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Steve Phurrough, MD, MPH, CPE
Director, Coverage and Analysis Group
Office of Clinical Standards and Quality
Centers for Medicare and Medicaid Services
Department of Health and Human Services
Mail Stop: C1-09-06
7500 Security Boulevard
Baltimore, Maryland 21244

RE: Formal Request for Reconsideration of the National Coverage
Determination for Erythropoiesis-Stimulating Agents in Non-Renal
Indications (CAG-00383N) and Supporting New Evidence

Dear Dr. Phurrough:

Amgen Inc. (Amgen), a science-based company committed to developing innovative products that treat grievous illnesses, is writing to formally request reconsideration of the National Coverage Determination (NCD) for Erythropoiesis-Stimulating Agents (ESAs) in Non-Renal Indications (CAG-00383N). In submitting this reconsideration request and supporting new evidence, Amgen would like to emphasize the following points:

- Patient safety has always been of great importance and remains an ongoing commitment for Amgen. As we have shared with Centers for Medicare and Medicaid Services (CMS) previously, Amgen takes seriously the recent safety concerns regarding ESAs, and we are sensitive to the concerns of CMS regarding the appropriate use of this class of products. To this end, the recent revisions to the U.S. Food and Drug Administration (FDA) label facilitate a full benefit-risk discussion between the prescribing physician and patient.
- Amgen has an ongoing pharmacovigilance program to address safety concerns raised at the May 4, 2004, Oncologic Drugs Advisory Committee (ODAC). We have recently announced that we have augmented our pharmacovigilance program to address outstanding questions about ESA safety in both investigational and labeled settings.

- Amgen has implemented a robust risk-communication plan to ensure that providers and patients are made aware of important new data related to ESA safety, including, but not limited to, communication with physicians via Dear Health Care Provider letters, and direct communications to patients via upcoming Medication Guides.
- Amgen is supportive of most aspects of the NCD and requests a very narrow reconsideration of a specific provision in the policy.

We believe that the NCD unnecessarily restricts the ability of physicians to use ESAs for many Medicare beneficiaries who may potentially benefit from them. Consequently, Amgen joins with numerous members of the oncology community who have formally requested a reconsideration of the NCD. Amgen appreciates the opportunity to engage with CMS and submit new evidence to support a reconsideration of this policy.

The oncology community, Amgen, and CMS have worked collaboratively to arrive at evidence-based, patient-centric consensus provisions for most aspects of the NCD. However, Amgen shares the serious concerns voiced by physicians and their patients that one aspect of the NCD, namely the restriction of reimbursement for ESAs when hemoglobin is greater than 10 grams per deciliter (g/dL), should be reconsidered. This restriction prevents physicians from using their discretion in appropriately managing chemotherapy-induced anemia (CIA) with ESAs in individual Medicare patients, subjects Medicare beneficiaries to an untested treatment regimen, and forces Medicare beneficiaries to receive otherwise avoidable blood transfusions.

Importantly, major U.S. health plans have announced that they will continue to base their coverage policies on evidence-based clinical-practice guidelines and not adopt the NCD. In this regard, the NCD has created a two-tiered healthcare system based solely on insurance status: one for patients covered by Medicare and another for those with private healthcare coverage.

Below, we provide an overview of our recommendation for CMS to implement changes to the NCD based on the new evidence and then discuss each of the new areas of new evidence.

OVERVIEW OF RECOMMENDATION

In a recent meeting with CMS, Amgen proposed a narrow reconsideration of the NCD, and the Agency requested that Amgen propose alternative language to the existing NCD to address the concerns raised by the oncology community. The alternative language and the

recommendations on the use of new claims-based tools to ensure appropriate use of ESAs are discussed in detail in Appendix B. The key points of the recommendations are as follows:

- Beginning in January 2008, CMS will have the ability to effectively monitor ESA utilization in cancer patients using Medicare claims submitted in real time, as hemoglobin levels will be required on the claim form for every ESA administration. This ability arises from the anemia quality indicators that Congress mandated in the Tax Relief and Health Care Act (TRHCA) of 2006.
- CMS may use the claim information required under TRHCA to effectively implement a revised NCD that has measures designed to ensure appropriate ESA utilization. Under the TRHCA authorities, CMS has stated that the Agency will require a hemoglobin level for each administration of an ESA administered to patients treated for oncology indications (as well as certain other uses).
- Based on the newly available data on each claim for an ESA, CMS will have the ability to strictly enforce, in real-time, important aspects of the revised NCD. Specifically, CMS can, upon narrowly reconsidering the NCD based on the new evidence presented to the Agency, provide coverage for ESA in the following manner:
 - Coverage of ESA use in oncology with hemoglobin levels < 10 g/dL on a claims basis without a special Healthcare Common Procedure Coding System (HCPCS) code or code modifier
 - Coverage of ESA use in oncology with hemoglobin levels \geq 10 g/dL but < 12 g/dL on a claims basis only if those claims also contain a HCPCS code or code modifier indicating that the patient has been informed of the benefits and risks of ESA therapy and that there is documentation in the medical record of anemia symptoms (e.g., shortness of breath or impaired exercise capacity), or specific co-morbid conditions predisposing patients to the health effects of anemia (e.g., limited cardiopulmonary reserve or underlying coronary artery disease)
 - Non-coverage for ESA use in oncology with hemoglobin levels > 12 g/dL on a claims basis

OVERVIEW OF NEW EVIDENCE TO SUPPORT RECONSIDERATION

After consultation with leading scientific and clinical experts, practicing physicians, and patients, Amgen is submitting this formal request for reconsideration based on a growing body of new information that supports the need for a change in the NCD-recommended hemoglobin ceiling of 10 g/dL. An appropriate modification of the position should enable oncologists to manage patients to maintain the lowest hemoglobin level sufficient to avoid transfusions, not to exceed the upper safety limit of 12 g/dL, recognized to represent the range at which risk/benefit profile for ESAs is favorable and subject to the warnings in ESA package inserts. The body of new information includes the following:

- On November 8, Amgen announced that it has updated the Aranesp[®] (darbepoetin alfa) and EPOGEN/PROCRIT[®] (Epoetin alfa) package inserts in collaboration with the FDA. The new package inserts strengthen the warnings about ESA risks and confirm that physicians should use the lowest dose that avoids transfusions, but retains physician discretion to use ESAs up to the upper safety limit of a hemoglobin of 12 g/dL to avoid transfusion. This upper safety limit stands in contrast to the NCD provision that limits physician discretion for ESAs above a hemoglobin level of 10 g/dL.
- On October 23, the European Agency for the Evaluation of Medicinal Products (EMA) issued a press release about upcoming changes to product information for ESAs stipulating a uniform target hemoglobin range across all licensed indications for ESAs of 10 g/dL to 12 g/dL with a warning not to exceed an upper safety limit of 12 g/dL. The treatment range approved by the EMA also stands in contrast to the NCD provision that denies coverage for ESAs above a hemoglobin level of 10 g/dL.
- On October 22, the American Society of Hematology and the American Society of Clinical Oncology (ASH/ASCO) revised their evidence-based clinical practice guidelines, following a rigorous review of all the available evidence by cancer experts, and reaffirmed a target range of 10 g/dL to 12 g/dL. Again, this treatment range recommended by the leading clinical authorities in the U.S. stands in contrast to the NCD provision that denies coverage for ESAs above a hemoglobin level of 10 g/dL.
- On November 4, the German Hodgkin Study Group presented interim results of one of the largest randomized trials on ESAs in cancer patients with Hodgkin's Lymphoma (HD15). The study maintained hemoglobin levels between 12 and 14 g/dL. The data from this study were submitted to the FDA on Nov. 2. The interim data on 688 patients show no significant

difference between Epoetin alfa and placebo on overall survival or freedom from treatment failure (FFTF) after 30 months of follow up. Also, at this interim data point, there were significantly fewer RBC transfusions in the Epoetin alfa group (median 2 red blood cell [RBC] units) compared with placebo (median 4 RBC units). This seems to add to the body of evidence indicating neutral long-term survival and progression outcomes associated with ESA use in patients with CIA. Further, based on the interim data from this study, no adverse outcomes were associated with maintaining hemoglobin levels above the NCD recommended hemoglobin level of 10 g/dL.

- Including data from HD15, there are now a total of 14 clinical trials in CIA across various tumor types that have measured long-term survival, 12 of which have shown neutral outcomes. In all 14 studies, ESAs were used to target hemoglobin levels above those currently recommended in the NCD. On Nov. 5, Amgen performed a meta-analysis of these data which showed an overall neutral survival risk. This meta-analysis represents new information that has not been previously considered by CMS.
- On September 26, Amgen presented new analyses of patient-level data from 6 Amgen-sponsored placebo-controlled CIA studies at the European Cancer Conference (ECCO). This analysis included all randomized, placebo-controlled studies of darbepoetin alfa that have been conducted in CIA. These analyses suggested that adverse outcomes were not associated with achieving hemoglobin levels > 12 g/dL or > 13 g/dL. The analyses also suggested that the vast majority of patients who received a transfusion (> 85%) exceeded the FDA-mandated rate of rise algorithm for ESAs (> 1 g/dL in 14 days). These patients who achieved > 1 g/dL in 14 day increases in hemoglobin after receiving transfusions had less favorable survival outcomes than those patients who achieved > 1 g/dL in 14 day increases in hemoglobin from ESA use and had not received a transfusion in the previous month. As the hemoglobin restrictions regarding ESA use in the NCD would likely increase transfusion requirements, these new analyses suggesting poorer survival outcomes among those transfused should be considered.
- In October 2007, a study was published showing that stored blood undergoes changes that may adversely affect the ability of RBCs to normally deliver oxygen to tissues. These data provide a medical explanation for the poorer outcomes that have been observed in patients receiving transfusions. The hemoglobin restrictions regarding ESA use in the NCD would likely increase transfusion requirements, yet transfusions do not provide an entirely safe alternative to ESAs and may in fact result in poorer survival outcomes.

- In a number of institutions that provide care for cancer patients, there is new evidence describing a trend towards increased transfusion utilization between July 2006 and September 2007 among cancer patients ≥ 65 years who are receiving chemotherapy. A potential explanation for this rise may be attributed to the ESA restrictions in the July 2007 NCD.

Amgen is providing this as new information that was not available for consideration during the NCD development process. The new information, which we discuss below in detail, provides compelling evidence for CMS to act on the concerns outlined by the clinical and scientific communities in their requests for reconsideration. We urge CMS to review these data and to act quickly to issue a revised NCD on this singular point of disagreement to make the NCD consistent with all of the new evidence presented.

DETAILED DISCUSSION OF NEW EVIDENCE THAT JUSTIFIES POLICY REVISIONS

New Evidence I: FDA ESA Label Changes Recommend an Upper Safety Limit of 12 g/dL

The product-prescribing information for darbepoetin alfa and Epoetin alfa was recently updated (November, 2007) in response to recent safety concerns regarding the use of ESAs in cancer patients, and to suggested class revisions for the ESA product labels made at the May 10, 2007, ODAC. In particular, these changes were prompted in response to safety concerns from 6 trials (2 in radiotherapy, 2 in anemia of cancer [AoC], and 2 in CIA) that have reported negative safety outcomes associated with ESA use.¹ The new package inserts strengthen the warnings about ESA risks and confirm that physicians should use the lowest dose that avoids transfusions, but retains physician discretion to use ESAs up to the upper safety limit of a hemoglobin of 12 g/dL to avoid transfusion.

Specifically, the new package inserts make the following recommendations regarding ESA dosing and titration:

- ESA dose should be adjusted to maintain the lowest hemoglobin level sufficient to avoid transfusions and not to exceed the upper safety limit of 12 g/dL
- ESAs should be discontinued upon completion of a chemotherapy course

The new package inserts also include a black box warning that states:

¹ Leyland-Jones et al., 2005; Amgen study 20000161; Henke et al., 2003; Overgaard et al., 2007; Wright et al., 2007; Glaspy et al., 2007.

- ESAs shortened overall survival and/or time-to-tumor progression in clinical studies in patients with advanced breast, head and neck, lymphoid, and non-small cell lung malignancies when dosed to a target hemoglobin of ≥ 12 g/dL
- The risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to a target hemoglobin of < 12 g/dL
- To minimize these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusions
- Use only for treatment of anemia due to concomitant myelosuppressive chemotherapy
- Discontinue following the completion of a chemotherapy course

Significance: Based in part on expert recommendations from ODAC, the FDA recently revised the product-prescribing information for ESA use in cancer patients. The revised prescribing information recommends titrating ESA use so that hemoglobin concentrations remain at a level that avoids a transfusion and not to exceed an upper safety limit of 12 g/dL. This allows for physician discretion in treating patients with CIA to avoid transfusions. The NCD recommends that ESA maintenance therapy only be reimbursed for cancer patients who maintain hemoglobin levels below 10 g/dL and leaves no room for physician discretion to treat up to the upper safety limit of 12 g/dL. The guidance issued by the FDA and CMS conflict.

New Evidence II: EMEA ESA Label Changes Recommend Hemoglobin Range of 10-12 g/dL

On October 23, 2007, the EMEA released a public statement in response to safety concerns regarding ESAs.² This review, authored by the Committee for Medicinal Products for Human Use (CHMP) and its Pharmacovigilance Working Party (PhVWP), concluded that clinical benefits associated with the approved use of ESAs outweighed recently communicated safety risks. The EMEA concluded that the cause of the increased adverse outcomes associated with ESA use is unexplained. However, in light of these recent safety concerns they recommended that specific changes should be made to the product prescribing information:

- Two recommendations concerned limitations to ESA use:

² European Medicines Agency. Public Statement October 23, 2007: Epoetins and the risk of tumour growth progression and thromboembolic events in cancer patients and cardiovascular risks in patients with chronic kidney disease.

- ESAs should be used only to treat symptomatic anemia
- The uniform target hemoglobin range across indications for all ESAs should be 10 g/dL to 12 g/dL, with a warning not to exceed the upper safety limit of 12 g/dL
- EMEA also stated that:
 - Trials have demonstrated a small unexplained excess mortality associated with high target hemoglobin concentrations
 - No significant benefits have been demonstrated from targeting hemoglobin levels beyond that necessary to control anemia symptoms and avoid transfusions

Significance: The EMEA is a well-respected international regulatory agency with extensive experience in the review of oncology products. The EMEA met to review the body of evidence for ESA use in oncology, including all recent data, and recommended a hemoglobin target range of 10 g/dL to 12 g/dL, not to exceed the upper safety limit of 12 g/dL, consistent with current ESA prescribing information.³ This range allows for physician discretion in treating patients with CIA to avoid transfusions, but lies outside the hemoglobin-maintenance range recommended by the recent NCD. The NCD recommends that ESA maintenance therapy only be reimbursed for cancer patients who maintain hemoglobin levels below 10 g/dL and leaves no room for physician discretion to treat to the upper safety limit of 12 g/dL. Labeling discussions between the EMEA and Amgen to finalize the EU labeling are ongoing.

New Evidence III: Revised ASH/ASCO Guidelines Recommend Hemoglobin Range of 10-12 g/dL

The American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) represent two of the preeminent U.S. oncology groups. In October 2007, ASH/ASCO updated their joint practice guidelines for use of ESAs.⁴ A select expert group of 11 oncology/hematology practitioners reviewed and analyzed data on ESA use published between 2002 and July 2007, focusing on available systematic reviews and meta-analyses of published

³ Amgen Inc. Aranesp® (Darbepoetin alfa) Package Insert. Breda, Netherlands.

⁴ Rizzo et al. American Society of Clinical Oncology/American Society of Hematology 2007 Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin. *J Clin Oncol* 2007; 25 (34): 1-17. Published online ahead of print on October 22, 2007. The latest version is at <http://jco.ascopubs.org/cgi/doi/10.1200/jco.2007.14.3396>

clinical trials. Data from the May 2004 and May 2007 ODAC meetings were also evaluated. This rigorous, systematic review of the evidence and publication of the findings in a peer-reviewed journal is considered important new evidence by most scientific bodies. The revised guidelines for patients with CIA provide ESA dosing recommendations similar to the previous guidelines issued in 2002:

- To increase hemoglobin and decrease transfusions, ESA treatment should be initiated as hemoglobin level approaches or falls below 10 g/dL
 - For patients with hemoglobin levels < 12 g/dL that have never fallen near 10 g/dL, the decision of whether to initiate ESA therapy immediately or wait until hemoglobin levels fall closer to 10 g/dL should be based on individual clinical circumstances
- Hemoglobin levels can be raised to (or near) 12 g/dL, at which time the ESA dosage should be titrated to maintain that level
 - Dose escalation should follow FDA recommendations
 - Therapy should be discontinued after 6-8 weeks in the absence of a < 1-2 g/dL rise in hemoglobin or absence of a diminution in transfusion requirements
 - Dose reductions are recommended when hemoglobin rise exceeds 1 g/dL in any 2-week period, or when hemoglobin level exceeds 11 g/dL

Significance: A group of 11 individuals with extensive experience in the treatment of oncology patients met to review the body of evidence for ESA use in oncology, including all recent data. The ASH/ASCO committee recommended initiating ESA therapy when hemoglobin levels approach or fall below 10 g/dL and titrating ESAs to raise hemoglobin levels to and maintain them at or near 12 g/dL, consistent with current U.S. ESA prescribing information. This range allows for physician discretion in treating patients with CIA to avoid transfusions, but lies outside the hemoglobin-maintenance range recommended by the recent NCD. The NCD recommends that ESA maintenance therapy only be reimbursed for cancer patients who maintain hemoglobin levels below 10 g/dL and leaves no room for physician discretion to treat to the upper safety limit of 12 g/dL.

New Evidence IV: Planned Interim Analysis of the HD15 Study Suggests ESAs Have No Impact on Death or Disease Progression

In November 2007, the German Hodgkin Study Group (GHSD) presented the results of a planned interim analysis of the HD15 study: a prospective, multicenter, randomized trial to reduce the toxicity of the cancer-therapy cocktail, BEACOPP in patients with advanced Hodgkin's lymphoma (HL) who had not received prior chemotherapy.⁵ BEACOPP causes acute hematological toxicity in HL patients, increasing the requirement for red blood cell transfusions. The data from this study were submitted to the FDA on November 2, 2007.

- The primary aim of HD15 was to reduce the toxicity of BEACOPP while maintaining high rates of freedom from treatment failure (FFTF). Secondary aims were to assess the effect of Epoetin alfa on patients' quality of life, tumor response, safety, and overall survival
- Patients were randomized into 3 chemotherapy groups (non-blinded), each receiving a different BEACOPP regimen
 - Within each of the 3 chemotherapy groups, patients received either Epoetin alfa (n = 350) or placebo (n = 338) (double blinded) to maintain hemoglobin between 12 and 14 g/dL. At the end of the chemotherapy period, Epoetin alfa or placebo was administered to maintain hemoglobin less than or equal to 12 g/dL for up to 6 weeks

These interim data indicate:

- BEACOPP decreased hemoglobin levels during the study, but higher hemoglobin levels and significantly lower transfusion requirements were observed in patients who received Epoetin alfa (median = 2 RBC units) versus placebo (median = 4 RBC units)
 - Tumor response and incidence of deaths were similar between the ESA and placebo groups
 - There was no statistically significant difference in the 30-month FFTF or 30-month overall survival between the ESA and placebo groups (data presented at 7th Annual Symposium on Hodgkin's Lymphoma). A hazards ratio comparing overall survival was not generated for this early interim analysis; however, the

⁵ Engert et al. Role of Erythropoetin (EPO) in patients with Hodgkin Lymphoma, presented at 7th Annual Symposium on Hodgkin's Lymphoma, November 4, 2007.

odds ratio was calculated by Amgen based on the reported number of deaths in each treatment arm (OR = 1.21; 95% CI: 0.32, 4.55).

Significance: In this large study of CIA patients, the interim data indicate ESA use had no impact on tumor response or overall survival at 30 months of follow up. This seems to add to a growing body of evidence, now totaling 12 studies in different tumor types, indicating a neutral long-term survival outcome associated with ESA use in cancer patients receiving chemotherapy. Further, based on the interim data from this study, no adverse outcomes were associated with maintaining hemoglobin levels above the NCD-recommended hemoglobin level of 10 g/dL.

New Evidence V: Meta-analysis of 14 CIA trials with > 1 Year Follow Up Demonstrates Neutral Effect of ESAs on Survival

There are 14 controlled clinical trials in CIA that have reported long-term survival data (> 1 year of follow up) (Table 1). Twelve of these reported neutral survival outcomes; the BEST study, and the Amgen study 20000161 (Hedenus 2003) had an increased mortality in the ESA-treated arm. None of the 14 studies (n=6241; 3190 ESA; 3051 control) reported an increase in disease progression associated with ESA use. When the data from all fourteen studies were meta-analyzed, there was an overall neutral survival risk for ESA use (OR: 1.02; 95% CI: 0.91, 1.16) (Figure 1).

Significance: This meta-analysis represents new information that has not been previously considered by CMS. In each of the 14 studies, hemoglobin levels of at least 12 g/dL were targeted; only BEST and the Amgen study 20000161 (Hedenus 2003, updated data) reported adverse outcomes. Overall, there was a neutral survival risk associated with ESA use.

New Evidence VI: ECCO Transfusion Analysis Suggests Outcomes are Worse Among Those Requiring Transfusions

In a recent analysis presented at ECCO,⁶ Amgen combined patient-level data from 6 randomized, placebo-controlled trials in which patients with CIA were treated either with

⁶ Glaspy et al. (2007). Evaluation of the association between hemoglobin (Hb) events and safety outcomes in cancer patients (pts) with chemotherapy-induced anemia (CIA): an integrated analysis of patient-level data from 6 randomized, placebo-controlled trials (RCTS) of darbepoetin alfa (DA). European Journal of Cancer Supplements, 5 (4); p.147 [abstract #P1120].

darbepoetin alfa or with placebo. This analysis included all randomized, placebo-controlled studies of darbepoetin alfa that have been conducted in CIA. There is a hypothesis that if patients treated with ESAs have large or rapid increases in their hemoglobin levels, they are at a greater risk of worse outcomes. Indeed, the product labeling for ESAs recommends ESA dose reductions if rapid hemoglobin rises occur, and a recent FDA briefing document for the Cardiovascular-Renal Drug Advisory Committee (CRDAC) determined them to be a negative risk factor in kidney patients. The objective of the analysis was to evaluate the association between hemoglobin events, transfusions, and safety outcomes:

- This analysis identified patients who experienced a rise in hemoglobin of > 1 g/dL in 14 days or > 2 g/dL in 28 days and the probable cause of this increase – either ESA or transfusion. The analysis did not discriminate between those in the placebo group and those in the ESA group, it identified patients who had a rapid hemoglobin rise and identified the cause.
- Of those transfused on study (regardless of treatment group), approximately 90% of all > 1 g/dL in 14 day increases and approximately 80% of all 2 g/dL in 28 day increases were found to be due to transfusion, demonstrating that transfusion is a common cause of such hemoglobin rises.
- Achievement of rapid rates of hemoglobin rise (> 1 g/dL in 14 days or > 2 g/dL in 28 days) due to ESA use (*i.e.*, no transfusion had been received within the previous month) were not associated with worse safety outcomes. In contrast, patients who had > 1g/dL in 14 days or > 2 g/dL in 28 days hemoglobin rise due to transfusions (*i.e.*, were observed within a month of a transfusion) had worse safety outcomes (Figure 2).
- Patients receiving transfusions had a greater risk of death and disease progression than patients who did not have transfusions. This may be because sicker patients require more transfusions and are more likely to have worse outcomes (Figure 3).

Significance: Transfusions are not a risk-free alternative to ESAs; complications include exposure to infection, immune-mediated reactions, and iron and circulatory overload. Data from this analysis suggest that survival and disease progression outcomes may also be negatively impacted. As the proposed hemoglobin restrictions regarding ESA use in the NCD would likely increase transfusion requirements, this potential for poorer survival outcomes among those transfused should be considered.

New Evidence VII: RBC Changes During Storage May Contribute to Poorer Outcomes in Patients Receiving Transfusions

In October 2007, a study was published suggesting that patients receiving transfusions may have poorer outcomes because of changes that occur to RBCs during blood storage.⁷ In this study, blood from 15 healthy volunteers was processed, stored according to AABB standards, and evaluated for the percentage of hemoglobin-carrying nitric oxide and associated RBC-dependent vasodilation.

- Results from this study showed:
 - The percentage of hemoglobin-carrying nitric oxide in RBCs decreased rapidly and remained low over the 42-day storage period
 - The associated RBC-dependent vasodilation was significantly lowered
 - RBC deformability decreased gradually over the 42 days

These deficiencies are likely to disrupt normal oxygen delivery to tissues. They may also account for the increased rate of venous thromboembolic events (VTEs) that have been observed⁸ among patients receiving transfusions: the shortage of nitric oxide in circulating blood promotes platelet aggregation and impairs erythrocyte deformability compromising flow within the microvasculature.⁹

Significance: Transfusions are not a risk-free alternative to ESAs; complications include exposure to infection, immune-mediated reactions, and iron and circulatory overload, and studies have shown that outcomes may be worse among those receiving transfusions. Data from this analysis may provide a medical explanation (*i.e.*, poorer oxygen delivery and increased incidence of VTEs) for the poorer outcomes observed. The proposed hemoglobin restrictions regarding ESA use in the NCD would likely increase transfusion requirements, yet transfusions do not provide a risk-free alternative to ESAs and may in fact result in poorer survival outcomes.

⁷ Bennett-Guerrero et al. Evolution of adverse changes in stored RBCs. PNAS. 2007; 104 (43): 17063-68.

⁸ Gangireddy, C, et al. Risk factors and clinical impact of postoperative symptomatic venous thromboembolism. J Vasc Surg. 2007; 45 (2): 335-341; Nilsson, KR, et al. Association between venous thromboembolism and perioperative allogeneic transfusion. Arch Surg. 2007; 142 (2): 126-32.

⁹ Bor-Kucukatay et al. Effects of nitric oxide on red blood cell deformability. Am J Physiol Heart Circ Physiol. 2003; 284 (5): H1577-84

New Evidence VIII: Early Trends Suggest an Increase in Transfusions in Medicare Eligible Patients After New ESA Safety Warnings and CMS Reimbursement Restrictions

Restrictions mandated by the NCD on approved ESA use for patients undergoing chemotherapy are likely to force a greater reliance on transfusions for anemia management. For this reason, Amgen has implemented measures to assess the impact on patients receiving transfusions. To evaluate the potential impact of the NCD, transfusions were captured using data from the Varian electronic medical record (EMR) database (Appendix C).¹⁰ The Varian EMR database comprises 52 clinics, 350 oncologists, and more than 150,000 patients; however only 7 of the clinics in this database had integrated transfusion data. Data were analyzed from these 7 clinics (10,803 eligible patient visits among those \geq 65 years old receiving chemotherapy) during the period July 2006 through September 2007. Key findings are summarized below:

- The number of patients exposed to transfusions increased 27% from July 2006 to September 2007
- The volume of transfusions increased 18% during the same period
 - Both parameters showed a sharp rise as of the second quarter 2007, with increases continuing in the third quarter 2007
- Over the same period the total number of 'transfusion opportunities' (sums of monthly patient visits) did not change

These data show that over the time period assessed, more patients are receiving transfusions. The increase in the volume of transfusions administered was less than the increase in the number of patients exposed to transfusions. This suggests that although more patients are receiving transfusions, the average number of transfusions administered to each patient is lower. Similar trends were also observed in patients younger than 65 years of age. Further analysis of transfusion rates in this population is currently being conducted, and we will continue to provide CMS updates on the data trends.

Significance: Compared to pre-NCD values, more patients overall are now receiving transfusions, but with a lower number of transfusions per patient. These preliminary data suggest that patients with less severe anemia, who previously have been appropriately managed with ESAs, may now require transfusions.

¹⁰ Amgen, data on file

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Amgen appreciates the opportunity to share this new evidence with CMS. We believe that our reconsideration request will provide useful data for CMS to consider as its staff work to consider the development of a revised NCD for ESAs in non-renal disease indications (CAG-00383N). If you would like any further information, please contact me personally by phone at (805) 447-0787 or by email at jofman@amgen.com. Alternatively, you may contact Andy Swire in Amgen's Global Government Affairs office at (202) 585-9611 or by email aswire@amgen.com. Thank you for your attention to these important matters.

Regards,



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cc: Kerry Weems, Acting Administrator, CMS
Herb Kuhn, Acting Deputy Administrator, CMS
Barry Straube, MD, Director, Office of Clinical Standards and Quality (OCSQ),
Chief Medical Officer, CMS

Appendices A – Supporting Clinical Data
B – NCD Edits Requested Based on New Evidence Presented and Proposed
Real-Time Claims Management Process
C – EMR Analysis on Transfusion Trends
D – Fulfillment of CMS Requirements for a Formal Request for Reconsideration
of an NCD
E – Supplementary Documents

APPENDIX A – SUPPORTING CLINICAL DATA

Table 1: Summary of 14 CIA Studies with Long-term Follow up for Survival

Study	Tumor Type	Hb target (g/dL)	Primary Endpoint	Odds Ratio for OS (95% CI)	Progression Endpoints (95% CI)	Duration of Follow up
Vansteenkiste 2002 ^a (n = 314)	Lung (all histologies)	13-15 M 13-14 F	RBC transfusions Wk 5 to EOTP	0.62 (0.38, 1.01)	Not evaluated	Median: 254 days for DA, 204 days for placebo
Pirker 2007 (20010145) ^a (n = 596)	Extensive stage SCLC	13-14	Change in Hb bL to end of Ctx + OS	0.79 (0.52, 1.21)	PFS HR: 1.02 (0.86, 1.21)	Patients followed until death ^b
Littlewood 2001 ^a (n = 375)	Mixed	12-15	RBC transfusions wks 1-4	0.83 (0.53, 1.30)	Not evaluated	Median 26 months
EPO-GER-022 ^a (Data on file, J&J PRD) (n = 389)	Stage 3 NSCLC	13-14	2 yr OS	0.90 ^c (0.60, 1.34)	Not evaluated	2 years planned
Blohmer 2004 (n = 257)	Cervical	13	Relapse-free survival	0.67 (0.33, 1.34)	Relapse or death 15% Epo 24% control (p = 0.034)	229 wks
Möbus 2007 (n = 658)	High risk adjuvant breast	12.5 – 13	Disease-free survival	0.99 (0.67, 1.46)	5 yr DFS: Epo 72%, ctrl 71%	Median: 62 months
Aapro 2006 (BRAVE) (n = 463)	Metastatic breast	Hb <12.9 required for study entry	OS, PFS & tumor response	0.98 (0.65, 1.48)	PFS: HR = 1.07 (0.89, 1.30)	24 wk tmt + 18 mo follow up
Witzig 2005 ^a (n = 344)	Mixed	13-15	QOL	1.02 (0.65, 1.59)	Disease progression 29% plc; 33% Epo	16 wk tmt + 1 yr follow up
Osterborg 2005 ^a (n = 343)	Hematological	13-14	Tfn-free survival wks 5-16	1.08 (0.69, 1.67)	Disease progression 23% plc; 18% Epo	16 wk treat + ≥1 yr follow up
Chang 2005 (EPO-CAN-17) (n = 354)	Breast Adjuvant (79%) Metastatic (21%)	12-14	QOL	0.97 (0.55, 1.73)	Not evaluated	Survival data: 2 years planned
Leyland-Jones 2005 (BEST) ^a (n = 939)	Metastatic breast	12-14	12 mo OS	1.42 (1.07, 1.90)	12 mo TTP: Epo alfa 41%, plc 43% HR = 1.00	12 mo

Study	Tumor Type	Hb target (g/dL)	Primary Endpoint	Odds Ratio for OS (95% CI)	Progression Endpoints (95% CI)	Duration of Follow up
Hedenus 2003 (updated data) ^a (n = 344)	Hematological	13-15 M 13-14 F	Hb resp ≥2 g/dL, no Transfusion in <28 d	1.48 (0.97, 2.27)	Not evaluated	12 wk study + 11 mo follow up
Grote 2005 (N93-004) ^a (n = 224)	SCLC (all stages)	14-16	Pts with CR or PR after 3 cycles chemotherapy	1.54 (0.64, 3.72)	PD (after 3 cycles) 7% epo, 8% pbo	3 years
Engert 2007 (HD 15) ^a (n = 688)	Hodgkin's Disease	12-14 during chemotherapy 12 after chemotherapy	QOL	1.21 (0.32, 4.55)	30 mo FTF: 85% (82%, 87%)	30 mo

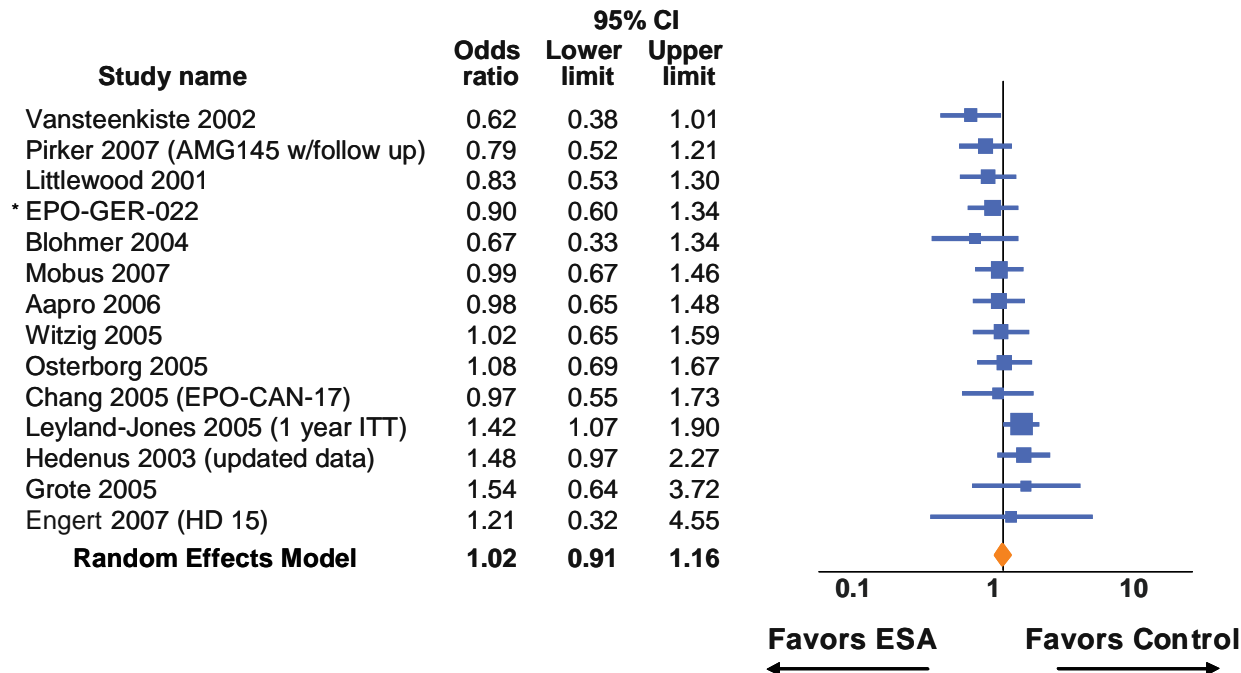
^a Placebo-controlled studies

^b Cut-off date of February 22, 2007; after 493 of 596 deaths had occurred.

^c Interim data from > 1 year of follow-up only; two-year follow-up ongoing.

Abbreviations: Hb, hemoglobin; OS, overall survival; CI, confidence interval; M, male; F, female; RBC, red blood cell; EOTP, end of the treatment period; HR, hazard ratio; DA, darbepoetin alfa; SCLC, small-cell lung cancer; bL, baseline; Ctx, chemotherapy; epo, epoetin; NSCLC, non-small cell lung cancer; wks, weeks; yr, year; DFS, disease-free survival; ctrl, control; PFS, progression-free survival; tmt, treatment; mo, month; QOL, quality of life; TTP, time to progression; resp, response; d, days; pbo, placebo; pts, patients; CR, complete response; PR partial response; PD disease progression; FTF, freedom from treatment failure

Figure 1: Survival is Risk Neutral for 14 CIA Studies with Long-term Follow Up¹¹



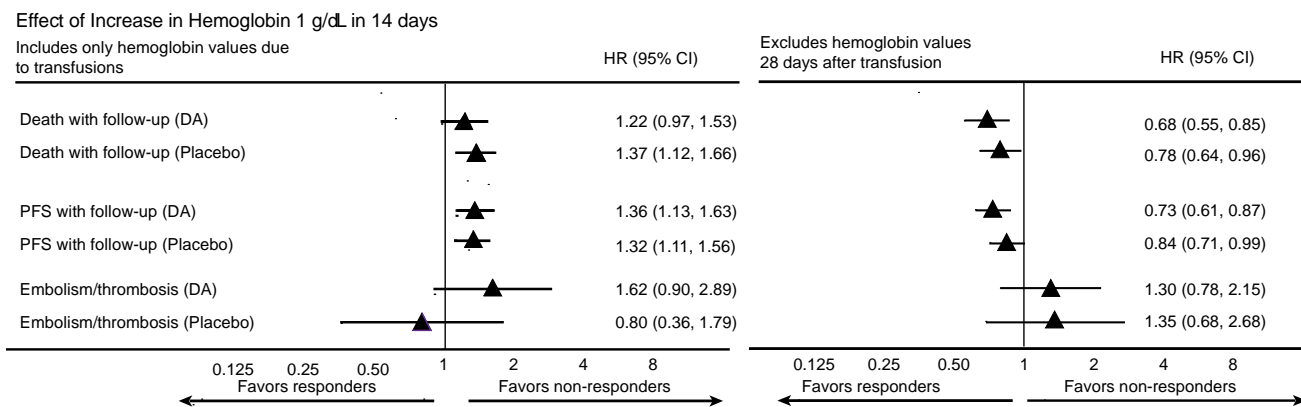
$I^2 = 0.0\%$; Fixed Effects Model = Random Effects Model
 Meta Analysis Using OR

- Note that for the Hedenus 2003 (20000161) study, the odds ratio indicates neutrality; however, the hazard ratio was 1.36 (95% CI: 1.02, 1.82) demonstrating a significant reduction in overall survival associated with ESA use. As hazard ratios cannot be combined unless patient-level data for each study are available, the odds ratios were used to obtain the overall point estimate.

¹¹

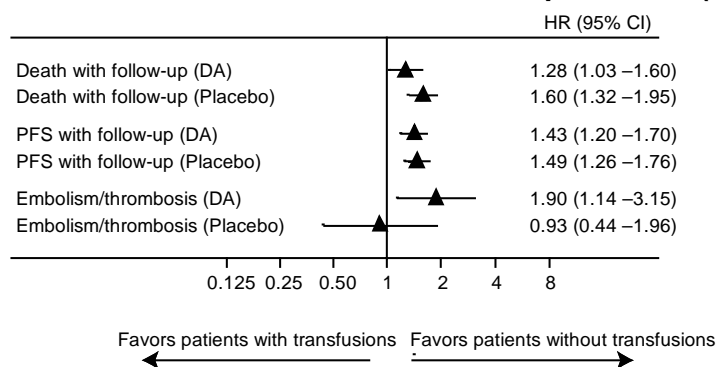
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Leyland-Jones et al. J Clin Oncol. 2005; 23: 5960-5972
 Updated data from **Hedenus** et al. Br J Haematol. 2003; 122: 394-403
Grote et al. J Clin Oncol. 2005; 23: 9377-9386
Engert et al. 7th Annual Symposium on Hodgkin's Lymphoma, November 4, 2007.

Figure 2: Effect of Rate of Hemoglobin Rise on Adverse Events and Survival Including (left) and Excluding (right) Transfusion: Patient-Level Data from Placebo-controlled CIA Studies of Darbepoetin alfa (DA)¹²



- On the left, the outcomes associated with a rapid hemoglobin rise due to transfusions are shown. This analysis shows that those who do not have the rapid rise do better.
- On the right, the outcomes associated with a rapid hemoglobin rise due to ESAs are shown. This analysis shows that those who do have the rapid rise do better.
- Overall, this means that rapid rate of hemoglobin rise is only associated with worse outcomes if the rise is due to transfusion.

Figure 3: Impact of Transfusions on Adverse Outcomes: Patient-Level Data from Placebo-controlled CIA Studies of Darbepoetin alfa (DA)



- This analysis shows that patients receiving transfusions during the study had worse death or disease progression regardless of whether they received ESA or placebo.
- The risk for thromboembolic events was increased among ESA-treated patients compared to placebo. This is a recognized risk associated with ESA use and is noted in the product labeling.

DA = darbepoetin alfa; HR = hazard ratio; PFS = progression-free survival

¹² Presented at ECCO on September 26, 2007.

APPENDIX B: NCD EDITS REQUESTED BASED ON NEW EVIDENCE PRESENTED AND PROPOSED REAL-TIME CLAIMS MANAGEMENT PROCESS

In response to the Agency's request, we outline below the specific changes that we are requesting that CMS implement through a reconsideration of the NCD for ESAs. As we note in our request for reconsideration, Amgen shares the serious concerns voiced by physicians and their patients that one aspect of the NCD, namely the hemoglobin ceiling of 10 grams per deciliter [g/dL], should be reconsidered. The following recommended revisions (shown as blue text and edits) where appropriate, would adopt language from the FDA-approved labeling to address those concerns.

NCD EDITS – COVERAGE CONDITIONS (PAGE 2), CONCLUSION (PAGE 25)

Current Language in NCD

We have also determined that ESA treatment for the anemia secondary to myelosuppressive anticancer chemotherapy in solid tumors, multiple myeloma, lymphoma and lymphocytic leukemia is only reasonable and necessary under the following specified conditions:

1. The hemoglobin level immediately prior to initiation or maintenance of ESA treatment is < 10 g/dL (or the hematocrit is < 30%).

* * *

3. Maintenance of ESA therapy is the starting dose if the hemoglobin level remains below 10 g/dL (or hematocrit is < 30%) 4 weeks after initiation of therapy and the rise in hemoglobin is > 1g/dL (hematocrit > 3%).

* * *

5. Continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin > 1 g/dl (hematocrit > 3%) over 2 weeks of treatment unless the hemoglobin remains below or subsequently falls to < 10 g/dL (or the hematocrit is < 30%). Continuation and reinstatement of ESA therapy must include a dose reduction of 25% from the previously administered dose.

Recommended Revisions to NCD

We have also determined that ESA treatment for the anemia secondary to myelosuppressive anticancer chemotherapy in solid tumors, multiple myeloma, lymphoma and lymphocytic leukemia is only reasonable and necessary under the following specified conditions:

1. The hemoglobin level immediately prior to initiation ~~or maintenance~~ of ESA treatment is < 10 g/dL (or the hematocrit is < 30%) **at the onset of anemia during a course of chemotherapy. Continued administration of the drug is reasonable and necessary to maintain a hemoglobin level in oncology between 10-12 g/dL, but not to exceed the**

upper safety limit of 12 g/dL. ESA use between a hemoglobin level of 10-12 g/dL in oncology must be accompanied by documentation in the medical record of the patient being informed of the benefits and risks of ESA use and of the presence of anemia symptoms (e.g., shortness of breath or impaired exercise capacity) or specific co-morbid conditions predisposing patients to the health effects of anemia (e.g., limited cardiopulmonary reserve or underlying coronary artery disease). ESA administration is not reasonable and necessary under any circumstance for use in oncology if the hemoglobin level is >12 g/dL (or the hematocrit is > 36%).

* * *

3. 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 the upper safety limit of 12 g/dL.

* * *

5. If the rate of hemoglobin increase is more than 1 g/dL per 2-week period or when the hemoglobin reaches a level needed to avoid transfusion, the dose should be reduced by 40% of the previous dose. If the hemoglobin exceeds 12 g/dL, dose should be temporarily withheld until the hemoglobin approaches a level where transfusions may be required. At this point, therapy should be reinitiated at a dose 40% below the previous dose.

Notes

- In making these suggested edits, Amgen is recommending that CMS adopt dose titration instructions that are consistent with the product package insert in the FDA-approved label.
- For the sake of clarity and simplicity, we have specifically recommended edits to the sections marked "Coverage Conditions" and "Conclusion" in the NCD. As CMS considers revisions to the NCD, we recommend that any other sections of the current NCD that contain similar language, such as the section labeled "Summary of Restrictions for Covered Indications," be similarly revised.

NCD EDITS – PROPOSED REAL-TIME CLAIMS MANAGEMENT PROCESS

In our recent meeting with CMS, we reviewed the Agency's new requirement under TRHCA to use provider-submitted healthcare claims to monitor the hemoglobin levels of patients receiving ESA therapy. Amgen supported this TRHCA provision, which was designed specifically to help ensure that patients receive ESAs appropriately.

Recommended Process

Under the TRHCA authorities, CMS has stated that the Agency will require a hemoglobin level for each administration of an ESA administered to patients treated for oncology indications (as well as certain other uses). Based on the newly available data on each claim for an ESA, CMS will have the ability to strictly enforce, in real-time, important aspects of the revised NCD.

Specifically, CMS can:

- Cover ESA use in oncology with hemoglobin levels < 10 g/dL on a claims-basis without a special Healthcare Common Procedure Coding System (HCPCS) code or code modifier
- Cover ESA use in oncology with hemoglobin levels \geq 10 g/dL but < 12 g/dL on a claims-basis only if those claims also contain a HCPCS code or code modifier indicating that the patient has been informed of the benefits and risks of ESA use and that there is documentation in the medical record of anemia symptoms (e.g., shortness of breath or impaired exercise capacity) or specific co-morbid conditions predisposing patients to the health effects of anemia (e.g., limited cardiopulmonary reserve or underlying coronary artery disease)
- Deny claims for ESA use in oncology with hemoglobin levels > 12 g/dL on a claims-basis

Method to Implement

CMS creates and implements new HCPCS codes and code modifiers on a quarterly basis, and the Agency could create a new HCPCS code or modifier that would be implemented to coincide with the use of the new TRHCA authority, starting on January 1, 2008. For the sake of clarity and simplicity, Amgen would recommend a new five-digit HCPCS code or a two-digit HCPCS code modifier with a descriptor that includes the same language as the suggested text in the revised NCD noted above. Specifically, the HCPCS code or code modifier could read as follows:

HCPCS	DESCRIPTOR
XXXXX or - XX	Documentation appears in the medical record of the patient being informed of the benefits and risks of ESA use and of the presence of anemia symptoms (e.g., shortness of breath or impaired exercise capacity) or specific co-morbid conditions predisposing patients to the health effects of anemia (e.g., limited cardiopulmonary reserve or underlying coronary artery disease)

This new claims-management process would allow CMS to enforce adherence to the revised NCD for ESAs in real-time, and would further permit the Agency to have a clear audit trail demonstrating that providers have documentation to support the use of ESAs in the patients that need them.

APPENDIX C – EMR ANALYSIS ON TRANSFUSION TRENDS

The Varian Medical Oncology electronic medical record (EMR) database comprises 52 community and hospital-affiliated outpatient clinics, 350 oncologists, and more than 150,000 patients from 1997 to present. Since the vast majority of transfusions for patients with chemotherapy-induced anemia occur outside the physician office setting (as most transfusions are provided in hospitals), transfusion data is limited in this data source.

However, seven of the clinics in this Varian database have integrated transfusion data with outpatient EMRs. Data were analyzed from these 7 clinics (representing 10,803 eligible patient visits among those 65 years old or older receiving chemotherapy) during the period July 2006 through September 2007.

In Tables 1 and 2 below, we provide the counts of transfusions and counts of patients receiving transfusions in the period analyzed.

**Table 1: Number of Transfusions,
Age 65+ with Chemotherapy**

Quarter / Year	Number of Transfusions
Q3 2006	123
Q4 2006	132
Q1 2007	121
Q2 2007	145
Q3 2007	148

**Table 2: Number of Patients Receiving Transfusions,
Age 65+ with Chemotherapy**

Quarter / Year	Number of Transfusions
Q3 2006	100
Q4 2006	106
Q1 2007	102
Q2 2007	125
Q3 2007	127

METHODOLOGY

For this analysis, we identified transfusion events for patients age 65 and over. For each event associated with chemotherapy administration, the count was incremented for that time period. The counts of transfusions and patients receiving transfusions are reported on a quarterly basis. Additional work is underway by Amgen to provide episode-of-care analyses of transfusion rates and to expand the number of clinics available for analysis. As further data are available, we will provide updates to the Agency.

**APPENDIX D – FULFILLMENT OF CMS REQUIREMENTS FOR A FORMAL
 REQUEST FOR RECONSIDERATION OF AN NCD**

Amgen’s formal request for reconsideration of the National Coverage Determination for Erythropoiesis-Stimulating Agents in non-renal indications (CAG-00383N) meets all requirements for reconsideration requests that CMS specifies in September 26, 2003, Federal Register notice (67 Fed. Reg. 55634 – 55641), as outlined below.

CMS Requirement	Fulfillment of Requirement by Amgen
Formal Request in Writing	Amgen’s request for reconsideration was provided as a written request
Electronic Submission	Amgen’s request for reconsideration was submitted electronically
Identify Request as “Formal Request for Reconsideration”	Amgen’s request for reconsideration was identified as a “Formal Request for Reconsideration”
NCD Development Track	CAG-00383N was developed as an “Internally Generated Request” by CMS
Benefit Category	Physician Services (Drugs and Biologicals Administered “Incident To” a Physician Service under Medicare Part B)
Full Complete Description of the item or Service	Amgen’s ESA product used in oncology indications, Aranesp [®] , is an erythropoiesis stimulating protein, closely related to erythropoietin that is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Aranesp [®] is a 165-amino acid protein that differs from recombinant human erythropoietin in containing 5 N-linked oligosaccharide chains; whereas recombinant human erythropoietin contains 3 chains. The two additional N-glycosylation sites result from amino acid substitutions in the erythropoietin peptide backbone. The additional carbohydrate chains increase the approximate molecular weight of the glycoprotein from 30,400 to 37,000 daltons. Aranesp [®] is formulated as a sterile, colorless, preservative-free protein solution for intravenous (IV) or subcutaneous (SC) administration.
A specific, detailed description of the proposed use of the item or service, including the target Medicare population and the medical condition	Aranesp [®] is indicated for the treatment of anemia (1) associated with chronic renal failure, including patients on dialysis and patients not on dialysis and (2) in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.

CMS Requirement	Fulfillment of Requirement by Amgen
Additional material medical and/or scientific information that was not considered during the initial review	Detailed information on this requirement is provided as part of this request for reconsideration on pages 6-19.
A compilation of the supporting medical and scientific information currently available that measures the medical benefits of the item or service	Detailed information on this requirement is provided as part of this request for reconsideration on pages 6-19.
An explanation of the design, purpose, and method of using the item or equipment, including whether the item or equipment is for use by health care practitioners or patients	Aranesp [®] is formulated as a sterile, colorless, preservative-free protein solution for intravenous (IV) or subcutaneous (SC) administration. Aranesp [®] is administered in a doctor's office as an "incident to" service.
A description of any clinical trials or studies underway that might be relevant to a decision regarding coverage of the item or service	Detailed information on this requirement is provided as part of this request for reconsideration on pages 10-11 and 14.
Information involving the use of a drug or device subject to FDA regulation as well as the status of current FDA regulatory review of the drug or device involved. An FDA regulated article would include the labeling submitted to the FDA or approved by the FDA for that article, together with an indication of whether the article for which a review is being requested is covered under the labeled indication(s)	The revised FDA-approved product labeling for Aranesp [®] is provided as part of this request for reconsideration.
An explanation of the relevance of the evidence selected	Detailed information on this requirement is provided as part of this request for reconsideration on pages 6-14.
Rationale for how the evidence selected demonstrates the medical benefits for the target Medicare population	Detailed information on this requirement is provided as part of this request for reconsideration on pages 6-14.

CMS Requirement	Fulfillment of Requirement by Amgen
<p>Information that examines the magnitude of the medical benefit</p>	<p>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 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.</p> <p>The approval of ESA therapy revolutionized anemia management for patients undergoing chemotherapy. 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 have shown that, compared with placebo, ESA treatment reduces 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 that provoke physicians to transfuse red blood cells. Clinical trials have also reported improvements in patient-reported outcomes associated with ESA treatment for chemotherapy patients.</p>
<p>Reasoning for how coverage of the item or service will help improve the medical benefit to the target population</p>	<p>Detailed information on this requirement is provided as part of this request for reconsideration on pages 6-14.</p>

APPENDIX E: SUPPLEMENTARY DOCUMENTS

1. Aranesp[®] USPDI
2. EMEA Press Release, October 23, 2007
3. Rizzo et al., 2007 (ASH/ASCO Guideline)
4. Glaspy et al., ECCO poster 2007