



July 16, 2010

Louis Jacques, MD
Director, Coverage and Analysis Group
Office of Clinical Standards and Quality
Centers for Medicare & Medicaid Services
C1-11-08
7500 Security Boulevard
Baltimore, MD 21244

Re: National Coverage Analysis for Erythropoiesis Stimulating Agents for Treatment of Anemia in Adults with Chronic Kidney Disease including patients on dialysis and patients not on dialysis (CAG-00413N)

Dear Dr. Jacques:

Amgen Inc. (Amgen) is pleased to submit comments on the CMS National Coverage Analysis (NCA) for Erythropoiesis Stimulating Agents (ESAs) in treating chronic kidney disease (CKD) and dialysis-related anemia (CAG-00413N) that was announced on June 16, 2010. ESAs are indicated for the treatment of anemia associated with chronic renal failure (CRF), including patients on and not on dialysis (NOD).

As a science-based, patient-care driven company, Amgen is committed to using science and innovation to dramatically improve people's lives and is vitally interested in improving access to innovative drugs and biologicals for Medicare beneficiaries. The highest levels of patient safety are an important part of this commitment throughout the lifecycle of our products. As such, we communicate proactively with the US Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services (CMS), as well as the nephrology community regarding the

safe and effective use of our products. Amgen remains steadfast in our commitment to working with all stakeholders to provide objective, rigorous, and evidence-based information.

We are attentive to the concerns of CMS regarding the appropriate use of this class of products. On March 24, 2010 Amgen participated in the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) meeting regarding the use of ESAs in treating anemia related to chronic kidney disease (CKD). The MEDCAC meeting served as a valuable forum to both explore and better understand the available clinical evidence regarding the treatment of anemia related to chronic kidney disease. Following the March MEDCAC meeting, CMS opened an NCA and requested public comments about the evidence regarding the effects of ESAs on health outcomes in adult CKD patients, both on dialysis and not on dialysis. Below, we provide a brief overview of evidence supporting the benefit:risk profile for ESAs, discuss key points underlying the available evidence regarding the effects of ESAs on health outcomes, and clarify misrepresentations and misinterpretations of the available evidence regarding the use of ESAs raised in the MEDCAC process. In addition, we are supplying CMS with a detailed summary of the current clinical evidence relevant to the agency's NCA (see Appendix A).

In determining coverage policy for ESAs, we urge CMS to ensure that policy decisions are evidence-based and aligned with FDA-approved product labeling, and avoid coverage policies that are based on unsupported or inappropriate extrapolations of data from existing trials and studies to clinical practice situations that may differ substantially. In 2007 the benefits and risks of ESA therapy for the anemia of CKD were discussed at a joint meeting of FDA's Cardiovascular and Renal Drugs Advisory Committee (CRDAC) and Drug Safety and Risk Management Advisory Committee (DSRMAC). An examination of the optimal use of ESAs was conducted and product labeling was changed to reflect these deliberations. Since 2007, the only new clinical trial information on the use of ESAs in CKD is from the recently reported Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study; FDA has signaled its intention to proceed with a comprehensive review of TREAT and other evidence later this year. Amgen looks forward to this 2010 FDA CRDAC meeting, where the full range of evidence on ESA benefits and risks can be discussed. The CRDAC deliberations may inform changes to product labeling, and thus, any deliberation of coverage policies should ultimately be consistent with product labeling.

I. EXECUTIVE SUMMARY

ESAs are used to elevate or maintain red blood cell (RBC) levels (as manifested by hemoglobin or hematocrit determinations) and to decrease the need for RBC transfusions. EPOGEN[®] and Aranesp[®] are approved for the treatment of anemia associated with CRF, which includes patients receiving and not receiving dialysis. Amgen's view on the appropriate balance of benefits and risks of ESAs in CKD was presented at the March 24, 2010 MEDCAC meeting. Amgen submitted a briefing book that describes the risks and benefits of ESA treatment for CKD patients (Appendix A).

This cover letter will summarize the key points from the briefing book and outlines Amgen's position that was presented at the recent CMS MEDCAC meeting. Chronic kidney disease patients on dialysis and not on dialysis (CKD-NOD) are distinctly different, and have a different benefit:risk profile as it relates to the criticality of transfusion avoidance, and thus ESA therapy for anemia management. Despite these differences, both patient populations demonstrate intrinsic hemoglobin variability necessitating the use of a hemoglobin range for clinical management, where ESA's are administered to maximize the clinical benefits for each patient. When safety signals from recent experimental studies are considered within the context of the existing data for ESAs from both experimental studies and observational analyses, the evidence supports the view that while targeting Hb levels ≥ 13 g/dL is associated with risk, achieved hemoglobin levels in the range of 10-12 g/dL is associated with clinical benefit. ESAs offer a clinically significant and unequivocal benefit of transfusion avoidance in dialysis patients, in whom profound anemia is commonplace and in the absence of ESAs, chronic transfusions are unavoidable. Additionally, improvements in exercise tolerance and patient-reported physical functioning in dialysis patients have been demonstrated and reflected in FDA labeling. CKD-NOD is a more heterogeneous disease and the accompanying anemia can range in severity. ESAs are an important therapy for those CKD-NOD patients with severe anemia in whom transfusion avoidance is a clinically meaningful benefit.

A. Important differences between Dialysis patients and Non-Dialysis patients make the benefit-risk profile of ESA use different in these two clinical settings.

There are significant differences between dialysis and CKD-NOD patients, including demographic characteristics, the extent of morbidity and risk of mortality, the extent of co-morbid conditions that complicate their clinical management, and the intensity of clinical

management required for their treatment[1, 2]. Most notable among these differences is that dialysis patients depend on regular dialysis treatments to sustain life and have profound anemia that is nearly universal in the absence of ESA treatment, due to the extent of native erythropoietin deficiency and the continuous blood loss from the dialysis procedure. As a consequence, hemoglobin levels in dialysis patients are quite low in the absence of therapy, contributing to a poorer quality of life and more limited ability to function. Prior to the introduction of ESA therapy, the majority of dialysis patients were maintained with transfusions and had Hb levels < 8 g/dL[3, 4], a level associated with anemia symptoms that would be unacceptable today. Dialysis patients have routinely expressed their belief that EPOGEN® has the ability to significantly improve their health and overall quality of life[5].

While the presence of anemia in dialysis patients is virtually universal, CKD-NOD patients are more heterogeneous; there is a greater range of renal dysfunction, erythropoietin levels and degree of anemia. Severe anemia and the increased risk of transfusions are more commonly present among patients with more advanced kidney disease. For CKD-NOD patients, ESAs offer clinical benefits in patients for whom transfusion avoidance is a meaningful clinical outcome.

Thus, the agency should separately consider the available evidence regarding the effects of ESAs on health outcomes for dialysis patients and CKD-NOD patients.

B. Transfusions carry significant risks specific to the CKD patient population and can delay or preclude kidney transplantation, the preferred ESRD treatment of choice

RBC transfusions are only transiently effective in a population that is chronically unable to produce sufficient RBCs[6]. Furthermore, RBC transfusions carry a range of well-known risks including transfusion reactions, transmission of viral and other infectious agents. Although less common in the general population, the risks of volume and potassium overload are particularly problematic for CKD patients because these patients are unable to adequately regulate volume and electrolytes due to decreased or absent kidney function. Thus CKD patients who are transfused may experience acute volume and potassium overload requiring hospitalization[7-11]. The most significant long-term risk related to transfusions is the potential for allo-sensitization to foreign antigens [2, 12, 13]; the development of such antibodies can *delay* or *preclude* kidney transplantation and impair the function of kidney transplants that do occur[2, 14]. Transplant is the preferred therapy for ESRD because of benefits such as a 50 percent higher five-year survival and one-third the cost of treatment[2]. Efforts to minimize transfusions and their potential consequences should be encouraged through Medicare coverage policy to preserve and enhance successful renal transplantation as an outcome.

C. *The ESA label is based on a development program completed in collaboration with the FDA*

Amgen conducted a full development program in collaboration with the FDA for both Epoetin alfa and darbepoetin alfa and received marketing authorization for the treatment of anemia in chronic renal failure patients to raise and maintain hemoglobin levels within the range of 10-12 g/dL in order to reduce the need for RBC transfusions. The primary Epoetin alfa registration trials (five studies) used for approval demonstrated correction of anemia and virtual elimination of transfusions (>90% reduction) in patients treated with ESAs, achieving a mean hematocrit of $35\pm 3\%$ (hemoglobin of 11.7 ± 1 g/dL). In placebo treated patients, hemoglobin levels remained low (< 8 g/dL) and these patients continued to receive multiple transfusions. One of these registration studies also demonstrated an improvement in exercise tolerance and patient-reported physical functioning in the Epoetin alfa treated patients compared to the placebo treated patients. Many other published studies of ESA therapy have demonstrated improvements in patient quality of life and patient reported outcomes, however, these studies have not met the FDA standard for product labeling.

D. *Transfusion requirements dropped significantly following the introduction of ESAs*

Following the introduction of EPOGEN[®] into clinical practice (June 1989), the transfusion rate among US hemodialysis patients fell sharply (USRDS), supporting the results seen in the registration trials. By 1992, almost 90% of US dialysis patients received ESA therapy, and this treatment prevalence continues today[15]. Between 1992, when the mean population hemoglobin was ~9.8 g/dL, and 2000, when, with increased treatment intensity, the mean population hemoglobin had risen to ~11.2 g/dL, the total transfusion rate (inpatient plus outpatient) was halved[15].

E. *Transfusion risks increase as hemoglobin drops below 10 g/dL*

As demonstrated in both clinical trials and in observational data, the risk of transfusion in dialysis patients rises significantly as the outpatient hemoglobin in the preceding month falls below 10 g/dL; this risk continues to increase as hemoglobin levels decline further[16, 17]. Thus, the goal of transfusion reduction/avoidance as well as of preservation of physical function and exercise tolerance is best served by maintaining hemoglobin levels above 10 g/dL[4]. The importance of maintaining hemoglobin levels above 10 g/dL is recognized by the nephrology community as well as CMS, and is currently incorporated as a quality metric by which dialysis units are evaluated[18].

F. Transfusions are not infrequent in CKD-NOD patients with anemia

In CKD-NOD patients, prevalence of severe anemia is less than in ESA-treated dialysis patients; however, in some CKD-NOD patients, particularly those with advanced CKD, the anemia can be profound. The use of ESAs in CKD-NOD patients is low as compared to the CKD-dialysis population, and the transfusion burden remains surprisingly high. Medicare data indicate that between 1992 and 2004 among anemic CKD-NOD patients the annual transfusion rate ranged from 17% to 25%[17]. This rate was three-fold higher than in CKD-NOD patients without anemia, and 10-fold higher than those without CKD[19]. Transfusions are significantly more common in non-treated patients when compared to patients receiving ESAs and iron, and increase markedly when hemoglobin levels fall below 10 g/dL[20]. The recently completed TREAT study provides additional evidence: *post-hoc* analyses of this study indicate that the risk of transfusion increased when the hemoglobin level was below 10 g/dL, as compared to when hemoglobin levels were higher[17].

G. RCT's were performed to test the hypothesis that treating to near-normal hemoglobin levels would improve Cardiovascular morbidity and mortality; these studies demonstrated risks when targeting hemoglobin levels above 12 g/dL

Observational studies have consistently shown that higher *achieved* hemoglobin levels are associated with improved outcomes (e.g., lower cardiovascular (CV) and mortality risk). These studies motivated the three large, randomized controlled trials (RCTs) that have been undertaken to test the hypothesis that raising hemoglobin levels in CKD patients would result in *decreased* CV morbidity and mortality. These three studies, NHCT, CHOIR, and TREAT, which targeted hemoglobin to normal or near-normal levels (hemoglobin 13.0 g/dL or greater), did not confirm this hypothesis, but instead, demonstrated hazards including CV events, mortality, and most recently, stroke. The risks demonstrated in these three studies were not consistent. NHCT and CHOIR demonstrated an increased risk in mortality, and, an increase in thrombosis and heart failure, respectively. TREAT, the only placebo controlled study, did not support an increase in these cardiovascular risks, but did demonstrate an increase in the rate of stroke, not seen in the previous studies. These inconsistencies may be related to differences in trial design and/or study populations. All of these risks once identified have been incorporated into product labeling and have resulted in more conservative use of ESA's in nephrology.

H. Hemoglobin levels in CKD patients are intrinsically variable necessitating careful management of ESA dosing to maintain Hb levels between 10 - 12 g/dL

Hemoglobin levels are known to vary within individuals over time (intra-patient variability)[21, 22]. Because the change in hemoglobin following a change in ESA dose is delayed by many

days to weeks [23], it is extremely difficult to maintain hemoglobin levels within a narrow range in many, if not most, patients[21]. In current clinical practice, the population mean intra-patient hemoglobin SD is near 0.9 g/dL and accounts for ~80% of the total Hb variability (1.4 g/dL)[24]. Both the original registration trials and the current FDA-approved ESA labels refer to a 2 g/dL hemoglobin range. The need for this range is based on the following: (i) the recognized need to maintain hemoglobin levels above 10 g/dL to avoid transfusion; (ii) the inherent variability in patient hemoglobin levels over time; (iii) the continued reduction in transfusions that is observed up to a hemoglobin level of 12 g/dL; and (iv) the demonstrated risk when targeting hemoglobin levels at or above 13 g/dL. Raising hemoglobin levels above 10 g/dL up to 12 g/dL has been shown to improve dialysis patient-reported outcomes including physical function and exercise tolerance in those undergoing chronic hemodialysis.

I. The association between ESA dose and clinical outcomes, independent of Hb targets, has not been studied in prospective randomized trials. However, well-conducted non-experimental studies have not shown an increased risk related to higher ESA doses

In the RCTs examining treatment to near-normal hemoglobin levels, those patients treated to the higher Hb targets required greater ESA doses, which has led some to infer that the risks seen in the studies were attributable to higher ESA dosing. To date there has not been a randomized study of ESA dose on clinical outcomes in CKD patients. However, there have been a number of non-experimental studies that have examined the association between ESA dose and mortality in dialysis patients using Medicare or dialysis provider data. Early observational studies showed an elevated mortality risk for patients requiring higher EPO doses[25, 26], but these analyses are widely recognized as being flawed due to confounding by the patient's clinical indication[27]. Subsequent observational studies that have applied appropriate statistical adjustment for this significant confounding-by-indication[28] have not shown an excess risk related to ESA dosing [28-32]. Therefore, the conclusions from these early observational studies should no longer be considered valid or informative given the limitations of these studies and the numerous studies that have since been published, including follow-up studies from the original authors, providing evidence to the contrary[28-32].

There has been only one analysis that has examined ESA dosing on clinical outcomes in non-dialysis CKD patients, a post-hoc analysis of the CHOIR study[33]. The results from this study have been used as evidence of an association between higher ESA doses and of an increased mortality risk. The major limitation of this post-hoc analysis is that the original study compared higher versus lower Hb targets—not different ESA doses (*note*: the CHOIR study tested whether treatment to a higher vs. lower Hb target with ESAs would improve CV morbidity and

mortality). As such, the post-hoc analysis of ESA dose did not benefit from randomization, and thus is subject to confounding bias. The analyses treated the dose comparison as though it did benefit from the initial study randomization, and was not adjusted for differences in case-mix or co-morbidity (e.g., confounding). Considering the impact that adjustment for confounding has had on the dose-mortality association in the dialysis studies (discussed above), one can have little confidence in the results of this post-hoc exploration.

Finally, during the 2007 CRDAC-DSRM meeting with FDA, considerable focus was placed on patients who do not respond to ESA therapy (hypo-responsive patients). Following this meeting, Amgen, in collaboration with the FDA, revised the ESA label to provide conservative dosing guidance regarding the treatment of hypo-responsive patients. The label now indicates that if a patient does not achieve the clinical target after three successive months of upward dose titration, then physicians should no longer increase the dose and search for other causes of hypo-responsiveness. If hypo-responsiveness persists and the patient requires transfusion(s), then physicians should discontinue ESA therapy and not resume until the hemoglobin level reaches the target range once again. In order to provide more definitive information on appropriate ESA dosing of hypo-responsive patients, Amgen is working with the FDA on the design of a study evaluating alternative dosing regimens to further characterize the benefit:risk profile of ESAs in patients who are hypo-responsive to ESA therapy.

J. Physicians have responded to safety concerns and changes in reimbursement policy and have increased the percentage of patients within the 10-12 g/dL target range

In current clinical practice, physicians are treating dialysis and CKD-NOD patients with ESAs to within the labeled hemoglobin range; the mean Hb in ESA treated patients is 11.46 g/dL in dialysis and 10.7 g/dL in CKD-NOD[17]. Reimbursement policies for ESAs have been dynamic over the last two decades, reflecting changes in label and practice guidelines for the treatment of anemia in CKD and the appropriate administration of ESAs with regard to safety and efficacy. Analyses of Medicare hemodialysis data suggested that prior to the implementation of the Erythropoietin Monitoring Policy (EMP), which took effect in April of 2008, the majority of physicians were appropriately reducing ESA exposure when hemoglobin levels exceeded the upper end of the target range[34]. Following the revisions to the ESA label in 2007 and the revisions to the EMP in 2008, physicians further modified their treatment patterns, which resulted in a decline in the mean population hemoglobin from 12.08 g/dL (SD 1.48) in June 2006 to 11.71 g/dL (SD 1.35) in November 2008[35]. More recently available hemoglobin data (as of March 2010) from ~87% of all US dialysis centers indicate that the mean hemoglobin has continued to decline and is approximately 11.46 g/dL[17]. These data provide further evidence

that the current reimbursement policy has been effective in reducing the proportion of patients above the target range and thereby increasing the proportion of patients maintained within the appropriate target range.

II. CLARIFICATIONS OF THE AVAILABLE EVIDENCE REGARDING THE USE OF ESAS IN CKD PATIENTS WITH ANEMIA

It is critical that CMS ensure that any policy regarding the coverage of ESAs in anemia related to chronic kidney disease reflects an accurate and appropriate interpretation of available evidence, and, is in the best interest of vulnerable Medicare beneficiaries with CKD. It is also imperative that coverage policy decisions be made based on a careful assessment of randomized clinical trials and observational data. With respect to the latter, it is critically important that the sources of confounding bias be understood and appropriately adjusted for. In addition, post-hoc analyses of RCTs are subject to the same kind of confounding bias as observational trials. Therefore post-hoc analyses of RCTs need to be approached with the same rigor and consideration of confounding as observational studies. To that end, Amgen is providing important clarifications and corrections pertaining to inaccurate and potentially misleading statements regarding the available evidence that have been made in the public domain leading up to, during and after the March MEDCAC meeting. Below, please find a short summary and description of these topics.

A. Hemoglobin is an appropriate guide to ESA therapy

The major RCTs examining ESA treatment in CKD patients provide indisputable evidence that hemoglobin targets are not a good surrogate for survival or CV events; that is, targeting higher hemoglobin levels does not confer a survival or CV advantage. It has been suggested that because Hb is not a valid surrogate for CV morbidity and mortality (M+M), Hb may not be an appropriate surrogate for anemia management in CKD. This argument is specious. ESA's were developed and approved based on their ability to treat anemia and reduce the need for RBC transfusions (this benefit is clearly established in the FDA-approved label). Anemia, as a clinical condition, is recognized and diagnosed by Hb level and is defined as a reduction in the hemoglobin level. The hemoglobin level is central to the identification and continued monitoring of anemia in patients, and is a necessary marker for administering anemia treatments. The hemoglobin level is an excellent predictor of transfusion, and for this reason, the original registrational studies used a hemoglobin target to guide therapy in order to demonstrate a reduction in transfusions. Moreover, because low hemoglobin levels (e.g., Hb < 10 g/dL) are strongly related to patient reported symptoms and physical functioning, and raising hemoglobin levels improves these outcomes, these two benefits, which were demonstrated in the original

registration studies, are also identified in the EPOGEN[®] (Epoetin alfa) label. Since the goal of therapy is to treat anemia in order to reduce the need for RBC transfusions and to improve patient reported symptoms and physical functioning, monitoring of hemoglobin levels is a valid surrogate for the goals of ESA therapy. This is understood by the nephrology community and is highlighted in their clinical practice guidelines for anemia management in CKD, which define treatment targets based on hemoglobin levels[36].

B. Hemoglobin targets in Amgen RCTs Have Been Mischaracterized

At the recent MEDCAC meeting and in several recent editorials, it was suggested that the lower target and placebo comparator arms in the NHCT and the TREAT studies, respectively, should be used to provide dosing guidance and hemoglobin target recommendations. These statements do not reflect the actual design of these Amgen-designed and executed studies. NHCT was a study of dialysis patients with pre-existing heart failure or ischemic heart disease comparing treatment with Epoetin alfa to a hemoglobin target of 14 g/dL (± 1 g/dL) to treatment with Epoetin alfa to **a hemoglobin target of 10 g/dL (± 1 g/dL)** on the risk of non-fatal CV morbidity and mortality. In this study, the protocol instructed investigators to target either 14 or 10 g/dL, respectively. At enrollment, hemoglobin levels were between 9 and 11 g/dL. TREAT was a randomized, double-blind, placebo-controlled study of anemic CKD patients not on dialysis with diabetes comparing treatment with darbepoetin alfa to a hemoglobin target of 13 g/dL versus treatment with placebo (with rescue darbepoetin alfa treatment when the hemoglobin level dropped below 9 g/dL) on the risk of cardiovascular events, death or progression to ESRD. **There was no hemoglobin target in the placebo arm.** At enrollment, patients had a hemoglobin level < 11 g/dL.

C. Appropriate Characterization of Incidence of Stroke in Previous RCTs

Given the concerns regarding the risk of stroke identified in TREAT, greater focus is now being placed on the occurrence of stroke in previous clinical trials including the NHCT study. In recently published editorials and at the MEDCAC meeting, the stroke risk in NHCT has been incorrectly cited as being as high as 39% vs. 29% in the higher and lower arms of NHCT respectively. According to the study report[17] the cerebrovascular accident event rates in the NHCT study, were similar in the high and low hemoglobin arms: 7% and 6%, respectively.

D. Characterization of the Disease State and ESA Utilization Should be Based on Medically Accepted Definitions

The Kidney Disease Outcomes Quality Initiative (KDOQI[™]) definition of CKD requires that kidney disease persist for ≥ 3 months. At the recent MEDCAC meeting, an analysis of ESA utilization using Medicare data defined "CKD" as two ICD-9 diagnoses of CKD within a 3-month window and "intermittent CKD" as having only a single diagnosis of CKD within a 3-month

window. The analysis categorized patients in a manner inconsistent with any recognized definition of CKD, either by textbook, guidelines or clinical practice. “Intermittent” kidney disease, is not a medically recognized condition and as such, it is unclear whether the patients identified using the “intermittent CKD” label truly have CKD and if so, whether they are similar to or different from those patients who would traditionally be identified as having CKD-NOD in terms of etiology, prognosis and co-morbidities. Given the novel methods for defining kidney disease used in this analysis, it is unclear whether the distribution of ESA treated patients is an accurate representation of actual ESA use in the Medicare population and is likely incompatible with prior analyses of Medicare data.

III. CONCLUSION

Amgen appreciates the efforts of CMS to develop coverage policy for ESAs. We recognize the need for a thorough evaluation of the evidence regarding the effects of ESAs on health outcomes for both dialysis and CKD-NOD patients, particularly since important questions have arisen as to the continued safe use of ESAs. We look forward to the upcoming FDA CRDAC meeting where the full range of evidence on ESA benefits and risks will be discussed in a forum that may result in changes to product labeling, and which could then inform changes, as needed, to CMS’ coverage policies.

The totality of the available evidence supports a favorable benefit:risk ratio for ESAs when patients are treated according to the FDA-approved label. ESAs offer a clinically significant and unequivocal benefit of transfusion avoidance as well as improvements in exercise tolerance and patient reported physical functioning in dialysis patients. Severe anemia is the rule, rather than the exception in dialysis patients and although CKD-NOD is more heterogeneous, profound anemia can be seen in some CKD-NOD patients as well. As with HD patients, these severely anemic NOD patients are also at high risk for transfusion. Transfusion avoidance protects against the acute hazards of volume and potassium overload, and the cumulative hazards of transfusion reactions, exposure to viral and other infectious agents, and allo-sensitization to foreign antigens—which decreases patients’ eligibility for and likelihood of more positive outcomes following renal transplantation. This is a particularly relevant issue for many potential transplant candidates, who typically spend many years on dialysis, thereby increasing both their exposure to the risks of transfusions as well as their mortality risk from being on dialysis. Clinical trial and observational data have demonstrated consistently that the risk of transfusion increases substantially when hemoglobin levels fall below 10 g/dL, which supports 10 g/dL as the appropriate lower limit of the labeled range. The transfusion rate decreases with increasing hemoglobin up to 12 g/dL. Evidence from clinical trials has added considerably to the

community's understanding of the cardiovascular and mortality risks of these agents when targeting to hemoglobin levels at or above 13 g/dL. These risks have been incorporated into product labeling. Management of ESA dosing is key to maintaining Hb levels within the range of 10-12 g/dL. In so doing, the benefit of transfusion avoidance (maintaining Hb levels above 10 g/dL) is maximized, while the risk of CV events associated with high hemoglobin targets (≥ 13 g/dL) is minimized. This allows physicians to effectively manage anemia in dialysis patients and in CKD-NOD patients for whom transfusion avoidance is an important clinical goal. Amgen also remains committed to working with the FDA on additional studies to further characterize the benefit:risk profile of ESAs.

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Amgen appreciates the opportunity to provide this important information to the agency. If you have any questions or would like to discuss further, then please do not hesitate to contact me. Thank you for your attention to these important matters.

Regards,



Joshua J. Ofman, MD, MSHS
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Attachment: Appendix A - Amgen's MEDCAC Submission

cc: Barry M Straube, MD, Director, Office of Clinical Standards and Quality (OCSQ), Chief Medical Officer, CMS
Elizabeth Koller, MD, FACE, Lead Medical Office, CAG, CMS
Kimberly Long, Lead Analyst, CAG, CMS

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