absurd. These agents were approved by the FDA for use in the treatment of chemotherapy induced anemia based on clinical evidence showing them to be effective in reducing the need for blood transfusion and their safety has been confirmed in many clinical studies when used within labeled doses. Recent negative studies have all been in uses outside of this approved indication or in patients who are not anemic. While additional studies are warranted to explain why these events occurred, I don't believe they should result in severely restricted use as this proposal suggests. Every agent, especially in oncology, carries with it a risk / benefit balance. Certainly, some clinicians may have forgotten about the risk and used these agents more than indicated as evidenced by recent reports in dialysis patients. Don't let this result in the loss of the ability of physicians to attempt to provide the best possible care they can for their patients. They deserve at least this much.

Thank you for the opportunity to comment.

Wane M. O'Neal, PharmD.

Title of NCA/CAL: Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications

Public Comment re: Erythropoiesis Stimulating Agents (ESAs) guidelines

As an employee of Utah Cancer Specialists, and patient care advocate, I am concerned about the proposed erythropoietic stimulating agent (ESA) guidelines under consideration. While I understand the need for proper use of these medications, the proposal falls short of providing the best standard of care recommended by oncology organizations such as NCCN, ASCO and ASH. The current proposals will result in a compromised quality of life for our patients, increased blood transfusion requirements with the associated co-morbidity and risk and, ultimately, prove more costly to society than judicious use of ESAs. Please reconsider these guidelines encouraging physicians to carefully weigh the risk/benefit with patients and allow providers to treat this growing population with the best and most compassionate standard of care.

Chemotherapy-induced anemia is a well-known side effect of myelosuppressive therapy. Furthermore it is quite responsive to ESAs when iron stores, vitamin B12 and folate deficiencies and other underlying processes have been corrected. Holding initiation of ESA until the hemoglobin drops to <9mg/dl will delay response and most likely result in transfusion for a greater number of our chemotherapy patients. Most chemotherapy regimens last a minimum of 16 weeks (and many are much longer). Therefore, limiting the covered treatment duration to 12 weeks annually will be inadequate treatment for many of our patients on continued myelosuppressive therapy.

According to the proposed guidelines, the Myelodysplastic Syndrome population will be denied access to any form of ESA under all circumstances. While a portion of the MDS patients will not respond to ESAs, a greater number benefit from these medications; reducing the number of necessary blood transfusions, eliminating the complications of iron overload that results from transfusion, enhanced productivity by limiting time spent in a healthcare facility, and an overall improved quality of life.

We do not dispute the recommendations to discontinue use of the ESAs if the patient is non-responsive to treatment, however:

- The recommended four weeks is an inadequate timeframe in which to evaluate patient responsiveness. Former guidelines allow 12 weeks to determine response. Clearly, four weeks is an irresponsible timeframe.
- The proposed maximum treatment dose is insufficient to provide standard doses within the recommended timeframes. The maximum covered four-week treatment dose is 126,000units of Procrit and 630mcg of Aranesp. At an average dose of 40,000 units of Procrit each week, we would need 160,000 units in four weeks. The average dose of Aranesp is 300mcg per 2 weeks – so the 630mcg would be sufficient.

We encourage you to reconsider the list of specified conditions to include other myeloid and erythroid cancers as well as anemia caused by radiotherapy. Some patients will respond, therefore a trial of an ESA medication seems prudent.

Thank you for your consideration of this request. As a community oncology practice we strive to provide the optimal care to our patients. Please allow us the support we need to continue this practice.

Respectfully,

Xylina T. Gregg, M.D.  
Utah Cancer Specialists  
Salt Lake City, UT

Ab