PUBLICCITIZEN

1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

April 15, 2011

Louis B. Jacques, M.D.
Director, Coverage and Analysis Group
Office of Clinical Standards and Quality
Centers for Medicare & Medicaid Services
7500 Security Boulevard, Mail Stop S3-02-01
Baltimore, Maryland 21244

RE: 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)

Dear Dr. Jacques:

These comments from the Public Citizen Health Research Group are being submitted in response to the Centers for Medicare & Medicaid Services' (CMS) March 16, 2011 proposed decision memo referenced above:

(1) We strongly oppose the proposal that CMS not issue a national coverage determination at this time for ESAs for treatment of anemia regarding ESAs for the treatment of anemia in adults with chronic kidney disease (CKD), including patients on dialysis and patients not on dialysis. Such a proposal (a) is not supported by the current evidence regarding the known risks and benefits of ESAs; (b) fails to align with the black box warning about the dangers of ESAs required by the Food and Drug Administration (FDA) for all ESAs currently marketed in the United States (U.S.); (c) is not consistent with protecting the public health; and (d) contributes to wasteful expenditures of Medicare dollars.

(2) We urge CMS to issue instead a national coverage decision that incorporates the following elements:

(a) For patients on dialysis, a coverage decision for ESAs should be issued that promotes maintenance of hemoglobin levels within the target range of 10-12 grams/deciliter (g/dL) recommended by FDA, and preferably within a level of 10-11 g/dL.

(b) For patients with CKD not on dialysis, a coverage decision for ESAs should be issued that limits ESA treatment to patients with hemoglobin levels less

than 10 g/dL. The goal of ESA treatment in these patients should be a hemoglobin level of 10 g/dL, but no higher.

Unless CMS implements a national coverage decision for ESAs that aligns with the FDA's recommendation for the upper limit of target hemoglobin levels, patients with CKD will continue to be needlessly harmed, and tens – if not hundreds – of millions of Medicare dollars will be wasted.

Background

ESAs are a class of drugs which stimulate red cell production. They are similar to the endogenous protein hormone erythropoietin, which is produced primarily in the kidney, but also in small amounts by the liver. Impaired production of erythropoietin, because of kidney disease, is one of several factors that contribute to the development of anemia in patients with CKD.

Since 1989, ESAs have been used to treat anemia in CKD patients. Two ESA products currently are marketed in the U.S. The first, epoetin alfa (marketed under the brand names of Epogen® and Procrit®; Amgen, Inc.), was approved in 1989 for the treatment of anemia associated with chronic renal failure "to elevate or maintain the red blood cell level and to decrease the need for transfusions."[1] The current indication is "for the treatment of anemia associated with chronic renal failure, including patients on dialysis or not on dialysis... 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."[2]

Darbepoetin alpha (marketed under the brand name Aranesp®; Amgen, Inc.), a second ESA, was approved for marketing in the U.S. in 2001 for "the treatment of anemia associated with chronic renal failure, including patients on dialysis or not on dialysis." In 2002, the FDA also approved darbepoetin alpha for treatment of anemia due to chemotherapy in patients with non-myeloid malignancy.[3]

Benefits of ESAs

From a benefit standpoint, epoetin alfa has been shown to be effective in increasing and maintaining hemoglobin levels and in decreasing the need for transfusions in patients with CKD. In non-inferiority studies comparing the efficacy of darbepoetin alpha to epoetin alfa, darbepoetin alpha was shown to be effective in increasing and maintaining hemoglobin levels in patients with CKD. However, despite these improvements in surrogate markers for anemia, there have been no well-designed, randomized clinical trials that have demonstrated important clinical benefits from ESAs in patients with CKD beyond the demonstrated improvements in hemoglobin level and reductions in transfusion requirements. Indeed, in terms of benefits of ESAs, CMS concluded the following:

ESAs are being used with supraphysiologic dosing at hemoglobin/hematocrit levels higher than those used to avoid transfusions. Despite an exhaustive search, 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. 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.[4]

Risks of ESAs

In contrast to the paucity of data on the benefits of ESAs, over the past decade there has been a steadily growing body of evidence indicating that ESAs pose significant risks of cardiovascular morbidity and death when attempts are made to give enough of the drug to achieve relatively higher hemoglobin levels and when high ESA doses are used in patients with CKD.

The Normalization of Hematocrit Trial (NHCT)

This study, published in 1998, was a randomized, open-label, multicenter study in 1233 patients with clinical evidence of congestive heart failure or ischemic heart disease who were undergoing hemodialysis: 618 subjects were randomized to receive increasing doses of epoetin with a target hematocrit of 42 percent (normal-hematocrit group); the other 615 subjects were randomized to receive epoetin at doses sufficient to maintain a hematocrit of 30 percent (low-hematocrit group). The median duration of study intervention was 14 months. The primary end point was length of time to death or a first nonfatal myocardial infarction. There were more deaths and nonfatal myocardial infarctions in subjects in the normal-hematocrit group (183 and 19, respectively) than in the low-hematocrit group (150 and 14, respectively) (risk ratio 1.3; 95 percent confidence interval; 0.9-1.9). The study was stopped early upon recommendation of an independent data monitoring committee based on concern about safety of subjects assigned to the high-hematocrit group at the third interim analysis. The study investigators concluded that use of epoetin to achieve a hematocrit of 42 percent in hemodialysis patients with congestive heart failure or ischemic heart disease was not recommended.[5]

Subsequently in 2006, results of two randomized, open-label, multicenter studies were published that assessed the effect of using ESAs to achieve a high hemoglobin target versus a low hemoglobin target in patients with CKD who were not on dialysis. The first was the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial, and the second was the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial.

The CHOIR Trial

The CHOIR trial was a randomized, open-label, multicenter study in 1432 patients with CKD not on dialysis: 715 subjects were randomly assigned to receive epoetin alfa to achieve a target hemoglobin level of 13.5 g/dL (high-hemoglobin group); 717 subjects were assigned to receive epoetin alfa to achieve a target hemoglobin level of 11.3 g/dL. The median study duration was 16 months. The primary study end point was a composite of death, myocardial infarction, hospitalization for congestive heart failure, and stroke. Mean hemoglobin values were close to the target of 11.3 g/dL in the low-hematocrit group, but were consistently below the target of 13.5 g/dL in the high-hematocrit group. In the high-hemoglobin group, 125 composite events occurred, compared to 97 in the low-hemoglobin group (hazard ratio, 1.34; 95 percent confidence interval 1.03-1.74; p=0.03). There also was no incremental improvement in quality of life measures in the high-hemoglobin group. This study was terminated early based upon the recommendation of a data and safety monitoring board at the time of the second interim analysis. The study investigators concluded that use of a target hemoglobin level of 13.5 g/dL in patients with CKD is associated with an increased risk of serious adverse outcomes in comparison to a target hemoglobin of 11.3 g/dL.[6]

The CREATE Trial

The CREATE trial also was a randomized, open-label, multicenter clinical trial, which involved 603 patients with CKD not on dialysis who had mild to moderate anemia: 301 subjects were randomized to receive epoetin beta to a target hemoglobin of 13.0-15.0 g/dL (high-hemoglobin group); 302 subjects were randomly assigned to achieve a target hemoglobin of 10.5 to 11.5 g/dL (low-hemoglobin group; in this group epoetin was not given unless the subject's hemoglobin level decreased to less than 10.5 g/dL). The primary end point was a composite of eight cardiovascular events, including sudden death, myocardial infarction, acute heart failure, stroke, transient ischemic attack, angina pectoris resulting in hospitalization for 24 hours or more or prolongation of hospitalization, complication of peripheral vascular disease, or cardiac arrhythmia resulting in hospitalization for 24 hours or more. There were several secondary end points including death from any cause, death from cardiovascular causes, and change in glomerular filtration rate (GFR). At the end of the study, there were 58 subjects in the high-hemoglobin group reached a primary composite end point, in comparison to 47 in the low-hemoglobin group (hazard ratio 0.78; 95 percent confidence intervals 0.53-1.14; p=0.20). Of note, more subjects progressed to needing hemodialysis in the high hemoglobin group than the low-hemoglobin group (127 versus 111; p=0.03).[7]

FDA-Required Black Box Warning for ESAs

In December 2007, based on a review of the above-referenced studies (particularly the NHCT and CHOIR trials) the FDA required that the following black box warning be added to the labels for ESA products marketed in the U.S.:

WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR and THROMBOEMBOLIC EVENTS, and TUMOR PROGRESSION

Renal failure: Patients experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemoglobin levels (13.5 vs. 11.3 g/dL; 14 vs. 10 g/dL) in two clinical studies. Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL.[8]

The FDA also required that the warning section of the label for ESA products marketed in the U.S. be modified to include the following:

Increased Mortality, Serious Cardiovascular and Thromboembolic Events

Patients with chronic renal failure experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemoglobin levels (13.5 vs.11.3 g/dL; 14 vs. 10 g/dL) in two clinical studies. Patients with chronic renal failure and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular events and mortality than other patients. EPOGEN® and other ESAs increased the risks for death and serious cardiovascular events in controlled clinical trials of patients with cancer. These events included myocardial infarction, stroke, congestive heart failure, and hemodialysis vascular access thrombosis. A rate of hemoglobin rise of > 1 g/dL over 2 weeks may contribute to these risks.[9]

Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT)

The most recent evidence of serious risks associated with the use of ESAs came from the TREAT trial. This study was a randomized, double-blind, placebo-controlled, multicenter study involving 4038 patients with diabetes mellitus, CKD (not on dialysis), and anemia: 2012 subjects were randomly assigned to receive darbepoetin alpha with a target hemoglobin of 13 g/dL (darbepoetin group); 2026 subjects were randomized to receive placebo, with rescue darbepoetin alfa administered whenever the hemoglobin level was 9.0 g/dL (control group). The primary end points were the composite outcomes of death or a cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial ischemia) and of death or end-stage renal disease. Death or cardiovascular event occurred in 632 subjects in the darbepoetin group and in 602 subjects in the placebo group (hazard ratio 1.05; 95 percent confidence interval 0.94-1.17; p=0.41). Death or end-stage renal disease occurred in 652 subjects in the darbepoetin group and in 618 control subjects (hazard ratio 1.06; 95 percent confidence interval 0.95-1.19; p=0.29). Fatal or nonfatal stroke occurred in 101 subjects in the darbepoetin group and in 53 control subjects (hazard ratio 1.92; 95 percent confidence interval 1.38-2.68; p<0.001). The investigators concluded that use of darbepoetin alfa in patients with diabetes mellitus, CKD, and moderate anemia who are not on dialysis did not reduce the risk of either primary

composite end point and was associated with an increased risk of stroke, and "for many persons involved in clinical decision making, this risk will outweigh the potential benefits."[10]

FDA Cardiovascular and Renal Drugs Advisory Committee (CRDAC) Meeting to Discuss the Results of the TREAT Trial

On October 18, 2010, the FDA convened its CRDAC to discuss the results of the TREAT trial. In the FDA briefing document for this meeting, the FDA noted the following:

> The TREAT trial results have been published, and the Agency agrees with the general conclusions that the trial failed to demonstrate the anticipated benefits of DA therapy on mortality, specific cardiovascular events (CV) (non-fatal myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial ischemia), and end-stage renal disease in the CRF population not on dialysis. In addition to failing to demonstrate benefit on either of the primary clinical endpoints, the trial provides evidence that DA usage, as prescribed in the DA treatment arm, increased the risk of stroke and increased the risk of death for those with a prior history of malignancy.[11]

A review of the transcript of the October 18, 2010 CRDAC meeting reveals the following important comments regarding the risks of ESAs:

Dr. Ann Farrell, Acting Division Director, Division of Hematology Products, Office of Oncology Drug Products (OODP), Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER), FDA, stated the following in opening remarks to the CRDAC:

> We are soliciting the Committee's advice now because we have three trials in subjects with anemia due to chronic kidney disease which have failed to demonstrate that targeting a higher hemoglobin level has resulted in an improvement in cardiovascular or renal outcomes. Some of the trials have suggested that targeting a high hemoglobin level is actually associated with a worse outcome.[12]

Dr. Paul Eisenberg, Senior Vice President, Global Regulatory Affairs & Safety, Amgen, Inc.:

> ...we believe additional risk mitigation is warranted and we have proposed significant revisions to the label including restricting the use to patients with chronic renal failure [not on dialysis] who have, at a minimum, a hemoglobin less than 10 g/dL, who have a high likelihood of frequent transfusion, and who would benefit from ESAs as treatment strategy for their anemia. We have also proposed more conservative dosing designed to achieve a hemoglobin of 10 but not greater and we continue to believe a hemoglobin target of 10 is appropriate

based on data we'll review today that this is the level that has been demonstrated to consistently achieve transfusion avoidance.[13]

Dr. Robert Kane, Acting Safety Deputy Director, Division of Hematology Products, OODP, OND, CDER, FDA:

An early assumption of ESA use was that full correction of the anemia would be beneficial, more ESA would be better, and this would reduce cardiovascular events and mortality. That assumption has been tested prospectively, and has been answered. Both the Normal Hematocrit Study and the CHOIR Studies, well-known to this committee, have been presented, and we will provide further information shortly. However, both of these trials were stopped early, not for efficacy reasons, but for safety concerns; evidence of higher mortality and more cardiovascular events when dosing to higher hemoglobin targets.[14]

...After three large trials, we know of no evidence to support ESA dosing to a higher target hemoglobin. In fact, these three large trials show that ESA dosing to higher hemoglobin target levels is unsafe.[15]

Dr. Shona Pendse, Medical Officer, Division of Cardiovascular and Renal Drug Products, OND, CDER, FDA:

...we analyzed the TREAT data using the more objective Major Adverse Cardiac Events, or MACE endpoints, of stroke, myocardial infarction, and cardiovascular mortality, which are shown here at the bottom of the forest plot. We have also included all-cause mortality at the top of the forest plot for reference. All of the point estimates, with the exception of myocardial infarction, are greater than one, and raise the concern for increased risk in darbepoetin alfa-treated subjects, with the upper bound at approximately 1.2 for both all-cause and cardiovascular mortality. Stroke, as can be seen in this forest plot, had the highest hazard ratio of all of the endpoints.[16]

...In a Normal Hematocrit Study, there are 183 deaths, or 29 percent in the Normal Hematocrit Group compared with 150 deaths, or 24 percent, in the low hematocrit arm, resulting in a hazard ratio of 1.3, with a P value of 0.009.[17]

...In CHOIR, there were 52 deaths, or 7.3 percent, in the higher target group compared to 36 deaths, or 5 percent, in the lower target arm, yielding a hazard ratio of 1.49, with a P value of 0.07.[18]

...The pathway from these three trials from Normal Hematocrit to CHOIR to TREAT has been characterized by successive lowering of target hemoglobin from 14 to 13.5 to 13. All of these have demonstrated no cardiovascular benefit, and, in fact, all suggest a detrimental effect on cardiovascular outcomes.[19]

Dr. Ajay Singh, a nephrologist at the Brigham Women's Hospital and the principal investigator for the CHOIR study, speaking during the open public hearing:

> ...I believe that TREAT was a successful trial in that it should change the paradigm by which we manage patients with CKD anemia. I think that the way we need to move forward is to adopt the control arm of the TREAT study with a hemoglobin threshold of 9 g/dL. That's why we do placebo-controlled randomized trials. And in TREAT, the control arm won when you compared it head-to-head with the intervention group.[20]

Dr. Wolfgang Winkelmayer, a nephrologist speaking on behalf of the American Society of Nephrology during the open public hearing:

> As you are deliberating today on how the evidence from TREAT may warrant a change in the current label of darbepoetin and epoetin, we would like to emphasize three important points. First, we would like to highlight that the results from TREAT are perfectly compatible with the results from previous trials--CREATE, CHOIR, and in CKD patients undergoing dialysis to Normal Hematocrit Study. All four trials have consistently shown that if a population is being treated to a target hemoglobin, above the upper limit of the current label, 12 g/dL, no meaningful benefits arise and adverse outcomes may occur.[21]

CMS Conclusions

Regarding the available data on risks of ESAs, CMS concluded the following:

> We 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. We identified no good drug interaction studies. Despite the absence of complete publications in easily accessible medical journals, we 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.

Medicare Expenditures for ESAs

According to the U.S. Renal Data System's (USRDS) 2010 Annual Data Report, total Medicare spending for end-stage renal disease care in 2008 rose to $26.6 billion, a 13.2 percent increase over 2007 spending. Of this total, Medicare spent $1.8 billion (6.7 percent) on ESAs for ESRD patients.[22] The USRDS report notes that Medicare payment policies for ESAs only decrease reimbursement for those patients in whom hemoglobin levels were greater than 13 g/dL for three months. As a result of these current policies, a significant proportion of the $1.8 billion spent on ESAs in 2008 covered ESA use in patients whose hemoglobin levels exceeded the FDA recommended upper limit of 12 g/dL.

Obviously, as the target hemoglobin levels in patients with CKD increase to levels greater than the upper limit recommended by the FDA, so too do the doses of ESAs that needs to be administered to achieve these targets. In one study on the cost-effectiveness of maintaining higher hemoglobin targets with epoetin alfa in hemodialysis patients, the average predicted doses of intravenous (IV) and subcutaneous (SQ) doses of epoetin alfa to achieve varying levels of target hemoglobin were as follows:[23]

Target Hemoglobin (g/dL)	Epoetin Alfa IV Dose Estimate (units/dialysis session)	Epoetin Alfa IV Dose Estimate (units/dialysis session)
9.5-10.5	3523	3030
11.0-12.0	5078	4367
12.0-12.5	6097	5243
14.0	9341	8033

Based on these predicted doses, an increase from a target hemoglobin of 9.5-10.5 g/dL to 11.0-12.0 g/dL in hemodialysis patients would require on average a 44 percent increase in the IV or SQ dose of epoetin alfa; an increase in the target hemoglobin to 12.0-12.5 would require a 73 percent increase in dose.

Risk:Benefit and Cost Assessment and Recommended Actions

With regards to benefits, CMS acknowledges that there have been no well-designed, randomized clinical trials that have demonstrated important clinical benefits from ESAs in patients with CKD beyond the demonstrated improvements in hemoglobin level and transfusion requirements. There certainly is no evidence from randomized clinical trials that there is significant clinical benefit from using ESAs (a) in patients on dialysis to achieve a target hemoglobin greater than 12 g/dL or even greater than 11 g/dL, or (b) in patients with CKD who are not on dialysis to achieve a target hemoglobin greater than 10 g/dL.

In contrast, all randomized, controlled trials comparing various high-hemoglobin targets to low-hemoglobin targets have consistently shown a safety signal indicating increased risks of serious adverse cardiovascular outcomes and death in subjects assigned to the high-hemoglobin targets.

Thus, there is compelling evidence that the risk of using ESAs increases at higher hemoglobin targets, and there is no evidence of an off-setting increased benefit at higher hemoglobin levels.

Furthermore, trying to achieve higher target levels of hemoglobin requires significant escalation in both the dose of ESAs and the accompanying Medicare spending for these drugs. Thus, higher hemoglobin targets not only result in more adverse outcomes in CKD patients, including more patient deaths, they waste significant amounts of Medicare resources.

Given this risk: benefit and cost analysis, we are astonished that CMS proposes to not issue a national coverage determination at this time for ESAs for treatment of anemia regarding ESAs for the treatment of anemia in adults with CKD, including patients on dialysis and patients not on dialysis. Such a proposal (a) is not supported by the current evidence regarding the known risks and benefits of ESAs; (b) fails to align with the black box warning about the dangers of ESAs required by the FDA for all ESAs currently marketed in the U.S.; (c) is not consistent with protecting the public health; and (d) contributes to wasteful expenditures of Medicare dollars.

The available evidence provides strong support for a policy under which ESAs are dosed in an individualized manner so as to achieve the lowest possible hemoglobin level necessary to minimize the need for blood transfusions. Therefore, in order to minimize harm to patients and avoid unnecessary spending of tens to hundreds of millions of Medicare dollars, we urge CMS to issue a national coverage decision that incorporates the following elements:

(1) For patients on dialysis, a coverage decision for ESAs should be issued that promotes maintenance of hemoglobin levels within a target range of 10-12 g/dL, and preferably within a level of 10-11 g/dL

(2) For patients with CKD not on dialysis, a coverage decision for ESAs should be issued that limits ESA treatment to patients with hemoglobin levels less than 10 g/dL. The goal of ESA treatment in these patients should be a hemoglobin level of 10 g/dL, but no higher. This approach is consistent with labeling changes proposed by Amgen, Inc., the manufacturer of ESAs marketed in the U.S, during the October 18, 2010 FDA CRDAC meeting.

Thank you for the opportunity to comment on the proposed national coverage decision memo.

Sincerely,

Michael A. Carome, M.D.
Deputy Director

Sidney M. Wolfe, M.D.
Director
Public Citizen Health Research Group

[1] Food and Drug Administration. FDA Draft Briefing Document for the Cardiovascular and Renal Drug Advisory Committee (CRDAC) meeting on October 18, 2010. Webpage 4. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM229326.pdf. Accessed April 11, 2011.

[2] Amgen, Inc. Epogen and Procrit labels. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103234s5199lbl.pdf. Accessed April 11, 2011.

[3] Food and Drug Administration. FDA Draft Briefing Document for the Cardiovascular and Renal Drug Advisory Committee (CRDAC) meeting on October 18, 2010. Webpage 4. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM229326.pdf. Accessed April 11, 2011.

[4] Centers for Medicare &Medicaid Services. 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). Webpage 108. http://www.cms.gov/medicare-coverage-database/shared/handlers/highwire.ashx?url=http://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx@@@NCAId$$$245***ver$$$4***NcaName$$$Erythropoiesis+Stimulating+Agents+(ESAs)+for+Treatment+of+Anemia+in+Adults+with+CKD+Including+Patients+on+Dialysis+and+Patients+not+on+Dialysis***bc$$$BACAAAAAEAAA***&session=ewfmf155k10eedfin1uhcp55&kq=222170812. Accessed April 11, 2011.

[5] Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998;339:584-590.

[6] Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355:2085-2098.

[7] Drüeke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease. N Engl J Med. 2006;355:2071-2084.

[8] Amgen, Inc. Drug label for Epogen and Procrit approved by FDA on December 17, 2007. http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/103234s5163lbl.pdf. Accessed April 11, 2011.

[9] Amgen, Inc. Drug label for Epogen and Procrit approved by FDA on December 17, 2007. http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/103234s5163lbl.pdf. Accessed April 11, 2011.

[10] Pfeffer MA, Burdmann EA, Chen C, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361:2019-2032.

[11] Food and Drug Administration. FDA draft briefing document for the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) meeting on October 18, 2010. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM229326.pdf. Accessed April 12, 2011.

[12] Food and Drug Administration. Transcript of the October 18, 2010 FDA Cardiovascular and Renal Drugs Advisory Committee Meeting. Webpage 18. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM233461.pdf. Accessed April 11, 2011.

[13] Food and Drug Administration. Transcript of the October 18, 2010 FDA Cardiovascular and Renal Drugs Advisory Committee Meeting. Webpages 34-35. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM233461.pdf. Accessed April 11, 2011.

[14] Food and Drug Administration. Transcript of the October 18, 2010 FDA Cardiovascular and Renal Drugs Advisory Committee Meeting. Webpage 113. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM233461.pdf. Accessed April 11, 2011.

[15] Food and Drug Administration. Transcript of the October 18, 2010 FDA Cardiovascular and Renal Drugs Advisory Committee Meeting. Webpages 145-146. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM233461.pdf. Accessed April 11, 2011.

[16] Food and Drug Administration. Transcript of the October 18, 2010 FDA Cardiovascular and Renal Drugs Advisory Committee Meeting. Webpage 130. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM233461.pdf. Accessed April 11, 2011.
[17] Food and Drug Administration. Transcript of the October 18, 2010 FDA Cardiovascular and Renal Drugs Advisory Committee Meeting. Webpage 132. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM233461.pdf. Accessed April 11, 2011.
[18] Food and Drug Administration. Transcript of the October 18, 2010 FDA Cardiovascular and Renal Drugs Advisory Committee Meeting. Webpage 132. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM233461.pdf. Accessed April 11, 2011.
[19] Food and Drug Administration. Transcript of the October 18, 2010 FDA Cardiovascular and Renal Drugs Advisory Committee Meeting. Webpage 133. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM233461.pdf. Accessed April 11, 2011.
[20] Food and Drug Administration. Transcript of the October 18, 2010 FDA Cardiovascular and Renal Drugs Advisory Committee Meeting. Webpage 211. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM233461.pdf. Accessed April 11, 2011.
[21] Food and Drug Administration. Transcript of the October 18, 2010 FDA Cardiovascular and Renal Drugs Advisory Committee Meeting. Webpage 239. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM233461.pdf. Accessed April 11, 2011.
[22] 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. http://www.usrds.org/2010/pdf/v2_11.pdf. Accessed April 13, 2011.
[23] Tonelli M, Winkelmayer WC, Jindal KK et al. The cost-effectiveness of maintaining higher hemoglobin targets with erythropoietin patients. Kidney Int. 2003;64:295-304.