Clinical White Paper Developed for the Centers for Medicaid and Medicare Services Regarding the Proposed Decision Memorandum 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)
April 15, 2011

Clinical white paper developed by Centocor Ortho Biotech Products, LP

SUMMARY

Centocor Ortho Biotech Products, L.P. (hereafter referred to as "the Company") concurs with the Centers for Medicare and Medicaid Services (CMS) proposal not to issue a national coverage determination at this time based on currently available evidence. Continued coverage of erythropoiesis-stimulating agents (ESAs) will allow patients, together with their healthcare providers, to consider a broader range of possible options for the treatment of anemia of chronic kidney disease (CKD). Erythropoiesis-stimulating agents provide an important treatment option for patients with anemia associated with CKD. Prior to the availability of ESAs, regular blood transfusions were a patient's primary option to raise and maintain hemoglobin levels.

This paper serves to provide additional commentary and analysis about the use of ESAs for treatment of anemia associated with CKD and supplements the submission of white papers to the CMS on July 15, 2010 and December 19, 2010 (also included with this response). Approximately 20 years of clinical experience have demonstrated that when used according to the U.S. Food and Drug Administration- (FDA) approved label, epoetin alfa effectively treats anemia associated with CKD.

The Company would like to use the public comment period following the release of the CMS proposed decision memorandum, dated March 16, 2011[*], to address the following 5 points, which are expanded upon, in order, in this white paper.

1. **Chronic kidney disease is a progressive disease spanning a spectrum from mild impairment of kidney function to severe impairment requiring dialysis or kidney transplant. The chronic anemia of CKD can be treated with red blood cell (RBC) transfusion; however, transfusion has been associated with clinically relevant complications, including infection, volume overload, and increased panel reactive antibody (PRA) titers, which may preclude or delay kidney transplantation.**
2. **The Company has provided commentary on several of the findings and conclusions included in the CMS proposed decision memorandum.**
3. **The decision to administer ESA treatment should only occur after the physician and patient have carefully evaluated the patient's unique clinical situation. Treatment should only be considered when the patient's hemoglobin concentration is < 10 g/dL, when anemia is chronic and clinically relevant, and when transfusion avoidance is a clinically important goal. Individualized care needs in anemia management are highlighted by pre-transfusion hemoglobin levels that ranged from 5.0 to 11.9 g/dL in randomized clinical studies of subjects with CKD not on dialysis.**

[*] "Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for Treatment of Anemia in Adults with CKD Including Patients on Dialysis and Patients not on Dialysis (CAG-00413N)"

4. **Expert panels in different regulatory settings have recommended treatment guidelines that are supportive of the current ESA label for patients with anemia associated with CKD who are not on dialysis:**
    - **In October 2010, the FDA's Cardiovascular and Renal Drug Advisory Committee (CRDAC) voted in a large majority to recommend that darbepoetin alfa continue to be indicated for treatment of anemia in CKD patients not on dialysis.**
    - **The United Kingdom National Institute for Health and Clinical Excellence (NICE) recently completed an analysis of anemia management in patients with CKD based on currently available evidence and issued revised guidelines that recommend maintaining hemoglobin levels between 10 and 12 g/dL with ESA use.**
    - **In November 2008, the Anaemia Working Group of European Renal Best Practice (ERBP) issued a position paper recommending that hemoglobin levels between 11 and 12 g/dL should be sought in the CKD population without intentionally exceeding 13 g/dL.**
5. **Preservation of ESA coverage is consistent with recent Health and Human Services (HHS)/CMS policy directives (eg, Shared Decision Making, Elimination of Disparities of Care, Quality Incentive Program). Furthermore, anemia associated with CKD is a significant unmet medical need with a limited range of treatment options, particularly among African-Americans and women. Consequently, restrictions on ESA use for the treatment of CKD-associated anemia may have a disproportionate impact on these groups.**

1. Chronic kidney disease is a progressive disease spanning a spectrum from mild impairment of kidney function to severe impairment requiring dialysis or kidney transplant. The chronic anemia of CKD can be treated with RBC transfusion; however, transfusion has been associated with clinically relevant complications, including infection, volume overload, and increased PRA titers, which may preclude or delay kidney transplantation.

Chronic kidney disease ranges from minor to severe impairment of kidney function and represents a continuum of metabolic and vascular abnormalities.[1] The kidney is the major site of human erythropoietin production. Erythropoietin is secreted when the kidney senses tissue hypoxia and stimulates the bone marrow to produce RBCs. Although anemia in patients with CKD may develop in response to a wide variety of causes, erythropoietin deficiency is the primary cause of anemia associated with CKD. Loss of the kidney's erythropoietin production with kidney disease leads to an inappropriately low level of circulating erythropoietin despite the presence of anemia.[2]

Before the advent of ESA therapy, the anemia of CKD was routinely treated with RBC transfusion,[2] and transfusion requirements increase with severity of anemia.[3] The risks and limitations of transfusion are still relevant today, and the decision whether transfusion avoidance is a clinically important goal should be assessed for each patient with CKD based on his or her individual clinical circumstances. In addition to risks for alloimmunization and iron overload, transfusion carries the risk of volume overload (especially in CKD patients, who have a reduced capacity to handle a fluid load as well as a high incidence of comorbid cardiac disease), allergic reaction, hemolytic reaction, acute lung injury, and infection.[4] Although donor screening and testing procedures for infectious disease continue to improve, a wide range of infectious pathogens, such as human immunodeficiency virus, hepatitis B, hepatitis C, human herpes virus 8, Trypanosoma cruzi (Chagas' disease), and the prion responsible for variant Creutzfeldt-Jakob disease, may still be transmitted through allogeneic blood transfusions.[5,6] Recent estimates suggest that 1 in every 130,000 RBC transfusions results in death (including deaths due to transmitted infectious disease).[4] Approximately one-third of these deaths are due to transfusion-related acute lung injury and hemolytic reactions.

2. The Company has provided commentary on several of the findings and conclusions included in the CMS proposed decision memorandum dated March 16, 2011[*].

The Company concurs with the CMS proposal not to issue a national coverage determination at this time based on currently available evidence, but would like to use the opportunity of the public comment period to respond to some of the specific findings and concluding statements from the CMS memorandum regarding the use of ESAs in patients with CKD.

CMS Conclusion: ***"ESAs are being used with supraphysiologic dosing at hemoglobin/hematocrit levels higher than those used to avoid transfusions…(ESA doses in the United States) exceed physiologic replacement and is approximately twice that in Europe despite equivalent hemoglobin results".***

Company Response: Individual responsiveness to ESAs dictate the dosage used; dosage should not exceed that sufficient to avoid transfusion. Given the differences in the accessibility to dialysis in the United States and Europe, differences in patient characteristics (including comorbidities, weight, etc.) alone may account for the differences seen in ESA dosing.

Patients who require higher doses of epoetin alfa to avoid transfusion should also be evaluated and treated for other causes of anemia. Hemoglobin levels in these patients should be monitored and if responsiveness improves, appropriate PROCRIT® dose adjustments should be made. PROCRIT® should be discontinued if responsiveness does not improve and the patient needs recurrent RBC transfusions.

CMS Conclusion: ***"…we identified no high quality, randomized clinical trials that were of sufficient design, duration, and power to definitely determine that ESAs provided clinical benefits other than increasing hemoglobin, a putative intermediate clinical surrogate in patients with documented erythropoietin-mediated anemia."***

And

CMS Finding: ***"No trials were structured to assess transfusion endpoints (number units, number persons, frequency, transfusion reason, antecedent hemoglobin) with a priori transfusion criteria based on accepted data-based criteria for transfusion."***

[*] "Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for Treatment of Anemia in Adults with CKD Including Patients on Dialysis and Patients not on Dialysis (CAG-00413N)", dated March 16, 2011.

Company Response: The currently labeled indication for PROCRIT (USPI dated February 2010) is for precisely that, treating "anemia associated with CRF [chronic renal failure], including patients on dialysis and patients not on dialysis. PROCRIT® is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients".[7]

Although transfusion rates were not a primary outcome of the early registration studies, a large study (N = 1,557) evaluating the safety and efficacy of epoetin alfa 10,000 units once weekly in nondialysis CKD subjects showed that transfusion rates significantly decreased from 11.1% (n = 149) during the 6-month pre-treatment period to 3.7% (n = 50) ($p < 0.0001$) during the 16-week study period, when using a hemoglobin treatment target range of approximately 10 to 12 g/dL (Study PR00-06-009 [POWER][8]). In addition, all health-related quality-of-life parameters improved significantly from baseline ($p<0.0001$). Mean Linear Analogue Self-assessment (LASA) scores for energy, activity, and overall quality of life increased from baseline to study completion by 27.9 mm (70.5%), 24.5 mm (57.0%), and 22.6 mm (47.4%), respectively. All 5 Kidney Disease Questionnaire (KDQ) domains showed statistically significant improvements ($p<0.0001$). Hemoglobin change was a strong predictor for all 5 KDQ domains and the overall score ($p<0.0001$).

A survey of anemia management practices in Europe (N=4,333) showed that approximately 27% of CKD patients starting dialysis received ESA treatment during the 12 months leading up to the start of dialysis. The mean (SD) hemoglobin concentration at the start of ESA treatment was 8.8 (1.3) g/dL. The mean (SD) individually set hemoglobin target was 11.6 (0.7) g/dL at the start of dialysis. Patients treated with an ESA before initiation of dialysis had significantly lower rates of blood transfusion than patients who did not receive an ESA (17% versus 21%, $p < 0.05$).[9] These data indicate that transfusion reduction is also a clinical benefit for nondialysis CKD patients.

Studies EPO-AKD-3001 and EPO-AKD-3002

More recently, 2 large registration studies were completed investigating commonly used extended-interval PROCRIT treatment regimens. All subjects in Studies EPO-AKD-3001[10] and EPO-AKD-3002[11] were assigned to receive active treatment with either the currently approved 3-times-weekly epoetin alfa treatment regimen or an alternative extended-interval dosing regimen. The hemoglobin treatment target range was 11.0 to 11.9 g/dL. Epoetin alfa was withheld when hemoglobin concentrations exceeded 11.9 g/dL and were not resumed until hemoglobin concentrations fell below 11.0 g/dL. A total of 805 subjects with CKD who were not

on dialysis were randomized in the 2 studies. Subjects were elderly (median group age, 71.0 -73.0 years) with moderately severe renal insufficiency (i.e., Stage 4 CKD) and multiple comorbidities (eg, hypertension, diabetes mellitus, cardiovascular disease, and hyperlipidemia).

In lieu of a control group for statistical comparison, a clinical case-by-case review of subjects who received RBC transfusion was performed. This assessment showed that across both studies, only 2 of the 48 subjects who received RBC transfusion during the treatment period were transfused for causes directly attributable to lack of treatment efficacy. In addition, 38 of the 48 transfused subjects were transfused primarily to treat acute decreases in hemoglobin concentration that developed while these subjects were hospitalized for intercurrent medical conditions, such as gastrointestinal bleeding, sepsis, or surgical procedures (Company data on file). PROCRIT is not intended for patients who require immediate correction of severe anemia. PROCRIT may obviate the need for maintenance transfusions but is not a substitute for emergency transfusion.[7] Therefore, consistent with its approved indication, treatment with epoetin alfa effectively reduced the need for transfusion to treat the anemia of CKD in this nondialysis population.

The mean pre-transfusion hemoglobin concentrations in Studies EPO-AKD-3001 and EPO-AKD-3002 were 8.2 g/dL (Table 1) and 8.3 g/dL (Table 2), respectively, regardless of the reason for transfusion. These data suggest that in practice, transfusion decisions are individualized to take into consideration a patient's full clinical situation, including antecedent hemoglobin concentration. Additionally, the median values at which transfusion occurred in these studies suggests that maintaining patients at a hemoglobin level approaching 9 g/dL may result in additional transfusions.

Table 1: Summary Statistics of Pre-transfusion Hemoglobin (g/dL) During Treatment: Excluding Data Collected Post-Dialysis
(Study EPO-AKD-3001)

Intent-to-Treat Population '	n	Mean	STD	Median	Minimum	Maximum
Pre-transfusion Hemoglobin (g/dL)	37	8.28	0.91	8.2	5.5	10.4

n = total number of transfusions with pre-tranfusion hemoglobin value not missing among all subjects.
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Table 2: Summary Statistics of Pre-transfusion Hemoglobin (g/dL) During Treatment:
Excluding Data Collected Post-Dialysis
(Study EPO-AKD-3002)

Intent-to-Treat Population '	n	Mean	STD	Median	Minimum	Maximum
Pre-transfusion Hemoglobin (g/dL)	43	8.16	1.18	8.3	5.0	11.9

n = total number of transfusions with pre-tranfusion hemoglobin value not missing among all subjects.
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Trial to Reduce Cardiovascular Events with Aranesp® (TREAT)

Subjects in Amgen's TREAT study (N=4,038) received transfusions at the discretion of the investigator based on his or her clinical judgment. The placebo group from TREAT provides some insight into the transfusion practices in place for CKD patients not receiving dialysis. Subjects in the placebo group received placebo if the hemoglobin concentration was ≥ 9.0 g/dL. If the hemoglobin concentration was < 9.0 g/dL, subjects received rescue therapy with darbepoetin alfa (once monthly) until their hemoglobin was ≥ 9.0 g/dL.

Significantly fewer subjects received ≥1 transfusion in the darbepoetin alfa group (297 subjects [15%]) compared with the placebo group (496 subjects [25%]), and treatment with darbepoetin alfa significantly increased the time to first transfusion compared with placebo (HR 0.56 [95% CI: 0.49, 0.65]; nominal p < 0.0001).[12,13] There was an approximately 2- to 4-fold increase in the risk of transfusion when hemoglobin concentrations were < 10 g/dL relative to when hemoglobin concentrations were ≥ 10 g/dL. In addition, the data suggest that maintaining hemoglobin concentration > 10 g/dL will reduce or avoid transfusions and that administering ESAs to patients with hemoglobin concentrations < 10 g/dL is appropriate.[13]

Veterans Administration Transfusion Study

Investigators conducted a retrospective study of 97,636 nondialysis patients in the Veterans Administration Healthcare System to describe the transfusion burden related to anemia in patients with CKD who were not on dialysis.[14] The study included data from patients with Stage ≥3 CKD and anemia (hemoglobin < 11 g/dL or received ESA therapy, iron therapy, or both). Transfusion events were evaluated in relation to the absolute hemoglobin concentration and changes in hemoglobin concentration overall and according to the type of treatment received (no treatment, iron, ESA, ESA and iron) concurrent with each hemoglobin measurement.

A total of 68,556 transfusion events were observed (61 events per 100 person-years). At all hemoglobin concentrations (and after adjusting for current patient characteristics), transfusion

events were highest during periods of no treatment and increased with declining hemoglobin levels. Between a hemoglobin concentration of 10.0 and 10.9 g/dL, the transfusion rate was 2.0% for those who received an ESA, iron, or both and 22% for those who received no treatment. At a hemoglobin concentration of 7.0 g/dL to 7.9 g/dL, the transfusion rate was 10 to 12% for treated and 58% for untreated patients.

The mean (SD) hemoglobin concentration was 8.9 (1.6) g/dL for transfusions occurring in an inpatient setting and was 8.5 (1.4) g/dL for transfusions occurring in an outpatient setting. Low absolute hemoglobin levels but not hemoglobin changes were most predictive of a transfusion even after adjustment for patient case mix.

CMS Conclusion: ***"The evidence for transfusion reduction is limited because of the absence of validated criteria for transfusion, the absence of defined study protocols for transfusion, and the use of non-inferiority (or equivalence) study designs that lacked a placebo arm."***

Company Response: There is evidence from the pivotal registration studies that ESAs reduce transfusion requirements. Consistent with these clinical study results, decreases in transfusion requirements were observed in the dialysis setting following the introduction of epoetin alfa,[15] which contributed to increased access to kidney transplants and improved renal transplant survival among kidney transplant patients.[16,17,18] In addition, there has been a reduction in the number of transfusions needed for dialysis patients and CKD patients not currently being dialyzed.[19] Only ESA treatment has been studied for chronic use as an alternative to RBC transfusion for this patient population. Clinical guidelines continue to recommend ESAs for symptomatic patients with anemia from CKD.[20]

CMS Conclusion: ***"(The Coverage and Analysis Group [CAG]) identified no randomized clinical trials that used fixed doses and stratification by ESA-naïve hemoglobin levels to better define the response rate to physiologic dosing, assess dose-related safety, and exclude the confounding associated with hemoglobin levels and targets."***

Company Response: The level of ESA required for "physiologic replacement" will vary with the individual patient, with their current disease state, and with the desired hemoglobin treatment target. Rather than dosing ESAs to an average "physiologic" range, the adequacy of ESA replacement is assessed by the resultant hemoglobin level achieved. For that reason, dose adjustments with dose adjustment guidelines are included in the PROCRIT USPI.[7] This allows the treating physician to tailor the ESA dose to the patient's specific needs at that point in time.

CMS Conclusion: **"…(CAG)** ***did identify emerging evidence for harm including increased mortality, tumor progression, cardiovascular-thromboembolic events, and stroke in patients with renal insufficiency and/or renal failure."***

Company Response: Two large studies in nondialysis patients have tested the hypothesis that normalization of hemoglobin levels (≥13 g/dL) with an ESA would result in greater improvement in cardiovascular, renal, and mortality outcomes when compared with either partial correction of hemoglobin levels with epoetin alfa (hemoglobin of 11.3 g/dL in CHOIR or rescue therapy with darbepoetin alfa for hemoglobin < 9 g/dL in TREAT).[21,12] The results of these studies failed to demonstrate the ability of targeting hemoglobin to levels greater than 12.0 g/dL to improve cardiovascular outcomes. These studies did reveal an increased risk of adverse events when the hemoglobin was targeted to levels of 13 g/dL or greater. As a result, ESA labels were amended to carry warnings advising clinicians not to target hemoglobin levels >12 g/dL. Safety data from clinical studies targeting hemoglobin concentrations ≥13.0 g/dL demonstrated a higher risk of death, cardiovascular events, and stroke (which is addressed in the current epoetin alfa label). These studies demonstrated that for subjects treated to hemoglobin levels <12.0 g/dL, the safety profile is consistent with events expected in this patient population.

Current PROCRIT labeling includes the following black box warning for patients with CKD: "In clinical studies, patients experienced greater risks for death, serious cardiovascular events, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target hemoglobin levels of 13 g/dL and above."

CMS Finding: ***"In the non-classic paradigm, a hormone is used at higher than physiologic levels because of hormone resistance or to supplement endogenous pathways to achieve supraphysiologic or accelerated physiologic responses."***

Company Response: The Company agrees that underlying causes of ESA resistance need to be assessed and identified whenever possible. ESA hyporesponders are the small subgroup of patients who account for the largest dose escalation.

All patients should receive the lowest ESA dose sufficient to avoid transfusion. Patients who require higher doses of epoetin alfa to avoid transfusion should also be evaluated and treated for other causes of anemia.

3. The decision to initiate ESA treatment should only occur after the physician and patient have carefully evaluated the patient's unique clinical situation. Treatment should only be considered when the patient's hemoglobin concentration is < 10 g/dL, when anemia is chronic and clinically relevant, and when transfusion avoidance is a clinically important goal. Individualized care needs in anemia management are highlighted by pre-transfusion hemoglobin levels that ranged from 5.0 to 11.9 g/dL in randomized clinical studies of subjects with CKD not on dialysis.

The decision to administer ESAs should be based on an individualized benefit/risk assessment performed by the clinician with the participation of the patient and should take into account the specific clinical context. This assessment should consider whether a particular patient is experiencing clinically relevant anemia of CKD and whether transfusion avoidance is a clinically important patient management goal.

Patients considering PROCRIT therapy should have their iron status assessed to ensure that levels are adequate to support erythropoiesis. Dosing should be individualized to achieve and maintain hemoglobin levels sufficient to avoid transfusion. If the patient fails to respond to treatment or fails to maintain a response, other etiologies should be considered and evaluated. Patients should continue to receive the lowest dose needed to avoid transfusion. The dose of epoetin alfa should be reduced as the hemoglobin concentration approaches 12 g/dL or increases by more than 1 g/dL in any 2-week period.

As described previously for the Company's registration studies EPO-AKD-3001 and EPO-AKD-3002, conducted in a nondialysis population, the decision to transfuse patients are individualized to take into consideration a patient's full clinical situation. The minimum and maximum pre-transfusion hemoglobin levels in those studies ranged from 5.0 to 11.9 g/dL, suggesting that factors in addition to antecedent hemoglobin concentration were considered when deciding whether to transfuse the subjects.

4. Expert panels in different regulatory settings have recommended treatment guidelines that are supportive of the current ESA label for patients with anemia associated with CKD who are not on dialysis.

In October 2010, CRDAC recommended in a 15 to 1 vote (1 abstention) that darbepoetin alfa continue to be indicated for treatment of anemia in CKD patients not on dialysis. Several committee members noted that the benefit/risk profile for particular subpopulations of patients with CKD is favorable and that there are insufficient data to support withdrawal from the labeled use. The CRDAC, by a 13 to 2 vote (2 abstentions), also agreed that the current dosing schedule for darbepoetin alfa should not be changed to the placebo group regimen that was used in the TREAT study. Panelists stated that there was insufficient evidence to support such a labeling change as it is important to maintain (permit) treatment according to individual patient needs. The CRDAC members who recommended a modification to the current label agreed that a conservative strategy is warranted in light of consistent evidence that supports increased safety risks when higher hemoglobin levels are targeted.[22]

A comprehensive and well-regarded clinical guideline, the Anemia Management in Chronic Kidney Disease clinical guideline, commissioned by NICE, has defined the adult "aspirational hemoglobin range" more precisely as a value between 10 and 12 g/dL. The NICE guidelines further recommend that health care providers should not wait until hemoglobin levels are outside the aspirational range before adjusting treatment (eg, take action when hemoglobin levels are within 0.5 g/dL of the range's limits or when the rate of change of hemoglobin suggests an established trend [eg, >1g/dL per month]).[2]

Additionally, in November 2008 the Anaemia Working Group of European Renal Best Practice (ERBP) issued a position paper recommending that hemoglobin levels between 11 and 12 g/dL should be sought in the CKD population without intentionally exceeding 13 g/dL.[23]

5. Preservation of ESA coverage is consistent with recent HHS/CMS policy directives (eg, Shared Decision Making, Elimination of Disparities of Care, Quality Incentive Program). Furthermore, anemia associated with CKD is a significant unmet medical need with a limited range of treatment options, particularly among African-Americans and women. Consequently, restrictions on ESA use for the treatment of CKD-associated anemia may have a disproportionate impact on these groups.

Shared Decision Making

Preservation of coverage for ESA use in the treatment of anemia in patients with CKD is consistent with key elements of the Patient Protection and Affordable Care Act of 2010 (PPACA) and the associated National Strategy for Quality Improvement in Health Care (National Quality Strategy). PPACA Section 3011 establishes the National Quality Strategy as part of PPACA. Two core principles of the National Quality Strategy include person-centeredness and family engagement and eliminating disparities of care.[24]

The principle of person-centeredness and family engagement is to foster the shared decision making process in which clinicians, patients, and their families work together to make health care decisions. The concept of shared decision making is a key element of PPACA. In section 3506 of PPACA, Shared Decision making is defined as a program:

> *"… to facilitate collaborative processes between patients, caregivers or authorized representatives, and clinicians that engages the patient, caregiver or authorized representative in decision making, provides patients , caregivers or authorized representatives with information about trade-offs among treatment options, and facilitates the incorporation of patient preferences and values into the medical plan…"*

Also within this section of PPACA, Preference Sensitive Care is defined as:

> *"…medical care for which the clinical evidence does not clearly support one treatment option such that the appropriate course of treatment depends on the values of the patient or the preferences of the patient, caregivers or authorized representations regarding the benefits, harms and scientific evidence for each treatment option, the use of such care should depend on the informed choice among clinically appropriate treatment options…"*

The health care decisions and plans developed through shared decision making incorporate a patient's needs, experiences, perspectives, and preferences. The care plans include an

assessment of the individual's tolerance of the potential risks and benefits of each treatment option resulting in an informed choice made in a collaborative, patient-centered manner. By preserving ESA coverage to treat anemia across the spectrum of CKD, this core concept of person-centeredness is supported. Continued coverage of ESAs allows patients and health care providers to consider all anemia treatment options during the shared decision making process. Policies restricting ESA coverage would undermine this key PPACA element. Rather than facilitating the patient/clinician dialogue reviewing the evidence of potential benefits and harms of ESA treatment, access to an important treatment option would be restricted. A patient may be forced to either forego the treatment option that best aligns with their values, preferences, and risk tolerance or they may be forced to bear the financial burden of that treatment option. Not all potentially impacted patients would be able to bear this financial burden, thus potentially creating disparities of health care based on socioeconomic or health care payer status.

Disparities of Care

PPACA contains several core elements to decrease disparities of health care by expanding both coverage and access to health care. Additionally, the elimination of disparities in care is another core element of the National Quality Strategy.[24] This core priority is to be an integral part of all strategies, goals, and health care improvement efforts. The goal is to foster collaborative efforts to eliminate disparities in care, including but not limited to those based on color, national origin, gender, age, disability, language, health literacy, sexual orientation and gender identity, source of payment, socioeconomic status, and geography. Preservation of access to ESAs as an option to treat anemia in CKD is supportive of this core goal to eliminate disparities in care. ESA coverage restriction could disproportionately impact groups including those of certain racial groups and to groups of lower socioeconomic status dependent upon Medicare as a payment source.

The burden of CKD disproportionately impacts certain racial and ethnic minority groups. African Americans have a higher prevalence and incidence of CKD across the spectrum of CKD (including both CKD patients on dialysis and not on dialysis) compared with Caucasians.[25,26] Additionally, American Indians and Hispanics have higher rates of CKD compared with Caucasians. Amongst populations impacted by CKD, the burden of anemia is disproportionately born by particular subpopulations, such as African Americans.[27,28]

Health care disparities currently exist as minorities and females are less likely to be registered on kidney transplantation waiting lists[29] and experience lower transplantation rates, predominantly due to longer wait times.[30] The mean time from transplant listing to transplantation is 2.3 years for Caucasians and 3.7 years for African Americans.[26] As the number of patients awaiting kidney transplantation continues to rise, growing 6% in 2008,[26] and the transplant wait time lengthens; this could exacerbate current health care disparities.

Based on the disproportionate burden of CKD born by racial and ethnic minorities and the higher rate of CKD-associated anemia in these populations, potential ESA coverage limitations could result in disproportionately greater impact on these populations. Unintended consequences of coverage limitations may be increased RBC transfusion use potentially lengthening wait times due to transfusion-associated sensitization.[26] Additionally, coverage limitations may further increase health care disparities rather than working toward the intended goal of PPACA and the National Quality Strategy to decrease disparities of care. If such a reimbursement policy were to be implemented, the impact of this policy on health disparity populations should be studied in a transparent manner to ensure that these groups are not disproportionately burdened and that disparities in care are not exacerbated.

End Stage Renal Disease (ESRD) Quality Improvement Program (QIP)

Two important payment changes for ESRD services were undertaken by CMS in early 2011. The first was the Medicare Improvements for Patients and Providers Act mandated bundling of payment for ESRD services (effective January 1, 2011), which includes payment for injectable drugs such as ESAs.[31,32] One objective of this change in payment policy is to reduce the incentives to overuse profitable, separately billable drugs. The CMS QIP became effective on February 4, 2011 and is intended to promote ongoing CMS strategies to improve the quality of care provided to ESRD patients. The initiative supports both quality improvement initiatives by providers and makes available quality information that will enable patients to participate in making health care decisions.[33] This program identified quality measures for ESRD services and established performance standards for those measures. Payment reductions will be imposed upon ESRD service providers that do not meet or exceed benchmarks for these performance measures. Three performance measures compose the total performance score to be used by CMS, two of which are anemia treatment related. These two anemia related performance measures are the percent of patients with an average hemoglobin level < 10 g/dL and the percent of patient with an average hemoglobin level of > 12 g/dL.

CKD is a continuum of metabolic and vascular abnormalities, with many of these abnormalities beginning early in the course of CKD.[1] With this in mind, a uniform policy of ESA coverage to include CKD patients not on dialysis and patients on dialysis should span that continuum as the potential sequelae of anemia span this continuum. Patients not on dialysis impacted by anemia may spend extended periods exposed to the potential consequences of anemia.[34]

From a historical perspective, the National Kidney Foundation led a team of key stakeholders to develop and publish the Dialysis Outcomes Quality Initiative (DOQI) in 1997.[35] DOQI was a set of clinical practice guidelines originally intended to improve outcomes in the dialysis population. Shortly thereafter, it became evident that a set of practice guidelines focusing solely on the dialysis population may not be enough to improve outcomes in the CKD population. In 2002, the DOQI evolved to the KDOQI to broaden the focus of the guidelines across the spectrum of CKD. This expansion of the guidelines was based on the concept that earlier identification of patients with CKD and treatment of associated comorbid conditions and CKD complications would have an impact on outcomes across the spectrum of CKD.[36,37] Waiting until a patient required dialysis to treat CKD complications would do nothing to improve the health status of patients reaching ESRD. The goal was to improve the outcomes and quality of life in CKD patients on dialysis and not on dialysis through appropriate care. Early intervention has the potential ameliorate organ dysfunction and comorbid conditions in those who subsequently progress to ESRD. With the current performance measures being used by CMS in the ESRD population, it is important to consider alignment of quality and performance measures in the CKD population across the spectrum, including the CKD population not on dialysis.

Conclusion

The Company concurs with the CMS proposal not to issue a national coverage determination at this time based on currently available evidence. Chronic kidney disease ranges from minor to severe impairment of kidney function and represents a continuum of metabolic and vascular abnormalities. Although anemia in patients with CKD may develop in response to a wide variety of causes, erythropoietin deficiency is the primary cause. Anemia associated with CKD remains a significant unmet medical need, particularly among African-Americans and women, with a limited range of treatment options. However, approximately 20 years of clinical experience has demonstrated that when used according to the FDA-approved label, ESAs can effectively treat the chronic anemia associated with CKD. The potential benefits, as well as the potential risks of treatment (particularly when ESAs are used to target hemoglobin levels higher than that sufficient to avoid transfusion), are described in the medical literature and current ESA labeling.

Therefore, consistent with the core concept of person-centered treatment of anemia across the full spectrum of CKD, the Company recommends that the decision to administer ESAs should occur only after a careful benefit/risk assessment of each patient's unique clinical situation by the patient and his or her health care provider. Continued coverage of ESAs allows patients and health care providers to consider all anemia treatment options, including RBC transfusion, during the shared decision making process. Treatment with ESAs should not be considered unless the patient's hemoglobin concentration is < 10 g/dL, the anemia is chronic and clinically relevant, and transfusion avoidance is a clinically important goal. If ESA therapy is determined to be appropriate, the dose of ESA used should be individualized so as to be no higher than that necessary to achieve and maintain hemoglobin at a level sufficient to avoid transfusion.

REFERENCES

1. Mehrotra R. The John F. Maher Award Recipient Lecture 2006. The continuum of chronic kidney disease and end-stage renal disease: challenges and opportunities for chronic peritoneal dialysis in the United States. Perit Dial Int. 2007;27:125-130.
2. National Institute for Health and Clinical Excellence (2011). CG114 Anaemia management in people with chronic kidney disease: full guidance. Available at: http://guidance.nice.org.uk/CG114/Guidance/pdf/English. Accessed 16 Mar 2011.
3. Lawler EV, Gagnon DR, Fink J, et al. Initiation of anaemia management in patients with chronic kidney disease not on dialysis in the Veterans Health Administration. Nephrol Dial Transplant 2010;25:2237-2244.
4. Despotis GJ, Zhang L, Lublin DM. Transfusion risks and transfusion related pro inflammatory responses. Hematol Oncol Clin N Am. 2007;21:147-161.
5. Blajchman MA, Vamvakas EC. The continuing risk of transfusion-transmitted infections. N Engl J Med. 2006;355:1303-1305.
6. Food and Drug Administration. News Press Release: FDA Approves First Test to Screen Blood Donors for Chagas Disease. 2006. Available at http: //www.fda.gov/bbs/topics/NEWS/2006/NEW01524.html. Accessed on 16 Mar 2011.
7. PROCRIT® Package Insert. Centocor Ortho Biotech Products, L.P., Raritan, New Jersey. Revised February 2010. Available at: http://www.procrit.com/sites/default/files/shared/OBI/PI/ProcritBooklet.pdf#page=1 Accessed 22 March 2011.
8. Provenzano R, Garcia-Mayol L, Suchinda P, et al, POWER Study Group. Once-weekly epoetin alfa for treating the anemia of chronic kidney disease. Clin Nephrol. 2004;61:392-405.
9. Valderrábano F, Hörl WH, Macdougall IC, Rossert J, Rutkowski B, Wauters JP. PRE-dialysis survey on anaemia management. Nephrol Dial Transplant 2003;18:89-100.
10. Pergola P, Gartenberg G, Fu, M, Wolfson M, Rao S, Bowers P. A randomized controlled study of weekly and biweekly dosing of epoetin alfa in CKD Patients with anemia. Clin J Am Soc Nephrol. 2009; 4:1731-1740.
11. Pergola P, Gartenberg G, Fu M, Sun S, Wolfson M, Bowers P. A randomized controlled study comparing once-weekly to every-2-week and every-4-week dosing of epoetin alfa in CKD patients with anemia. Clin J Am Soc Nephrol. 2010; 5(4):598-606.
12. Pfeffer MA, Burdmann EA, Chen C-Y, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361:2019-2032.
13. The Cardiovascular and Renal Drugs Advisory Committee. Background information for the Cardiovascular and Renal Drugs Advisory Committee; 18 October 2010. Results of the trial to reduce cardiovascular events with ARANESP® therapy (TREAT). Amgen Inc., Thousand Oaks, CA. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ UCM229328.pdf. Accessed 15 Mar 2011.
14. Lawler EV, Bradbury BD, Fonda JR, Gaziano JM, Gagnon DR. Transfusion burden among patients with chronic kidney disease and anemia. Clin J Am Soc Nephrol. 2010;5:667-672.
15. Eschbach, JW. Erythropoietin: the promise and the facts. Kidney Int Suppl. 1994; 44: S70-76.
16. Lietz K, Lao M, Paczek L, et al. The impact of pretransplant erythropoietin therapy on late outcomes of renal transplantation. Ann Transplant 2003;8:17-24.
17. Braun WE. Update on kidney transplantation: increasing clinical success, expanding waiting lists. Cleve Clin J Med 2002;69:501-504.
18. Nicol D, MacDonald AS, Lawen J, Belitsky P. Early prediction of renal allograft loss beyond one year. Transpl Int. 1993;6:153-157.

19. U.S. Renal Data System, USRDS 2008 Annual Data Report: USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008.
20. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. Am J Kidney Dis. 2006; 47:S11-145.
21. Singh AK, Szcech L, Kezhen L, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355:2085-2098.
22. CRDAC Transcript. Transcript of the October 18, 2010 CRDAC Meeting. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM238530.pdf Accessed 6 April 2011.
23. Locatelli F, Covic A, Eckardt KU, Wiecek A, Vanholder R. Anaemia management in patients with chronic kidney disease: a position statement by the Anaemia Working Group of European Renal Best Practice (ERBP). Nephrol Dial Transplant 2009;24:348-354.
24. U.S. Department of Health and Human Services (2011). Report to Congress: National Strategy for Quality Improvement in Health Care. Available at: http://www.healthcare.gov/center/reports/quality03212011a.html#es. Accessed 4 April 2011.
25. Evans K, Coresh J, Bash LD, et al. Race differences in access to health care and disparities in incident chronic kidney disease in the US. Nephrol Dial Transplant 2011;26:899-908.
26. U.S. Renal Data System, USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2010.
27. McFarlane SI, Chen SC, Whaley-Connell AT, et al. Prevalence and associations of anemic of CKD: kidney early evaluation program (KEEP) and national health and nutrition examination survey (NHANES) 1999-2004. Am J Kidney Dis. 2008;51(2):S46-S55.
28. McClellan W, Aronoff SL, Bolton WK, et al. The prevalence of anemia in patients with chronic kidney disease. Curr Med Res Opinion 2004;20(9):1501-1510.
29. Agency for Healthcare Research and Quality National Health Care Disparities Report. U.S. Dept. of Health and Human Services. AHRQ publication No. 11-0005. February 2011.
30. Hall YN, Choi AI, Xu P, O'Hare AM, Chertow GM. Racial and ethnic differences in rates and determinants of deceased donor kidney transplantation. J Am Soc Nephrol. 2010;22: Epub online.
31. Inglehart JK. Bundled payment for ESRD-including ESAs in Medicare's dialysis package. N Engl J Med. 2011;364(7):593-595.
32. Federal Register 75:49029-49214; August 12, 2010. Available at: http://edocket.access.gpo.gov/2010/pdf/2010-18466.pdf. Accessed 1April 2011.
33. U.S. Department of Health and Human Services, Centers for Medicare & Medicaid Services (2011). Available at: https://www.cms.gov/ESRDQualityImproveInit/. Accessed 1 April 2011.
34. Mujais SK, Story K, Brouillette J, et al. Health-related quality of life in CKD patients: correlates and evolution over time. Clin J Am Soc Nephrol. 2009;4:1293-1301.
35. National Kidney Foundation (2011). Available at: http://www.kidney.org/professionals/KDOQI/aboutHistory.cfm. Accessed: 1 April 2011.
36. KDOQI Guidelines (2002). Available at: http://www.kidney.org/professionals/kdoqi/guidelines_ckd/p1_exec.htm. Accessed 5 April 2011.
37. Eknoyan G, Levin NW. American Journal of Kidney Diseases, Supplement Forward. Am J Kid Dis. 2002;39(2 Suppl 1):S14-S16.