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

Dear Dr. Phurrough,

Thank you for the opportunity to further discuss the decision memorandum regarding the national coverage determination (NCD) for erythropoietic stimulating agents (ESAs). This letter outlines several clinical challenges identified after careful consideration of the NCD. While some clinical challenges may be addressed through clarifications from the agency and instructions to carriers, the current NCD language may not accommodate all the changes needed for health care professionals to ensure the delivery of safe and effective patient care to Medicare beneficiaries.

Clarification of Coverage for 40,000 Units weekly for epoetin alfa

We appreciate your clarification (August 2nd conference call) that epoetin alfa 40,000 Units once weekly dosing is an "equivalent dose" to 150 U/kg/three times weekly dosing within the meaning of the term "equivalent dose" as used in the decision memorandum. Your clarification means that 160,000 Units is the maximum allowed epoetin alfa dose in the 4-week initiation period when using weekly dosing, superceding the 1,800 U/kg cited in the decision memo. Such direction will allow providers to initiate dosing in accordance with FDA-approved prescribing information. However we have received feedback from providers that the initiation dosing described in the decision memorandum is not clear to them, and it could affect clinical practice to the detriment of patient care. Coverage for epoetin alfa dosing at 40,000 Units weekly in the initiation phase should be published for the benefit of the entire medical community.

Significant Clinical Challenges With the NCD

You requested that we identify where the memorandum presents clinicians with serious challenges in appropriately managing patients. As we understand it, you are also willing

to consider whether the memorandum should be reopened in order to address serious defects in the memorandum.

The most serious clinical issue created by the NCD is limiting coverage to a treatment target or "cap" of 10 g/dL. This cap would restrict treatment below the level that FDA permits in the approved labeling for ESAs and ignores the treatment guidelines of the American Society of Hematology/American Society of Clinical Oncology and the National Comprehensive Cancer Network. In addition, there are no clinical studies or evidence to support the effectiveness and safety of such dosing recommendations. We realize that this issue cannot be addressed by clarifying the existing NCD, but would require a reopening of the NCD.

To date, at least six different and significant clinical scenarios have been identified for which the recently finalized NCD does not provide clear direction. These are expected to be sufficiently commonplace and should be clarified:

- Patients with chemotherapy-induced anemia and specific co-morbid conditions associated with greater risk of and from transfusion whose hemoglobin is >10g/dL
- Patients with chemotherapy-induced anemia whose hemoglobin is >10g/dL and whose physician recommends a transfusion, but who refuses to be transfused on personal, religious, or other grounds
- Patients receiving multiple chemotherapy regimens
- The ability to dose escalate at only one fixed point in the eligibility period
- Dose escalation and reduction directions for epoetin alfa and darbepoetin alfa that could result in patients receiving either lower or **higher** doses than recommended by the FDA
- The treatment of hemoglobin values following transfusion

For each of these, a brief description is provided.

<u>Patients with chemotherapy-induced anemia and specific co-morbid conditions associated with greater risk of and from transfusion whose hemoglobin is >10 g/dL</u>

The decision memorandum states that transfusions are not required for hemoglobin levels <u>≥</u>10 g/dL. While this may be true for certain populations (e.g. surgical patients), it may not be true for cancer patients receiving chemotherapy. This group of Medicare beneficiaries often has complicating cardiopulmonary co-morbidities, and they receive most of their cancer care in community clinic settings as ambulatory outpatients. **ESA clinical trial and observational data have reported that there are patients with chemotherapy-induced anemia and a hemoglobin of >10 g/dL who do receive transfusions.** Additionally, the decision memorandum states "ASCO and ASH guidelines recommended evaluating patients for the need for ESA therapy when the hemoglobin is at or below 10 g/dL." However, this is only a part of published ASH/ASCO guideline, which continues with the following:

> *"For patients with declining hemoglobin levels but less severe anemia (those with hemoglobin concentration < 12 g/dL, but who have never fallen below 10 g/dL), 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...*

The recommendation for use of epoetin in patients with baseline hemoglobin levels of 10 to 12 g/dL based on clinical judgment is premised on the assumption that patients with specific comorbid conditions face a higher absolute probability of anemia or a higher risk of adverse events related to this degree of anemia than do other patients with this hemoglobin concentration. 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"[1]

The final NCD makes no allowances for the fact that transfusions still take place at hemoglobin concentrations greater than 10g/dL in the cancer chemotherapy population, and that certain types of cancer patients may be at higher risk of and from transfusion.

Patients with chemotherapy-induced anemia whose hemoglobin is >10 g/dL and whose physician recommends a transfusion, but who refuse to be transfused on personal, religious, or medical grounds

If, in the previous scenario, the only available option for coverage under the NCD is transfusion, there is no accommodation within the NCD for those situations where the patient refuses transfusion on personal, religious or medical grounds. Patients requiring multiple transfusions are at increased risk of transfusion reactions due to alloimmunization. Such experiences may lead patients to decline transfusion based on previous adverse transfusion-related events. ESA administration should be allowed as an alternative in such scenarios.

Patients receiving multiple chemotherapy regimens

Oncology patients with locally advanced or metastatic disease are frequently treated with multiple chemotherapy regimens as the malignancy becomes resistant to initial interventions. Chemotherapy regimens have unique myelosuppressive side effects with progressive and cumulative toxicity. Each chemotherapy regimen may be considered a course of chemotherapy. The NCD remains silent on this question and should allow a new ESA initiation/maintenance cycle with each new chemotherapy regimen.

The ability to dose escalate at only one fixed point in the eligibility period

According to our reading of the final NCD, there is only one covered opportunity for dose escalation, which is at week 5. However, as patients receive successive cycles of chemotherapy, the myelosuppresssive effects accumulate, and therefore the need for dose escalation may occur later in the covered eligibility period than at 5 weeks. There is no accommodation for this clinical scenario, and the memorandum's inflexibility has the potential to negatively impact patient care.

Dose escalation and reduction directions for epoetin alfa and darbepoetin alfa conflict with the FDA label and could result in patients receiving doses either lower or **higher** than those recommended by the FDA

[1] Rizzo et al JCO (2002) 20: 4082-4107

The NCD actually encourages use of ESAs that is contrary to the FDA label. For instance, the NCD covers dose escalation of only 25% for epoetin alfa when an inadequate response is achieved and Hb is still below 10g/dL, which is well below the dose escalations recommended in the product label of 100% for the 150 Units/kg TIW regimen (to 300 Units/kg TIW) and 50% for 40,000 Units weekly regimen (to 60,000 Units weekly). The allowed 25% dose escalation is also well below the recommended dose escalation for darbepoetin alfa weekly dosing, which is 100%, from 2.25mcg/kg to 4.5mcg/kg. However, the coverage as written does not preclude dose escalation of 25% for the darbepoetin alfa 500mcg every 3 weeks (Q3W) regimen, which would translate into 625mcg Q3W. The FDA label for darbepoetin alfa has no allowance for dose escalation of this particular regimen. In fact, in the darbepoetin alfa registration trial for the Q3W regimen, 72% of patients required a dose reduction.

Coverage for darbepoetin alfa includes a dose reduction of 25% when hemoglobin has risen >1g/dL in two weeks. For the covered 2.25mcg/kg weekly regimen (QW), this dose reduction translates into 1.6875 mcg/kg, or roughly 118mcg weekly for a 70kg patient. However, the FDA label for darbepoetin alfa calls for the dose to be reduced by 40% of the previous dose in the event of a rapid rise in hemoglobin, to 1.35 mcg/kg or 94.5 mcg weekly for a 70 kg patient. If hemoglobin has risen more than 1g/dL over 2 weeks in a patient receiving the covered 500mcg Q3W regimen for darbepoetin alfa, the NCD calls for a dose reduction of 25%, to 375mcg Q3W. However, the FDA label for darbepoetin alfa calls for the dose to be reduced by 40% of the previous dose in the event of a rapid rise in hemoglobin, to 300mcg Q3W.

Coverage within the NCD supports dose escalations for epoetin alfa that are well below the levels recommended in the product label, and dose escalations for darbepoetin alfa that are both lower and higher than FDA recommendations. The NCD also covers dose reductions in the event of a rapid rise in Hb for darbepoetin alfa that will result in doses that are 25% higher (118mcg vs. 94.5 mcg weekly, or 375mcg vs. 300mcg Q3W) than those recommended by FDA. The impact of these higher doses on patient safety is unknown. CMS should be concerned with covering doses that are lower than recommended, and it should be very concerned with covering doses that are **higher** than recommended, as beneficiary safety related to higher dosing of ESAs was ostensibly the impetus for the NCD.

<u>The treatment of hemoglobin values following transfusion</u>

How does the NCD affect coverage when a patient's hemoglobin has fallen below 10g/dL, he or she is transfused, and then their hemoglobin value at a subsequent visit is above 10g/dL due to the transfusion? Will this beneficiary receive coverage for further ESA treatment? Our reading of the final NCD is that it does not address hemoglobin values subsequent to a transfusion. As recent transfusions significantly influence hemoglobin concentrations, hemoglobin concentrations that are independent of transfusion should be considered for purposes of policy implementation. It would be inappropriate to apply the rapid rate of rise criteria in the memorandum for calculating ESA dose reductions if the hemoglobin occurred as a result of a transfusion. Published clinical trials have considered such effects and excluded hemoglobin values that occur for 28 days following a red blood cell transfusion.

Conclusions

We request that CMS clarify in writing, immediately, confusing aspects of the NCD to provide clinicians with appropriate direction in treating patients. Specifically, we appreciated your clarification that epoetin alfa weekly dosing of 40,000 Units is covered. As you acknowledged, this means that 160,000 units is the maximum epoetin alfa dose allowed in the 4-week initiation period when using weekly dosing. We have learned that clinicians are concerned about having confirmation in writing from CMS about this clarification.

We urge CMS to make the changes in the current NCD necessary to support appropriate clinical use of ESAs in the treatment of chemotherapy-induced anemia. In addition, we believe that CMS should withdraw the hemoglobin target of 10 g/dL set forth in the NCD and substitute instead the treatment limit of 12 g/dL as described in the FDA-approved labeling. CMS can achieve this through one or more of the following options:

- Withdraw those portions of the NCD, including the Hb treatment target of 10g/dL, the 4 week initial dose caps, and the one-time dose escalation of 25% of the initial dose, for which there is no clinical basis. CMS is permitted to do this because the statutory deadline has not yet passed for issuing the final NCD. CMS can then reopen portions of the NCD immediately or await FDA's review prior to reopening the NCD.
- Delay the effective date of those provisions in question until 6 months after the beginning of the next quarter, or until April 2008, in accordance with the statute and the September 26, 2003 Federal Register, while CMS considers revising the policy.
- Reopen the NCD, seeking public comment on the provisions described above. This should be done in a streamlined way, in order to ensure minimal confusion and disruption to patient care. Key issues in a reopening will include:
    - Changing the Hb treatment target from 10g/dL to 12g/dL
    - Eliminating the dosing caps, as the treatment target makes those unnecessary
    - Allowing dose escalation in accordance with the FDA label, in lieu of the one-time escalation of a 25% increase over the initiation dose

Thank you for your consideration of these questions. We would be happy to clarify any of the points above, and look forward to the upcoming conference call.

Sincerely,

Joaquin Duato

President
Ortho Biotech Products, L.P.

CC: Herb Kuhn, Barry Straube, MD, Louis Jacques, MD, Shamiram Feinglass, MD, MPH