

AMGEN JUNE 1, 2007, SUBMISSION IN RESPONSE TO THE PROPOSED DECISION MEMORANDUM FOR ERYTHROPOIESIS STIMULATING AGENTS FOR NON-RENAL DISEASE INDICATIONS (CAG-00383N)

On June 1, 2007, Amgen Inc. (Amgen) submitted comments to the Centers for Medicare and Medicaid Services (CMS) in response to the agency's Proposed Decision Memorandum for Erythropoiesis Stimulating Agents for (ESAs) Non-Renal Disease Indications (CAG-00383N).

Below, we provide the Executive Summary of our comments. The full text of our submission is available on www.amgen.com and should be publicly available on the CMS website at http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca_id=203 shortly.

I. EXECUTIVE SUMMARY

Anemia—defined as a below-normal level of red blood cells, hemoglobin, or both—is a debilitating complication that is common in cancer patients receiving chemotherapy, patients with cancer not receiving chemotherapy, and patients with myelodysplastic syndrome. Individuals with cancer-related anemia may present with a range of symptoms—most frequently fatigue, but also potentially including dizziness, shortness of breath, palpitations, lack of endurance, and angina, among others.

ESA therapy revolutionized anemia management. For nearly 15 years, ESAs have been employed by physicians to reduce the burden of red blood cell transfusions in patients receiving myelosuppressive chemotherapy. Clinical studies make plain that, compared with placebo, ESA treatment reduces by half the number of transfusions in such patients and extends the time to first transfusion. In addition, ESA treatment helps alleviate the signs and symptoms of anemia, which provoke physicians to transfuse red blood cells, and clinical trials report improvements in patient-reported outcomes for chemotherapy patients.

While CMS has a legitimate role to play in determining coverage policy for ESAs under the authority granted to it by Congress (*i.e.*, to determine the uses that are “reasonable and necessary”), in finalizing a NCD for these products, we urge CMS to guide its decisions by several important principles, including:

- That the coverage policy should be based strictly on the principles of evidence-based medicine, avoiding a physiologic rationale as a basis for coverage restriction and also avoiding coverage parameters that have never been studied in clinical trials or utilized in clinical practice;
- That CMS should acknowledge the role of the FDA in its judicious evaluation of the safety profile of the ESAs, and avoid using coverage policy to play the role of the FDA by issuing prescribing instructions;
- That the agency's decisions should reflect the paramount importance of the physician's role in delivering optimal cancer treatment for his or her patients;
- That the agency's actions should be made in full compliance with relevant laws, regulations, and past CMS statements on the development of coverage policies; and
- That the agency should ensure that the coverage process is open and transparent to all stakeholders.

Importantly, CMS has proposed broad coverage restrictions to the FDA-approved indication for ESAs in chemotherapy-induced anemia (CIA),⁴ as well as broad restrictions to off-label uses. However, there is an absence of compelling clinical evidence in CIA patients on which to base

these restrictions. The underlying logic of the PDM, which restricts coverage for ESAs in CIA in addition to off-label uses, appears to be based on the following three suppositions:

1. That safety signals observed in isolated off-label, experimental, or investigational uses should be extrapolated to ESA therapy in CIA and that these isolated studies are apparently judged to be of greater weight than the entire body of relevant data in CIA patients.
2. That the hypothesis that erythropoietin (EPO) receptors (EPO-R) may be expressed on tumors is valid, that these receptors—interacting with ESAs—could perhaps promote tumor growth, and that this unproven phenomenon would prove deleterious to cancer patients.
3. That a hemoglobin initiation level not to exceed 9.0 g/dL will minimize any risks while maintaining patient benefit.

In response to the first supposition, Amgen encourages CMS not to extrapolate the safety signals in off-label and experimental conditions to CIA based on individual studies, but rather to rely on a robust analysis of all available evidence to guide coverage policy.

The reasons that the approach adopted in the PDM is scientifically and clinically unjustified are summarized as follows:

- CMS can be confident that Amgen has been diligent in our pharmacovigilance, has supplied all available data to the FDA in a timely manner, and has proactively shared these data with health care professionals. The entire body of relevant data is included in the analyses contained herein.
- Robust analyses of CIA studies, including both study-level and patient-level meta-analyses, support a neutral impact of ESAs on survival.
- Although subgroup analyses point to decreased overall survival in ESA-treated patients with head and neck cancer undergoing radiotherapy, and in patients with anemia of cancer (AOC) who have active cancer not receiving or planning to receive chemotherapy or radiation therapy, these findings should not be extrapolated to the broad population of CIA patients.
- Several ongoing studies will continue to inform CMS, health care providers, and patients about the safety of ESAs.
- Several prominent medical societies and experts have also questioned the evidence base underlying the PDM.

In response to the second supposition, Amgen urges CMS to complete a careful, critical assessment of the clinical literature and evidence-base regarding EPO-R.

Such an assessment leads to a conclusion that there is no definitive evidence of EPO receptor involvement in tumor progression for the following reasons:

- While published papers provide data seemingly consistent with the hypothesis of EPO-R involvement in tumor progression, examination of the evidence shows it to be either flawed or circumstantial. This view has been confirmed by independent reviews of the literature, and is shared by several experts in the fields of oncology and immunohistochemistry.
- Several additional facts, which help support this view, are as follows:
 - EPO-R is not expressed at significant levels in human cancer cells, and EPO itself does not stimulate tumor growth.
 - The EPO-R gene does not behave as an oncogene.

- There exist no satisfactory antibody reagents for detecting EPO-R, and the most commonly used EPO-R polyclonal antibody (*i.e.*, Santa Cruz C-20) was shown to detect heat shock protein HSP70, not EPO-R, in tumor samples.
- Experiments designed to detect cell surface EPO-R on tumor cell lines by measuring binding of radio-labeled EPO showed no evidence of EPO binding, and therefore no evidence that EPO-R is present on these cells.

In response to the third supposition, Amgen notes that the agency's proposed policy of initiating therapy at 9.0 g/dL in each month is not supported by scientific evidence.

Importantly, CMS has not provided any clinical or scientific rationale for setting an implicit hemoglobin upper limit at 9.0 g/dL (*i.e.*, initiation at 9.0 g/dL in each month) when the recently revised FDA label is not to exceed 12.0 g/dL.

Key Points on Initiation Level

- Almost all randomized clinical trials (RCTs) have initiated ESA therapy when the hemoglobin level is less than 11.0 g/dL. As a result, evidence-based clinical practice guidelines have recommended the initiation of ESA therapy in cancer patients when the hemoglobin level is less than 11.0 g/dL.
- In placebo-controlled trials, when ESA-treated patients initiate therapy at hemoglobin < 9.0 g/dL, 68 percent receive at least one transfusion; however, if the hemoglobin is between 10.0 and 11.0 g/dL, only 26 percent receive at least one transfusion. Thus, the agency's proposed policy would increase the percentage of patients who receive at least one transfusion.
- A meta-analysis of studies with an average hemoglobin level between 10.0 to 12.0 g/dL at baseline showed neutral outcomes with respect to overall survival (odds ratio, 0.86; 95 percent CI 0.69 – 1.08).
- Comparison of strategies for early intervention (generally, initiation of therapy at approximately 12 g/dL) and later intervention (generally, initiation of therapy when hemoglobin level drops below 10 g/dL) have been evaluated in a number of RCTs. A meta-analysis of these studies has demonstrated an approximate 50 percent reduction in the risk of transfusion favoring the early intervention approach (relative risk, 0.55, 95 percent CI 0.42 – 0.73).

Key Points on Hemoglobin Target Level

- Most of the RCTs that define the efficacy and safety of the ESAs targeted hemoglobin levels of 11.0 to 13.0 g/dL, with dose withholding at a minimum of 13.0 g/dL. These data represent the highest level of evidence upon which CMS typically bases coverage policies.
- Current evidence-based clinical practice guidelines (*i.e.*, American Society of Hematology [ASH]/ American Society of Clinical Oncology [ASCO], National Comprehensive Cancer Networks (NCCN), European Organisation for Research and Treatment of Cancer [EORTC]) recommend targeting hemoglobin levels in the range of 11.0 to 13.0 g/dL.
- The recent FDA label change, in response to safety findings, includes a change from a target hemoglobin of 10.0 to 12.0 g/dL to a hemoglobin limit of 12.0 g/dL. **The recent FDA Oncology Drugs Advisory Committee (ODAC) panel voted, based on an analysis of existing data, that this level not be changed.**

- When survival outcomes are evaluated through meta-analysis in CIA, the hemoglobin threshold of 12.0 g/dL to 13.0 g/dL is not associated with an increase in mortality, with an odds ratio for overall survival of 0.87 (95 percent CI, 0.54, 1.38).
- Finally, in a recent Agency for Healthcare Research and Quality (AHRQ) meta-analysis of ESA safety, the relative risk of venous thromboembolism (VTE) does not vary when hemoglobin thresholds range from > 13.0 g/dL to 16.0 (Seidenfeld et al., 2006).
- While Amgen does not recommend that physicians target a hemoglobin level > 12.0 g/dL in anemic cancer patients, clinicians must practically manage hemoglobin targets and variability. To manage patients effectively, physicians need discretion to determine, for the individual patient, whether to reduce the dose or withhold the dose when the hemoglobin level temporarily exceeds 12.0 g/dL.

CMS has proposed a limit of 12 weeks per year for ESA treatment. This timeframe is without support in the clinical evidence and should be re-evaluated carefully in light of the best available data.

Chemotherapy regimens in cancer patients are frequently prolonged, and may last beyond 12 weeks. Moreover, patients experience a variable number of courses of chemotherapy in a year depending on tumor type, extent of disease and response to therapy. As such, the agency's proposal could inadvertently discriminate against Medicare beneficiaries who are prescribed chemotherapy regimens in excess of 12 weeks or who require multiple courses in a year. There is insufficient evidence to support this recommendation.

Moreover—as Amgen has commented previously and ASH has recommended—the duration of ESA therapy might need to be up to 90 days after completion of chemotherapy with longer durations depending on individual patient circumstances due to the myelosuppressive effects of chemotherapy.

Overview of Amgen's Recommendations

While there is little scientific basis to support many of the coverage restrictions proposed by CMS, there are aspects of the policy that are clinically and scientifically reasonable, and where Amgen and CMS share common views. Amgen agrees with several of the agency's non-coverage recommendations provided that specific clarifications (noted below in italics) are made, as detailed in Table 1.

Table 1: Overview of Amgen’s Recommendations on Eight Areas of Agreement with the PDM

Proposal to Restrict Coverage in Eight Areas	Amgen Recommendation
<ol style="list-style-type: none"> 1. Anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis 2. Anemia of myeloid cancers, <i>specifically acute myeloid leukemia (AML) and chronic myeloid leukemia (CML)</i> 3. Anemia associated with the treatment of myeloid cancers or erythroid cancers 4. Anemia associated with <i>primary treatment with radiotherapy</i> 5. Prophylactic use to prevent chemotherapy-induced anemia <i>in patients who have never suffered from CIA</i> 6. Prophylactic use to reduce tumor hypoxia <i>in non-anemic patients</i> 7. Patients with erythropoietin-type resistance due to neutralizing antibodies 8. Anemia due to cancer treatment if patients have uncontrolled hypertension 	<p>Consider Finalizing These 8 Proposed Coverage Limitations</p>

Note: The italicized text represents specific clarifications that would make the proposed policy clearer.

In light of the clinical evidence, Amgen recommends that CMS reconsider a series of proposed coverage restrictions, as noted in Table 2.

Table 2: Overview of Amgen’s Recommendations on 10 Restrictions for CMS to Reconsider Based on Clinical Evidence

Proposal to Restrict Coverage in 10 Areas	Review of Clinical Evidence	Coverage Recommendation
<ol style="list-style-type: none"> 1. Use with anti-angiogenic and anti-epidermal growth factor receptor (EGFR) monoclonal antibody therapies 	<ul style="list-style-type: none"> • ESAs do not stimulate angiogenesis based on a comprehensive review of the literature and Amgen’s experimental results • The PDM appears to have blended the results from two separate and unrelated studies: (1) the PACCE study of Vectibix™ (panitumumab) in colon cancer patients and (2) the study of darbepoetin alfa in patients with AOC (Amgen Study 20010103) 	<ul style="list-style-type: none"> • Because this recommendation is not based on any clinical evidence, it should not be finalized

Proposal to Restrict Coverage in 10 Areas	Review of Clinical Evidence	Coverage Recommendation
2. Anemia of cancer (AOC)	<ul style="list-style-type: none"> • Anemia of cancer represents a heterogeneous group of patients with solid and hematologic tumors in various stages of disease • There is published evidence of benefit from controlled clinical trials, without evidence of detrimental survival outcomes, in certain subgroups of patients receiving ESAs for AOC • We urge caution in extrapolating the safety finding in a specific subgroup of patients with active cancer not receiving or planning to receive chemotherapy or radiation therapy, to all AOC patients 	<ul style="list-style-type: none"> • CMS should not provide coverage in AOC patients with active cancer not receiving or planning to receive chemotherapy or radiation therapy • CMS should provide coverage for other patients with AOC
3. Patients with thrombotic episodes related to malignancy	<ul style="list-style-type: none"> • There is insufficient evidence of increased relative risk in patients with prior thrombosis • ESA use in patients with thrombotic episodes is not a contraindication or a warning in the prescribing information 	<ul style="list-style-type: none"> • Because this recommendation is not based on clinical evidence, it should not be finalized
4. Myelodysplastic syndrome (MDS)	<ul style="list-style-type: none"> • A systematic review of 59 studies (2,106 patients) with epoetin alfa and single arm studies of darbepoetin alfa support the safety and efficacy of ESAs in treatment of anemia associated with MDS (Ross et al., 2007) • Without ESA therapy, many MDS patients must undergo chronic red blood cell transfusions, carrying substantial risks, such as iron overload 	<ul style="list-style-type: none"> • The restriction is unwarranted based on the available scientific evidence, and should not be finalized

Proposal to Restrict Coverage in 10 Areas	Review of Clinical Evidence	Coverage Recommendation
5. Limits on hemoglobin level for ESA initiation and hemoglobin target	<ul style="list-style-type: none"> • The PDM blends initiation threshold and target hemoglobin level, and ESAs have never been studied with an initiation level of hemoglobin < 9.0 g/dL • Scientific evidence suggests that the greatest avoidance of transfusion occurs when ESAs are initiated at hemoglobin < 11.0 g/dL • There is practical evidence of a target hemoglobin level, allowing physician flexibility in managing individual patients who require a dose reduction rather than a dose withholding at hemoglobin > 12.0 g/dL 	<ul style="list-style-type: none"> • CMS should implement an initiation level of hemoglobin < 11.0 g/dL, which is evidence-based • CMS should consider the need for physician discretion to dose reduce rather than withhold when hemoglobin exceeds 12.0 g/dL during chemotherapy
6. Limits on duration of ESA therapy	<ul style="list-style-type: none"> • Chemotherapy regimens in cancer patients are frequently prolonged and last beyond 12 weeks, and the number of courses of chemotherapy in a year is highly variable 	<ul style="list-style-type: none"> • Duration of therapy should be individualized for the particular patient • Because this recommendation is not based on clinical evidence, it should not be finalized
7. Limits on ESA dosing	<ul style="list-style-type: none"> • ESAs are dosed to achieve hemoglobin targets, and there is no known association between ESA dose and suboptimal outcomes • FDA label specifies to use lowest dose necessary to achieve hemoglobin objectives, and the dose and hemoglobin levels cannot be managed independently 	<ul style="list-style-type: none"> • Because this recommendation is not based on clinical evidence, it should not be finalized
8. Limits on dose adjustments	<ul style="list-style-type: none"> • The criteria in the PDM are not predictive of response based on published literature 	<ul style="list-style-type: none"> • Because this recommendation is not based on clinical evidence, it should not be finalized • CMS should allow for dose titration and continued product use based on the prescribing information

Proposal to Restrict Coverage in 10 Areas	Review of Clinical Evidence	Coverage Recommendation
9. Limits on patients with weight gain and fluid retention	<ul style="list-style-type: none"> • This proposal is not founded in scientific evidence 	<ul style="list-style-type: none"> • Because this recommendation is not based on clinical evidence, it should not be finalized
10. Limits on ESA use within clinical research programs	<ul style="list-style-type: none"> • In CIA, the evidence supports a positive benefit-to-risk profile when used according to the prescribing information and a neutral risk on survival and tumor progression • Well-described risks and patient-monitoring recommendations are included in the FDA-approved product labeling 	<ul style="list-style-type: none"> • Such a restriction for an FDA-approved indication would be inappropriate and unprecedented for any Medicare covered drug or biological • It is not justified given the multitude of published evidence supporting ESA use • Therefore, this consideration should not be finalized