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Re: National Coverage Analysis (NCA) for ESAs for Treatment of Anemia in Adults with CKD Including Patients on Dialysis and Patients not on Dialysis (CAG-00413N)

Dear Ms. Long and Ms. Koller,

On behalf of the American Society of Nephrology (ASN), thank you for the opportunity to provide comment to the Food and Drug Administration (FDA) regarding the National Coverage Analysis for Erythropoiesis Stimulating Agents (ESAs) for Treatment of Anemia in Adults with Chronic Kidney Disease (CKD) Including Patients on Dialysis and Patients Not on Dialysis. ASN is a not-for-profit organization of 11,000 physicians and scientists dedicated to promoting excellence in the care of patients with kidney disease. Foremost among ASN's concerns is the preservation of access to appropriate, high-quality care for patients with kidney disease.

ESAs in Patients with CKD on Dialysis versus Patients with CKD not on Dialysis

The society recognizes that questions have been raised regarding the use of ESAs in patients with CKD and supports FDA's commitment to protecting patient safety through the NCA and technology assessment. In each of these review efforts, ASN encourages FDA to differentiate among patients who are on dialysis and non-dialysis-requiring CKD patients. The two patient populations are clearly distinct in their characteristics and prognosis. Accordingly, they also have different treatment needs. Specifically, ESA treatment may have quite different effectiveness and safety profiles in patients on dialysis compared with those not requiring dialysis treatment. It is imperative that any FDA activity relating to ESAs reflect this distinction.

ESAs and Patients with CKD on Dialysis

Anemia is a common complication in patients with advanced CKD and occurs in the vast majority of patients undergoing maintenance dialysis. Prior to the availability of erythropoietin treatment, patients with advanced CKD were often anemic, blood transfusions were common, and many patients experienced laboratory signs or clinical sequelae of iron overload, a dreaded side effect of repeat blood transfusions. Thus, the burden of renal anemia and its treatment constituted a pronounced and unmet medical need. Epoetin alfa was approved by the US FDA based on studies demonstrating its efficacy in reducing the requirement for blood transfusions. A pivotal phase III study enrolled 333 chronic hemodialysis patients who had a mean hematocrit of approximately 22-24% and who had required 0.5 blood transfusions each month, on average. Many of those study participants had pronounced iron overload. Within

just few weeks or months, epoetin alfa increased these patients' hematocrit to approximately 34%. After 8 weeks of such treatment, these patients were essentially maintained transfusion free for the remainder of follow up. At the time of approval, however, it was also quite evident that there were certain safety issues with ESA use. Specifically, increases in blood pressure during ESA treatment were noted and uncontrolled hypertension was listed as a contraindication for use.

Availability of the drug for clinical use in 1989 led to a demonstrable effect on reduced transfusion rates on a population level, as both average epoetin doses and hemoglobin concentrations increased markedly subsequent to marketing approval. In 1993, a large randomized trial was launched in hemodialysis patients who also all had severe cardiac disease. The trial compared two clinical strategies: targeting a "normal" hematocrit of 42% versus targeting a hematocrit of 30%. The trial was terminated early, after interim analyses had revealed an increased risk of vascular access thrombosis and a strong trend towards increased mortality among patients randomized to the "normal" hematocrit target group. Almost as an aside, the trial also confirmed that using a higher hematocrit treatment target significantly reduced the need for blood transfusions. Soon thereafter, however, a Canadian multicenter study demonstrated clear benefits of ESA treatment on important patient-reported outcomes. Compared with placebo, anemic hemodialysis patients were randomized to hemoglobin treatment targets of 9.5-11 g/dL and 11.5-13 g/dL, respectively. Compared to patients receiving placebo—who remained at a mean hemoglobin concentration of 7 g/dL throughout the study—ESA-treated patients experienced significant improvements in fatigue, physical symptoms, relationships, and depression in the kidney disease questionnaire, as well as in the global and physical scores on the sickness impact profile. These findings arose despite yet another signal towards increased risks of vascular access thrombosis in patients receiving ESA treatment.

ESAs and Patients with CKD Not on Dialysis

While anemia is commonplace in patients requiring maintenance dialysis, it is also rather prevalent in patients with earlier stage CKD, who do not yet require dialysis. A national study demonstrated that among patients with CKD Stage III-V who did not yet require dialysis, at least one quarter were anemic, amounting to at least 4 million individuals in the US alone. This observation came from a subset of patients who had sufficient iron stores. It can be assumed that the proportion of anemic patients is even greater in CKD patients with iron deficiency, who were not captured in this description.

The effectiveness and safety of epoetin in patients with CKD not requiring dialysis, however, was not formally examined in large trials until many years later.

In 2006, results from two landmark trials of patients with CKD were presented. The CREATE trial studied 603 patients with advanced CKD to respective target hemoglobin concentrations of 13-15 g/dL or 10.5-11.5 g/dL using epoetin beta. It showed no differences between the study arms in the risk of the composite cardiovascular endpoint. Higher hemoglobin targets, however, did result in improved quality of life measures.

The CHOIR trial compared hemoglobin targets of 13.5 g/dL versus 11.3 g/dL in 1432 patients with CKD not requiring dialysis. The higher hemoglobin target group experienced a 34% increased risk of the composite endpoint of death and cardiovascular events. As a direct consequence of these findings, FDA added a black-box warning to ESA labels in March 2007.

More recently, the TREAT trial studied 4038 patients with CKD not requiring dialysis, diabetes, and anemia. Patients were randomized to treatment with darbepoetin to a target hemoglobin of

13 g/dL or placebo with rescue darbepoetin treatment at hemoglobin ≤ 9 g/dL. TREAT revealed that both study groups had similar rates of the primary and several secondary endpoints. Quality of life was significantly but not meaningfully different between the two groups. There was, however, an increased risk of stroke in the higher hemoglobin target group as well as higher mortality in patients with preexisting cancer.

Thus, the hypothesized benefits of more aggressive hemoglobin targets and, implicitly, higher ESA dosing, did not materialize, with important safety signals from more aggressive approaches discovered in two of these three trials in patients with CKD not requiring dialysis.

At present, most scientists and clinicians familiar with the evidence would agree on two things regarding the appropriate place of ESAs in the treatment of anemia in patients with CKD. First, ESAs are doing exactly what they were originally approved for—helping avoid blood transfusions—as reaffirmed in CHOIR, CREATE, and most recently in TREAT, during which twice as many patients required transfusions in the placebo arm compared to the darbepoetin arm.

Secondly, more aggressive anemia management does not yield better outcomes, at the very least, and may actually be harmful in some patients. Thus, the value proposition in favor of using ESAs to treat patients with CKD towards more normal hemoglobin concentrations compared with strategies that maintain more moderate hemoglobin concentrations is not supported by the evidence.

The difficult question faced by clinicians, regulatory agencies, and payors is what level of ESA treatment or what hemoglobin target may optimize the balance among benefits, risks and costs. The answer to this question is currently unknown. Importantly, the answer to this question may vary qualitatively or quantitatively between dialysis and non-dialysis populations. The available evidence differs markedly between CKD patients on dialysis and those not requiring it. Among dialysis patients, we have a randomized trial that treated severely anemic patients with placebo versus ESA, targeting two different hemoglobin targets. Very clearly, compared with patients in the placebo arm who had a mean hemoglobin of 7 g/dL, ESA treatment markedly improved patient-reported outcomes such as physical functioning and mental health.

No similar information is available in CKD patients not on dialysis, where the lower treatment arms of all trials studied patient groups whose mean hemoglobin concentrations were consistently higher than 10 g/dL. Even the placebo arm in TREAT ended up representing a group of patients with mean hemoglobin concentrations in the mid-to-upper end of the 10-11 g/dL range, a treatment cohort compatible with current guidelines and labels. As such, the comprehensive evidence from these landmark trials – both in dialysis and non-dialysis CKD patients – supports only one point about hard study outcomes (rather than patient-reported outcomes): treating CKD patients with ESAs beyond the current label is at best not efficacious and at worst harmful, when compared to the lower hemoglobin or placebo groups, which all had a population mean hemoglobin within the currently recommended hemoglobin target range of 10-12 g/dL. No convincing evidence on the effect on hard study outcomes of any treatment strategies that would target a population mean below the current label and guidelines versus within the current label and guidelines is currently available. Thus, it cannot currently be refuted that an intermediate hemoglobin *does* indeed yield clinical benefits in terms of reduced morbidity, mortality, or increased quality of life, target compared with a low-hemoglobin rescue strategy or no treatment at all.

Thus, the crucial question of whether conservative ESA treatment with intermediate target hemoglobin concentrations, as currently recommended, may yield important clinical and patient-reported benefits over no treatment or rescue treatment strategies remain unanswered.

While observational in nature, a recent study in JAMA hinted that such benefits may actually arise. Dialysis facilities that treat patients with severe anemia relatively aggressively had lower mortality among their patients compared to facilities using less aggressive ESA treatment. While this analysis cannot establish causality, it clearly indicates that ESAs used in moderation among severely anemic patients may be beneficial, a hypothesis that ought to be tested in future trials.

In addition, it remains an important treatment and policy goal to avoid transfusions in the CKD population. This is based on the very important consequences of immune sensitization in these patients. Many patients with CKD will eventually reach end-stage renal disease, with kidney transplantation being the preferred option. Each transfusion that these patients receive may reduce the likelihood of receiving a transplant, and those who receive a transplant face diminished chances of long-term function of their transplant kidney. Thus, it is clinically of the utmost importance to avoid transfusions in order to not jeopardize these patients' prospects of receiving and maintaining a kidney transplant.

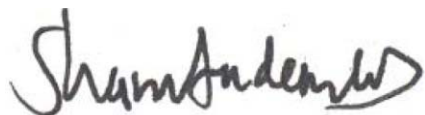
Considerations of equity also come into play. Women and African Americans are at increased risk of requiring transfusions and these population subgroups would be particularly endangered by any unreasonable barriers to receiving ESAs, particularly in that both groups face heightened challenges following transplantation owing to higher rates of sensitization even absent of transfusion exposure.

In summary, it can be derived from the available evidence that current ESAs may be dangerous if used for overly aggressive treatment targets compared with practices that are compatible with current treatment guidelines. Continued access to these medications is required, however, to give patients with CKD—both requiring and not requiring dialysis—a better chance at first receiving and then maintaining the function of a kidney transplant. Swift action is needed to support comparative effectiveness research that closes the evidence gap in the optimal role of ESAs in the treatment of relatively severe anemia and to more modest treatment targets while maintaining these patients transfusion-free.

Given the available evidence, it is vital that any decision regarding ESA treatment for anemia made by the FDA at this time must 1) differentiate among patients with CKD on dialysis and those not on dialysis and 2) protect patient access to necessary therapies, recognizing the variations in appropriate anemia care in a diverse patient population.

Again, thank you for your time and consideration. To discuss ASN's comments, please contact ASN Director of Policy and Public Affairs, Paul C. Smedberg, at (202) 416-0640 or at psmedberg@asn-online.org.

Sincerely,

A handwritten signature in black ink that reads "Sharon Anderson". The signature is written in a cursive, flowing style.

Sharon Anderson, MD, FASN
President