

# Community Oncology Alliance

*Dedicated to high quality, affordable, and accessible cancer care*

1101 Pennsylvania Ave., NW  
Suite 700  
Washington, DC 20004  
(202) 756-2258  
communityoncology.org

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June 8, 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:

On behalf of the Community Oncology Alliance (COA), an association of private practice oncologists throughout the country, I am submitting comments for the public record on the *Proposed Coverage Decision Memorandum for the Use of Erythropoiesis Stimulating Agents in Cancer and Related Neoplastic Conditions* (CAG-00383N), herein referred to as the "proposed NCD" that was issued by the Centers for Medicare & Medicaid Services (CMS) on May 14, 2007.

COA supports a National Coverage Determination (NCD) for the use of Erythropoiesis Stimulating Agents (ESAs) in cancer and related neoplastic conditions based on medical evidence and clinician experience. Unfortunately, the proposed NCD is not based on scientific data and ignores expert opinion in determining appropriate utilization of ESAs. If the proposed NCD is enacted, CMS would set back cancer care in the United States, with devastating impact on those Americans who rely on the Medicare program to provide them with quality cancer treatment.

In summary, the proposed NCD should not be enacted because of the following reasons:

- The conclusions supporting the proposed NCD are based on studies of patients treated in non-FDA approved indications and then extrapolated to cancer patients overall.
- Inappropriate restrictions on ESA use that ignore a large body of scientific data and medical experience will have a severe negative impact on the treatment and quality of life (QOL) of cancer patients due to untreated anemia.
- Blood transfusions are not an appropriate substitute for ESAs in the treatment of anemia in cancer patients. Additionally, the increased need for blood transfusions as a result of restrictions on ESAs would unnecessarily overwhelm the national blood supply, as well as put cancer patients at serious risk for medical complications avoidable with ESAs.

It is disconcerting that CMS issued an extensive memorandum on a proposed NCD only days after an FDA Oncology Drug Advisory Committee (ODAC) meeting, which drew conclusions not supported by scientific data and medical experience. This appears to be a rush to judgment by CMS, which would in effect usurp the medical decision making of oncologists backed by standards of evidence-based medicine and close to 15 years of documented safe use of ESAs, as documented in a large meta-analysis.

We call on CMS to carefully consider the serious ramifications of the proposed NCD. We urge CMS to substantially revise the proposed NCD so that it is based on sound scientific data and analysis, and to make it reflective of the important on-label use of ESAs in enhancing the treatment and QOL of cancer patients.

## Background

ESAs have been used in the supportive care of cancer patients for almost 15 years. Numerous studies have shown decreases in transfusion requirements, improvements in QOL, and

improvements in functional status for patients prescribed ESAs for treatment of chemotherapy-related anemia.

### **Clinical Trials and Safety Data**

ODAC met on May 10, 2007 to discuss data regarding safety issues relating to ESA use and reviewed several recent publications that raised issues regarding the safety of ESAs.

The concerns raised by ODAC are not supported by the safety data in the literature. Specifically, the studies that caused concern for ODAC involved uses of ESAs in non-FDA-approved indications. No safety signals have been raised in multiple studies involving ESAs using approved indications. Experts in the field of supportive care of cancer patients agree that ESAs are safe and effective when given according to accepted treatment guidelines.

The proposed NCD issued by CMS days following the ODAC meeting is seriously flawed, is not supported by safety data, and will ultimately serve to harm patients dealing with anemia from cancer and its treatment with chemotherapy. There are several portions of the proposed NCD that are particularly worrisome:

- The proposed NCD would restrict reimbursement for ESAs to patients with a hemoglobin less than 9 g/dL or hematocrit less than 27%. There are no clinical trials to support this restriction and as a result it is not clear if ESAs used in this manner will be effective in either improving QOL or decreasing blood transfusions. The National Comprehensive Cancer Network (NCCN) expert consensus panel cites multiple randomized studies supporting the initiation of ESAs at hemoglobin levels less than 11 g/dL.
- The proposed NCD prevents reimbursement for ESAs in patients receiving anti-angiogenesis drugs such as bevacizumab, or those receiving antibodies directed against the epidermal growth factor receptor such as cetuximab and panatumimab. This restriction is based solely on pre-clinical models using suprathreshold doses of ESAs. No adverse clinical effect has ever been demonstrated with the combination of these agents.
- The proposed NCD prohibits reimbursements for ESAs in patients with anemia secondary to myelodysplastic syndrome. The NCCN recommends ESAs in patients with anemia due to certain types of myelodysplastic syndrome as first-line therapy. Many patients have been successfully maintained for years without transfusion due to the use of ESAs. These patients would have no recourse but to resort to transfusion if the proposed NCD is enacted.
- The proposed NCD states 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." This statement is based on a misunderstanding of the significance of erythropoietin receptors (EpoR) on tumor cells. EpoR does not function as an oncogene and it has not been implicated in either the initiation or growth of tumor cells. The technical assays reportedly documenting EpoR in the studies quoted in the ODAC meeting are not specific for EpoR, and many questions remain regarding the significance of these assays.

### **Impact on QOL**

Patients with cancer and anemia are usually symptomatic. They complain of fatigue, shortness of breath, decreased stamina, and dizziness. The impact of anemia on QOL can be quantified utilizing several established tools. ESAs have been shown to improve QOL and functional status in multiple randomized studies.

The proposed NCD would severely restrict the use of ESAs in cancer patients with anemia. American physicians have been using evidence-based treatment decisions for many years, but these directives from the proposed NCD regulating when ESA therapy could start are not based on either clinical experience or clinical trials. The limit of 12 weeks of ESA therapy for

patients also appears to have been arbitrarily chosen, as there is no data to support this restriction.

Guidelines for the appropriate use of ESAs have been in place for some time. The consensus of expert opinion is that ESAs are not effective in decreasing transfusion requirements or improving QOL when they are started in patients with a hemoglobin of <9 g/dL. It takes several weeks for the bone marrow to respond to ESAs, and a patient with a hemoglobin <9 g/dL is almost always quite symptomatic.

The NCCN guidelines are written by experts in the field of supportive care of cancer patients. They are based on reviews of randomized clinical trials when available, and consensus opinion when they are not. COA would welcome the opportunity to assist CMS in a professional review of the NCD guidelines.

### **Blood Transfusions**

Packed red blood cell transfusions are not without risk. Risks include major and minor transfusion reactions, fevers, rash, hypotension, transfusion-related acute lung injury and death. Although the risk of infection has decreased with better donor screening, the incidence of transfusion-related infectious diseases which cannot be currently screened for is not insignificant.

Patients will be harmed if the proposed NCD is implemented as written. Anemia in cancer patients is a very serious disorder, and the proposed NCD would prevent many people from receiving appropriate therapy. Oncologists may be forced to select less intensive and possibly less effective treatments if they are concerned that appropriate supportive care drugs will not be available.

These unwarranted restrictions on the use of ESAs will directly lead to an increase in the number of blood transfusions for cancer patients. Placebo-controlled trials show that when an ESA is started at hemoglobin <9 g/dL, 68 percent of patients will require at least one blood transfusion. If ESA therapy is started when the hemoglobin is between 10 and 11 g/dL, only 26 percent of patients require transfusion.

The national blood supply cannot support this increased demand on such a scarce resource. The American Red Cross agrees, stating "Transfusion is typically a treatment of last resort, so much so that the Red Cross recommends that they not be used in cancer where there are other alternatives."

### **Expansion of CMS' Role in Regulating Medical Practice**

The proposed NCD is an unwarranted expansion of the role of CMS into the decision making process of physicians. Medical oncologists are trained in the appropriate use of chemotherapy agents and supportive care drugs. NCCN and other national expert panels have published evidence-based utilization guidelines for ESAs.

It is the FDA's responsibility to regulate appropriate prescribing of drugs. Although CMS can determine uses of drugs that are "reasonable and necessary," it is overstepping its authority in this proposed NCD. CMS should not use coverage policy to replace the FDA's responsibility in setting appropriate drug indications.

### **Summary**

The proposed NCD appears to be based on concerns raised by preclinical models utilizing supratherapeutic doses of ESAs, trials utilizing ESAs in non-approved indications and then extrapolating the results to cancer patients in general, and arbitrary restrictions not based on clinical experience. If implemented as written, the PDM would have a devastating impact on cancer patients.

Guidelines for the appropriate use of ESAs have been established and updated as warranted by the FDA and consensus expert panels. CMS should reassess the proposed NCD in light of the scientific data, medical evidence/experience, and the documented years of safe use of ESAs, and should seek the input of recognized experts in the field of cancer supportive care in crafting an appropriate NCD.

Very truly yours,

A handwritten signature in black ink that reads "Frederick M. Schnell". The signature is written in a cursive, slightly slanted style.

Frederick M. Schnell, MD  
President