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August 30, 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: Formal request for reconsideration of NCD for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-000383N)

Dear Dr. Phurrough,

The American Society of Clinical Oncology (ASCO) is the national organization representing physicians who specialize in the treatment of cancer. We are writing to formally request reconsideration of CMS's National Coverage Decision Memorandum for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-000383N) pursuant to the procedures outlined by CMS in the *Federal Register*.¹ This coverage decision was made under CMS Track #3 and was internally generated. This NCD applies to Erythropoiesis Stimulating Agents (ESAs) used in the treatment of cancer, which fall under the drugs and biologicals benefit category. We request notification of a decision regarding acceptance of this reconsideration request by September 13, 2007.

The NCD materially misinterpreted the existing evidence at the time the NCD was made in several respects. These are discussed in detail below and can be summarized briefly as follows:

- The clinical studies supporting FDA approval of ESAs did not involve stopping administration of the ESAs when the patient's hemoglobin exceeded 10 g/dL. There are no clinical studies demonstrating that the NCD's rules for administering ESAs result in their safe and effective use. CMS's implicit conclusion that the NCD provides for safe and effective therapy is based on a material misinterpretation of the clinical evidence.
- The NCD assumed that additional blood transfusions will not be required, since it misinterpreted the existing evidence and based a definitive policy on a body of evidence that is unclear and therefore does not allow for the definitive policy adopted. In addition, the NCD did not properly interpret evidence concerning patients with conditions that put them at increased risk.
- The NCD's policies on dose escalation and timing of a dose increase are inconsistent with the FDA-approved labeling and therefore with the underlying clinical studies. CMS has misinterpreted the clinical data in assuming that the NCD's rules on dose escalation and timing of a dose increase have been shown to be safe and effective.

¹ See 68 Fed. Reg. 55636-7 (2003).

In addition to these fundamental concerns, we discuss below a number of aspects of the NCD that are confusing and inconsistent.

I. CMS misapplied clinical evidence or did not apply relevant, currently available scientific information when restricting coverage of ESA use in patients with hemoglobins above 10g/dL.

The final decision covers ESAs for patients with anemia secondary to anticancer chemotherapy when the hemoglobin is less than 10 g/dL. The new policy also denies coverage of ESAs whenever a patient's hemoglobin goes above 10 g/dL. This latter restriction is inconsistent with both the FDA-approved labeling and national guidelines.²

The FDA-approved label for epoetin (Procrit®, Epogen®) states, “The dose of [epoetin] should be titrated for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for blood transfusion *and not to exceed 12 g/dL*” (emphasis added). The FDA-approved label for darbepoetin (Aranesp®) states, “For both dosing schedules, the dose should be adjusted for each patient to maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion *and not to exceed 12 g/dL*” (emphasis added). The FDA license indication was informed by a series of randomized clinical trials, not one of which stopped ESA therapy once a hemoglobin of 10 g/dL was reached.

The updated ASCO and American Society of Hematology (ASH) guideline recommends the use of epoetin or darbepoetin, “as a treatment option for patients with chemotherapy-associated anemia and a hemoglobin concentration that is approaching, or has fallen below, 10 g/dL, to increase hemoglobin and decrease transfusions...hemoglobin can be raised to (or near) a concentration of 12 g/dL, at which time the dosage of epoetin or darbepoetin should be titrated to maintain that level.”² Absent additional data to support a change in the FDA-approved label, the ASCO-ASH guideline recommendation was not revised in the 2007 update. A confidential, pre-publication version of the guideline was shared with CMS last week.

It is worth highlighting that CMS, in its NCD, states that it “...is not changing the FDA indication for ESA therapy for cancer patients who have anemia related to chemotherapy. CMS’ coverage provision is the FDA label indication and ensures that cancer beneficiaries who have anemia related to chemotherapy can avoid transfusions by receiving ESA therapy that will gradually increase the hemoglobin (or hematocrit) concentration to the lowest level sufficient to avoid the need for transfusion, as stated in the FDA labeled Black Box Warning.” Missing from the quote by CMS, of course, is the key element from the label that allows for an ESA to be titrated for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for blood transfusion *and not to exceed 12 g/dL* (p. 25 of product label, emphasis added).³ CMS fails to provide either a rationale for, or new evidence in support of, their policy relating to coverage of ESA use in patients with hemoglobins above 10g/dL.

It should also be noted that, at the May 2007 Oncologic Drugs Advisory Committee (ODAC) meeting convened by the FDA, the Committee voted overwhelmingly to maintain that part of the current FDA-approved label which sets an upper limit of 12 g/dL for hemoglobin in ESA-treated patients.

² For a more detailed explanation of the rigorous review procedure, please refer to the ASCO/ASH guideline, page 4 – 5.

³ Epogen/Procrit Product Label. Revised 03/09/07 Available at:

<http://www.fda.gov/cder/foi/label/2007/103234s5122lbl.pdf>

Aranesp Product Label. Issue date: 04/2007 Available at: http://www.amgen.com/pdfs/misc/aranesp_pi.pdf

Also omitted from discussion in this restriction is any consideration of patients with comorbid conditions or in clinical circumstances where experienced clinical judgment may suggest the need for ESAs at initial hemoglobins above 10 g/dL. Patients with, for example, limited cardiopulmonary reserve, underlying coronary artery disease, or certain types of cancers, may be at increased risk from milder anemia than that tolerable by an otherwise healthy person. CMS has completely removed clinicians' ability to use their best judgment when treating individual patients; in fact, CMS has focused on a number—in this case, an absolute hemoglobin level—to the exclusion of the individual patient. This insistence on rigid adherence to a laboratory value, discounting relevant patient factors, clinician judgment, the available evidence, and the recommendations of professional societies, can lead only to less individualized care for patients.

II. Restrictions of ESAs above a hemoglobin of 10g/dL may result in more patients needing blood transfusions.

Under the current NCD, ESAs are not covered above a hemoglobin of 10g/dL. A possible effect of this policy may be that more patients will require red blood cell (RBC) transfusions.

CMS acknowledges that the level at which anemia requires intervention is not well established, and that “by tradition” patients have received transfusions at hemoglobin levels of 7 g/dL or 8 g/dL and relies on the British Blood Transfusion Society⁴ as support. The BBTS guidelines state that transfusions are indicated in patients with hemoglobin levels less than 7 g/dL, and should not be used in patients with hemoglobin greater than 10 g/dL. CMS applies the stringent restriction of non-coverage of ESA therapy when a patient's hemoglobin is above 10 g/dL, even while admitting that the management of patients with hemoglobin levels between 7 g/dL and 10 g/dL “remains unclear.” Apparently, therefore, CMS has made a de facto judgment on the appropriate management of these patients—that they should be kept in this “unclear” area. Neither national guidelines nor the FDA-approved labels for ESA therapies agree with this restriction.

Although all patients are potentially at risk of increased need for blood transfusions under the new policy, of particular concern are patients with conditions that already put them at increased risk. Patients with comorbidities such as cardiac or pulmonary disease may exhibit anemia symptoms with hemoglobins higher than 10 g/dL, and as discussed above, restricting ESA therapy to those with hemoglobins of 10 g/dL or below, regardless of patient symptoms or other factors, is anticipated to be detrimental to patient care.

III. The Final Coverage Decision Ignores Established Studies, the FDA Label, and Clinical Guidelines by Restricting the Allowable Dose Increase and the Timing of Dose Escalation.

Allowable Dose Increase

For hypo- or non-responders (patients with a rise in hemoglobin of less than 1 g/dL over 4 weeks of treatment), the CMS policy allows for a one-time dose escalation of 25%. The weight-based starting doses for darbepoetin and epoetin are, respectively, 2.25 mcg/kg (weekly) and 150 U/kg (three times a week). The FDA-approved labels allow that, for hypo- or non-responders, weight-based dosing can be increased by 100% (i.e., up to 4.5 mcg/kg for darbepoetin, and to 300 U/kg for epoetin); fixed dosing can

⁴ Murphy MF, Walington TB, Kelsey P, et al: Guidelines for the clinical use of red cell transfusions. *Br J Haematol* 113:24-31, 2001

be increased by 50% for hypo- or non-responders. There has been no new evidence published since 2002 that would support variations to the FDA-approved dose or dosing schedule. As such, the ASCO-ASH guidelines continue to offer recommendations that are consistent with the FDA label.

The FDA-approved label and available guidelines are based on clinical trials in which doubling the dose of an ESA in hypo- or non-responders converted some proportion of trial participants to responders. Demetri et al reported, for example, that with the planned increase in epoetin dosing [from 10,000 U t.i.w. to 20,000 U t.i.w. after four weeks of therapy], 44% of non-responders, defined as those who had an increase in hg level < 1.0 g/dL at four weeks, went on to achieve a meaningful increase in hemoglobin (≥ 2 g/dL) by the end of the study.⁵ By contrast, the basis for the CMS's policy in this regard is not clear; CMS fails to provide an explicit rationale for, or to cite evidence to substantiate, its 25%, one-time dose escalation policy.

Timing of Dose Increase

CMS has stated that the allowance for the 25% dose escalation applies only to the 5th week of ESA therapy within any one course of chemotherapy. This restriction is at odds with both national guidelines and the FDA label. The effects of myelosuppressive chemotherapy can be cumulative within any one course of chemotherapy⁶, and this new restriction does not allow for dose escalation further into a course of chemotherapy.

Evidence from randomized clinical trials indicates that the mean hemoglobin levels for untreated control patients decline over the course of chemotherapy. Cascinu et al reported, for example, that patients in the placebo control group went from a baseline of 8.7 (+/- 0.5) to 8.1 (+/- 1.1) over the course of their clinical trial. (Patients who received an ESA in this trial went from a baseline of 8.6 [+/- 0.6] to 10.5 [+/- 0.9].)

The lack of a steeper decline in hemoglobin over the study period in placebo-control groups from existing randomized clinical trials is likely a function of a substantial number of patients in those groups having received a blood transfusion over the course of the trial.⁷ The pooled percentage of transfused patients across the control arms of all randomized clinical trials of ESAs vs. controls is 47.2%; in trials with a mean baseline hemoglobin of less than or equal to 10 g/dL, the majority of trials reported that more than 50% of control patients required transfusions to maintain hemoglobin levels.⁸

⁵ 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* 16:3412-25, 1998

⁶ Groopman JE, Itri LM: Chemotherapy-induced anemia in adults: incidence and treatment. *J Natl Cancer Inst* 91:1616-34, 1999

⁷ 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* 23:2606-17, 2005; 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* 19:2865-74, 2001

⁸ 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

Multiple factors may further impact a patient's individual response to ESA therapy over the course of treatment, including but not limited to existing comorbidities, recent transfusions, and infections. These multiple factors may all have an impact on an individual patient's requirement for ESA dosing over the course of therapy.

IV. Implementation of many of the NCD's restrictions are confusing and inconsistent.

On July 30, the final NCD was issued with significant changes from the proposed NCD and became effective immediately. Subsequent to that issuance, CMS released clarification in the form of a question-and-answer document. CMS has issued no instructions to the Medicare carriers. ASCO and other groups have also had numerous calls with CMS in which we have had the opportunity to ask questions about the application of this policy. However, many of clarifications we have received to date have been inconsistent or inapplicable in practice. Outlined below are just some of the areas where the NCD and CMS' guidance are causing confusion for the providers and patients.

“Initiation” vs. “Maintenance”

“Initiation,” according to the NCD, consists of the first 4 weeks of ESA therapy within a given course of chemotherapy, while “maintenance” consists of the rest of the time through the end of that chemotherapy course, plus eight weeks. While there is a requirement in the initiation phase for a hemoglobin below 10 g/dL before starting ESA therapy, there is no requirement—within that 4 week window—for documentation of another hemoglobin below 10 g/dL with each dose of an ESA; in fact, during this phase, ESA therapy may continue even if the hemoglobin goes above 10 g/dL. The requirement for documentation of a hemoglobin lower than 10 g/dL begins at week 5, at which point every single subsequent dose of an ESA must be immediately preceded by a documented hemoglobin below 10 g/dL. This requirement is onerous to both patients and clinicians, as well as being internally inconsistent.

Rapid Rise in Hemoglobin

Adding yet more to the confusion is the “hyper-responder” provision, wherein a patient who responds with a hemoglobin rise of more than 1 g/dL within a 2-week window must have the ESA discontinued or the dose decreased, depending on whether the hemoglobin is less than 10 g/dL. If the hemoglobin is above 10 g/dL, when the ESA is reinstated, it must be reinstated at a 25% dose decrease. This “hyper-responder” provision applies throughout the entire eligibility period (“initiation” and “maintenance”), unlike the hemoglobin remaining below 10 g/dL provision, which applies to the “maintenance,” but not the “initiation” phase.

CMS's own policy in this regard is again inconsistent with the FDA label. For darbepoetin, the FDA label indicates that the dose should be reduced to 40% of the previous dose with a 1 g/dL increase in hemoglobin within a two-week period or if the hemoglobin is greater than 11 g/dL; for epoetin, the label requires a 25% dose reduction with a 1 g/dL increase in any two-week period or if the hemoglobin

approaches 12 g/dL. There is nothing in the label for either agent that calls for discontinuing ESA therapy in reference to a 10 g/dL threshold.

We assume CMS is aware that there is no direct evidence from randomized clinical trials that bears on the approach to managing the hyper-responder. The FDA-approved label recommendations were based on dose modification instructions developed for randomized clinical trial protocols that were, in turn, based on input from advisors who had extensive experience in the care of anemic oncology patients and who applied their best clinical judgment in arriving at the recommendations for the conduct of the pivotal trials. The FDA-approved label is arguably a much stronger basis than the policy issued by CMS, the basis for which, in light of the admitted lack of direct evidence, is not at all apparent.

Myelodysplastic Syndromes

While CMS states that “[W]e are making no decision on MDS [myelodysplastic syndromes] in this final decision,” we wanted to take this opportunity to emphasize that patients with MDS have been shown to benefit from ESA therapy, as detailed in earlier communications with CMS (also see the American Society of Hematology comments to CMS filed on June 13, 2007). We request this NCD provide explicit coverage of ESAs in MDS, as outlined below:

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.

We recommend that Medicare cover treatment with ESAs in patients with MDS who meet the following criteria:

1. Initial hemoglobin (Hgb) of 10 g/dl or Hematocrit (Hct) of 30% or less
2. Patients who need or are anticipated to need frequent transfusions
3. 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 ($p=0.002$). 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. 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. (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).

Contractor Interpretation

CMS has informally indicated that the carriers may interpret the NCD to be inapplicable in settings where the exact clinical scenario is not outlined in the NCD. This, according to CMS, could include, but is not limited to, patients with co-morbidities, recently transfused patients, and patients treated at a high-altitude. CMS contends it is prohibited by law from communicating this to the carriers. We assert that contractors should be aware of specific areas where they have discretion, for example, in patients with comorbid conditions.

V. FDA Review is Ongoing.

In the Federal Register notice issued by CMS outlining the criteria for a reconsideration, CMS asks the requestor, if they are asking for reconsideration of a decision relating to a drug, to relate the status of current regulatory review by the FDA. Further, CMS states that “if, during our review, the labeled



indication or status of a pending FDA approval or clearance changes, we expect the requestor to notify us.”⁹ That request implies that the status of the FDA label is relevant to our consideration decision.

Earlier this year, the Food and Drug Administration (FDA) convened a meeting of its ODAC to review the full range of issues and data related to the safety use of ESAs for cancer patients. The FDA has already mandated a “black box” warning and is considering the recommendations from ODAC, and may make amendments to the labeling for these products. In order to avoid further confusion with patients and providers, and provide optimal care to Medicare beneficiaries, CMS should reconsider the final decision based on the parallel regulatory actions taken by the FDA.

Sincerely,

A handwritten signature in black ink that reads "Joseph S. Bailes". The signature is written in a cursive, flowing style.

Joseph S. Bailes, MD
Chair, Government Relations Council

⁹ See 68 Fed. Reg. 55637 (2003).