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August 3, 2007

Steve Phurrough, MD, MPA
Director, Coverage & Analysis Group
Centers for Medicare & Medicaid Services
Mailstop C1-09-06
7500 Security Blvd
Baltimore MD 21244

Re: Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-000383N)

Dear Dr. Phurrough:

The American Society of Clinical Oncology (ASCO) appreciates the opportunity to again raise our serious concerns about the July 30 national coverage determination on Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications. As you know, ASCO is the national society for physicians who specialize in the treatment of patients with cancer. As such, we would like to take this opportunity to outline the challenges we foresee for clinicians in treating cancer patients as a result of this policy, which may result in limiting physicians' ability to provide the care they judge most appropriate for their patients. We respectfully request that portions of this decision be reopened to allow for CMS to address concerns with the provisions discussed below.

COVERAGE RESTRICTIONS ON HEMOGLOBINS ABOVE 10 g/dL

The final decision states that, for patients with anemia secondary to anticancer chemotherapy, ESAs are appropriate 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, and we strongly disagree with this restriction. The FDA-approved label for 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." The FDA-approved label for 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." The ASCO/ASH guidelines recommend consideration of ESA therapy when the hemoglobin falls below 10 (for most patients), with a treated hemoglobin not to exceed 12 g/dL.

The stated premise of the new policy is that the objective of ESA use is to maintain the patient's hemoglobin level above 8 g/dL and that administration of ESAs only when the level is below 10 g/dL will accomplish that result. That approach is entirely different



from the instructions for use specified in the FDA-approved label. CMS should follow the ASCO/ASH guidelines and make the policy consistent with the FDA label.

DOSE ESCALATION: DOSE ALLOWED AND TIMING

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 new policy allows for a one-time dose escalation of 25%. Again, this is inconsistent with the FDA-approved label and with national guidelines. 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 state 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). The ASCO/ASH guidelines offer similar recommendations.

Timing of Dose Increase

Moreover, as clarified on the August 2nd call, the allowance for the 25% dose escalation applies only to the 5th week of ESA therapy within any one course of chemotherapy. The effects of myelosuppressive chemotherapy can be cumulative within any one course of chemotherapy, and this new restriction does not allow for dose escalation further into a course of chemotherapy.

Challenges and Concerns Associated with Dose Escalation Restrictions

If a patient initially responds to standard starting doses in the first 4 weeks, but their hemoglobin remains below 10 g/dL, according to this policy they then enter the “maintenance” phase. After the fifth week, if a patient fails to respond as well to the standard dose, for example, due to the cumulative toxic effects of myelosuppressive chemotherapy, the clinician does not have the option of even the arbitrarily set 25% dose increase, and is allowed only to continue with the standard dose. This restriction interferes with the clinician’s ability to titrate the dose as clinical judgment and the best interests of the patient dictate. Furthermore, it could also set the stage for the patient to become a “hypo-responder” by CMS criteria, at which point CMS will no longer provide coverage for ESA treatment for the rest of that course of chemotherapy. As a result, this policy could force a situation where ESAs will not be covered at all, even at a “standard” dose, when that patient could have continued to respond to and benefit from ESA treatment if CMS allowed for clinically appropriate dose escalation.

CMS should revise this provision to allow for the judgment of the clinician in the course of titrating the dose for best patient benefit.

HEMOGLOBIN MONITORING & “INITIATION” VS. “MAINTENANCE”

Hemoglobin Monitoring in the “Maintenance” Phase

As clarified by CMS on the call, once the initial 4 week period (“initiation”) has passed, a hemoglobin below 10 g/dL must be documented immediately before every single dose of an ESA. This presents a huge burden to both patients and clinicians, and will be extremely difficult to implement in practice. We are aware that there is a requirement that, starting January 1, 2008, information on a patient’s hemoglobin or hematocrit must be submitted with any claim for an ESA. However, that rule does not provide further specific guidance or instructions, so it is unclear how it will be implemented in practice.

“Initiation” vs. “Maintenance”

Furthermore, it is not at all clear how CMS arrived at the distinction between “initiation” and “maintenance.” “Initiation,” according to CMS, 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. As discussed above, 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. As stated above, we strongly disagree with CMS on the basic premise of disallowing ESAs above a hemoglobin of 10 g/dL, and these rules as written will only add to patient and clinician confusion.

COVERAGE OF ESAS IN THE CONTEXT OF BLOOD TRANSFUSIONS

Given that ESAs are not covered above a hemoglobin of 10 g/dL, the situation in which a patient has received a red blood cell (RBC) transfusion with a subsequent rise in hemoglobin is problematic. In this setting, it is not clear how the new regulations apply to hemoglobin monitoring and subsequent ESA treatment. If a patient has recently received a transfusion, and has a hemoglobin above 10 g/dL due to the exogenous source of RBCs, but had a hemoglobin of around 8 g/dL immediately preceding the transfusion, how should the clinician interpret the rules regarding hemoglobin levels acceptable for ESA coverage as they apply to a transfused patient?



CONCLUSION

CMS should review the appropriate clinical evidence and reopen the National Coverage Decision (NCD) in the areas mentioned above. The current NCD does not allow for interpretation consistent with clinical practice, national guidelines, or the FDA-approved labels in this area. This reopening should occur as soon as possible to avoid continued confusion and uncertainty both physicians and patients. Until these issues are clarified, we also strongly recommend that CMS delay the effective date for the entire NCD.

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