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Steve E. Phurrough, MD, MPA
Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services
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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

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CMS Restriction by Disease State	NCCN Comment
<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, www.nccn.org).</p> <p>Studies assessing the long term use of erythropoietin with or without GCSF in MDS patients compared to either randomized controls¹ or historical controls^{2,3,4} 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 database⁵). 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 life⁶. 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 ≤ 500, 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</p>	<p>Recommendations: NCCN has not made recommendations regarding the use of ESAs in treatment of treatment-related anemia</p>

<p>treatment of myeloid cancers or erythroid cancers</p>	<p>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>
<p>9. Patients with erythropoietin-</p>	<p>NCCN do not address the restriction</p>

type resistance due to neutralizing antibodies	
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
1. The hemoglobin/hematocrit levels immediately prior to initiation of dosing for the month should be <9 g/dl/27% in patients without known	Hemoglobin levels at initiation: NCCN guidelines recommend consideration of ESAs with a hemoglobin < 11 g/dL. Numerous studies have documented the efficacy of ESAs

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.)

in reducing red cell transfusion requirements and improving quality of life parameters in cancer patients receiving chemotherapy^{7,8,9}. 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 transfusions¹⁰. Guidelines recommendations from ASCO/ASH¹¹ and NCCN¹² which are based on results of clinical trials all recommend initiating ESA therapy at a hemoglobin level \leq 10 g/dL with treatment continued as long as the patient is receiving therapy and remains anemic.

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.

Transfusion: 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 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.

Most medical centers have a limited blood

	<p>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 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 <1 g/dl/<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 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</p>
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	Memo will result in patients who could benefit from the agent being denied it.
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	No comment
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	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 > 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.

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 is 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,



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Chief Executive Officer

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