



MEDICAL TECHNOLOGY

June 15, 2009

Barry M. Straube, MD
Director and Chief Clinical Officer
Office of Clinical Standards and Quality
Centers for Medicare & Medicaid Services
7500 Security Boulevard Mail Stop S3-02-01
Baltimore, MD 21244

RE: Request for a National Coverage Determination(NCD) for Recombinant human erythropoietin (rHuEPO, or epoetin) for treatment of chronic kidney disease and dialysis related anemia

Dear Dr. Straube:


I am president of MTPPI (www.mtppi.org), a 501(c)3 non-profit institute established in 1986 to conduct assessments of the clinical effectiveness of new healthcare technologies. *I am requesting that CMS undertake request for a National Coverage Determination (NCD) for recombinant human erythropoietin (rHuEPO, or epoetin) for treatment of chronic kidney disease related anemia.* I have enclosed supplemental materials that address the requisite issues related to the conduct of an NCD.

With regard to epoetin therapy, we have extensively studied and published the causal relationship between treatment and both surrogate and clinical outcomes. In over two decades of research on this issue, we have concluded that epoetin therapy offers benefit to those who would otherwise be transfusion dependent, but more importantly, creates cardiovascular-mortality risks to those targeted to high hematocrit levels as well as those who are exposed to large epoetin doses. Our findings are consistent with Ms. DeParle's (HCFA Administrator) March 13, 1998 letter to Senator Specter where she states, "In fact, there was evidence of the potential for harm to patients with cardiac conditions if hematocrits were maintained above that range [FDA's 30-36% hematocrit target]." This conclusion has been sustained by valid studies since 1998.

CMS' Monitoring of Erythropoietin Stimulating Agents for Beneficiaries with End Stage Renal Disease (January 2008) creates a perverse financial incentive to treat dialysis patients to high hematocrit levels and use large epoetin doses. This monitoring policy does not adequately address the safety concerns documented by clinical trials and valid observational studies. Therefore, a NCD is justified and will ultimately lead to improved patient outcomes while reducing Medicare costs.

I am available for a meeting or conference call to discuss this issue, should you feel it necessary. Please let us know if you need any further information. Thank you for your consideration of this request.

Sincerely,


Dennis Cotter
President

cc: Secretary Kathleen Sebelius, DHHS; Jeanne Lambrew, Ph.D., Director of the HHS Office of Health Reform, DHHS; Nancy-Ann DeParle, J.D., Director, The White House Office of Health Reform

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Supporting documentation:

—A full and complete description of the item or service in question.

Recombinant human erythropoietin (rHuEPO, or epoetin) for treatment of dialysis related anemia has been covered by Medicare since its FDA approval, in June 1989, as a treatment to avoid use of red blood cell transfusions.

—A specific, detailed description of the proposed use of the item or service, including the target Medicare population and the medical condition(s) for which it can be used.

Prior to availability of epoetin, blood units were frequently administered to approximately 10% of the ESRD patients (another 6% received an occasional blood unit for mild anemia). The remaining 84% of patients did not receive blood unit infusion for treatment of anemia. Epoetin therapy was intended for patients who were blood-transfusion dependent to avoid the need for frequent blood transfusions. However, by 2005, 99% of in-center hemodialysis patients received epoetin treatment although there are no reported valid studies that support the broader use among the non-transfusion dependent hemodialysis patient population. Another issue that has caused much confusion in the use of Epoetin therapy has been the target hematocrit for treatment. No reported valid studies have supported an appropriate hematocrit target, although clinical trials (cited below) have determined that targeting above 36% might not be safe.

—A compilation of the supporting medical and scientific information currently available that measures the medical benefits of the item or service. This may include portions of primary study data that have been separately submitted to the FDA as part of its submission package and are deemed most relevant for our review.

Over a year has passed since FDA issued a Black-Box warning related to aggressive use of Epoetin agents to raise hemoglobin to a target of 12 g/dL or higher, noting an associated with "serious and life-threatening side-effects and/or death." Contained in the warning was also a call to use the lowest possible dose to slowly raise the hemoglobin to the lowest level that will avoid the need for a blood transfusion. Although these warnings applied to both the cancer and renal failure indications, the preponderance of evidence of misuse and inappropriate use was based on cancer indication study results. The results related to the renal failure population are summarized below in Table 1.

Table 1. Summary of Ad Hoc and Observational Study Findings

Study	High vs. Low Dose/wk, Target Hct	CV-Mortality Risk (high dose or Hct)
NHT (1998) ^a	30,000U vs 10,000U, 42 vs. 30%	HR for high-Hct arm 1.28
CHOIR (2006) ^b	12,000U vs 5,000U, 42 vs. 33%	HR for high-Hct arm 1.47
CREATE (2006) ^c	5,000U vs 2,000U, 42 vs. 33%	HR for high-Hct arm 1.51
Re-CHOIR (2008) ^d	12,000U vs 5,000U, 42 vs. 33%	HR for high-Dose arm 1.57
MTPPI (2009) ^e	40,000U, controlled for Hct	HR > 40,000u/wk 1.26

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Current Medicare epoetin policies are not evidence-based and instead are heavily weighted to accommodate hematocrit variability. These policies also promote and facilitate potential overuse of Epoetin therapy in the renal failure population.

—If the requestor has submitted an application to the FDA for market approval of the product for which coverage is sought, then a copy of the “integrated summary of safety data” and “integrated summary of effectiveness data,” or the combined “summary of safety and effectiveness data,” portions of the FDA application should be included in the request for an NCD. These documents will ensure that our review is comprehensive.

NOT APPLICABLE.

—An explanation of the design, purpose, and method of using the item or equipment, including whether the item or equipment is for use by health care practitioners or patients.

Epoetin therapy is intended to be used by health care practitioners (not patients) and administered either via intravenous or subcutaneous routes of administration.

—A statement from the requestor (in cases in which there is an aggrieved party, the statement must be from that party) containing the following:

++An explanation of the relevance of the evidence selected.

The referenced RCTs, post hoc analysis, and our observational study cited in Table 1 are the only known valid evidence of risk related to epoetin therapy in the renal failure population.

++Rationale for how the evidence selected demonstrates the medical benefits for the target Medicare population.

Other than studies cited by FDA in support of epoetin's effectiveness in elevating hematocrit to avoid transfusions, there are no known valid studies of reported benefit.

++Information that examines the magnitude of the medical benefit.

USRDS reports “the use of transfusions in the outpatient setting has dropped dramatically. In the late 1970s and early 1980s, 15–19 percent of hemodialysis patients received at least one transfusion in a three-month period. This number fell after the introduction of EPO, and since the middle of 2002 has been at less than 1 percent.”

++Reasoning for how coverage of the item or service will help improve the medical benefit to the target population.

Similar to CMS' NCD for Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions, the requested NCD should clarify the extent of epoetin coverage for dialysis related

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anemia, a safe hematocrit target, and a safe epoetin dose in relation to improved patient outcomes.

++In the case of an aggrieved party, how that party is “in need” of the item or service.

By 2005, about 99% of all hemodialysis patients received epoetin. In the case of epoetin, unwarranted access and large doses are the concern, particularly in light of known risks related to epoetin therapy.

—A description of any clinical trials or studies currently underway that might be relevant to a decision regarding coverage of the item or service.

The referenced RCTs, post hoc analysis, and our observational study cited in Table 1 are the only known valid evidence of risk related to epoetin therapy. The TREAT study, currently underway, is designed to determine the impact of anemia therapy with darbepoetin alfa on mortality and nonfatal cardiovascular events in patients with CKD and type 2 diabetes mellitus. It will look at no epoetin treatment versus epoetin treatment targeted to high hemoglobin levels.^f

—Information involving the use of a drug or device subject to FDA regulation as well as the status of current FDA regulatory review of the drug or device involved. An FDA regulated article would include the labeling submitted to the FDA or approved by the FDA for that article, together with an indication of whether the article for which a review is being requested is covered under the labeled indication(s). (We recognize that the labeling on FDA-approved products sometimes changes. For purposes of our review, we are interested in the labeled indications at the time a requestor submits a formal request. If, during our review, the labeled indication or status of a pending FDA approval or clearance changes, we expect the requestor to notify us.)

FDA approved (11-19-08) epoetin labeling can be found at:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/103234s5195Medguide.pdf

—In the case of items that are eligible for a 510(k) clearance by the FDA, identification of the predicate device to which the item is claimed to be substantially equivalent.

NOT APPLICABLE

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Attachment A

**MTPPI Epoetin Research Activities
1991-2009**

Background

Since 1991, MTPPI (www.mtppi.org) has engaged in a multi-year project that has amassed CMS data on over one million ESRD patients to examine epoetin therapy; *a service intended to treat blood transfusion dependent dialysis patients (~10-30% of the ESRD patient pool) is provided to virtually all dialysis patients, costing Medicare in excess of \$20 billion and ESRD patients over \$4 billion since 1989.* This research has produced 14 publications and numerous presentations to public agencies and professional groups (listed below). The long-term study, entitled "Human Recombinant Erythropoietin Utilization in the Medicare Patient Populations," provided an ongoing opportunity, originally using HCFA REBUS and now USRDS Medicare claims data. In conducting this research, we have worked closely with MTPPI's Technical Advisory Committee (TAC, see Attachment B), first convened June 1992, and commissioned to examine access, utilization and costs of epoetin therapy among the U.S. ESRD population. The eighteenth gathering of this group, was comprised of nationally recognized nephrologists, Federal agency representatives (CMS, FDA, NCI, NHLBI, NIDDK, VA, & others) and private sectors groups (ESRD Network, RPA, and others). Currently there is no outside sponsorship of the TAC. Between 1991-98 Ortho Biotech sponsored the research effort and 2004-06 the research was partially funded by an NIDDK grant.

Publications related to our long-term study:

10. Thamer M, Ray NF, Richard C, Greer JW, Pearson BC, Cotter DJ. Excluded from universal coverage: ESRD patients not covered by Medicare. *Health Care Financ Rev.* 1995 Winter;17(2):123-46.
11. Thamer, Mae; Richard, C., Ray, N.F., Greer J., Cotter, D.J., Pearson, B: "The Effect of Insurance Status on Recombinant Erythropoietin Therapy in Three States." *American Journal of Kidney Diseases* 1996;28:235-49.
12. Cotter, D.J., Thamer, M, Kimmel, PL, Sadler, JH: "Secular Trends in Recombinant Erythropoietin Therapy Among the U.S. Hemodialysis Population: 1990 - 1996." *Kidney International* 1998;54:2129-39.
13. Thamer M, Richard CM, Klinkmann J, Ivanovich P, Lang G, Cotter DJ. Use of clinical guidelines for treatment of anemia among hemodialysis patients. *Artif Organs.* 2000 Feb;24(2):91-4.
15. Cotter, D.J., Stefanik K, Zhang Y, Thamer M. Improved survival with higher hematocrits: where is the evidence? *Semin Dial.* 2004 May-Jun;17(3):181-3.
16. Cotter, D.J., Stefanik K, Zhang Y, Thamer M, Scharfstein D, Kaufman J, Evaluation of Hematocrit as a Surrogate Endpoint for Survival Among Epoetin-Treated Hemodialysis Patients. *J Clin Epidemiol, J Clin Epidemiol.* 2004 Oct;57(10):1086-95.
17. Cotter, D.J. Challenges in Establishing a Clinically and Scientifically Robust Epoetin Policy, *Clin Nephrol* 2004 Jul;62(1):69-70.
18. Zhang Y, Thamer M, Stefanik K, Kaufman J, Cotter DJ. Epoetin requirements predict mortality in hemodialysis patients. *Am J Kidney Dis.* 2004 Nov;44(5):866-76.

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19. Zhang Y, Thamer M, Stefanik K, Cotter DJ. Does dose matter? *Nephrol Dial Transplant*. 2004 Jun;19(6):1658;
20. Yi Zhang, Mae Thamer, Firas Marayati, Dennis J. Cotter, James Kaufman, Factors Influencing Route of Administration for Epoetin Treatment Among Hemodialysis Patients in the United States, *Am J Kidney Dis*. 2006 Jul;48(1):77-87
21. Cotter D, Thamer M, Narasimhan K, Zhang Y, Bullock K. Translating epoetin research into practice: the role of government and the use of scientific evidence. *Health Aff (Millwood)*. 2006 Sep-Oct;25(5):1249-59.
22. Thamer M, Zhang Y, Kaufman J, Dong F, Cotter D, Hernan MA Dialysis Facility Ownership and Epoetin Dosing in Patients Receiving Hemodialysis *JAMA*, 2007 Apr 18;297(15):1667-74.
23. Cotter D, Thamer M, Zhang Y, Kaufman J, Hernan MA The Effect of Epoetin Dose on Hematocrit, *Kidney Int*. 2007 Oct;72(8):1247.
24. Zhang Y, Thamer M, **Cotter D**, Kaufman J, Hernan MA "The Estimated Effect of Epoetin Dose on Survival among Elderly Hemodialysis Patients in the United States " *Clin J Am Soc Nephrol*. March 1 2009, Volume 4, Issue 3

Letters To-the-editor:

1. Cotter DJ. Is the evidence for high hematocrit targets valid? *Am J Kidney Dis*. 2003 Feb;41(2):520.
2. Cotter D. Does the evidence for anemia treatment support a survival benefit? *Arch Intern Med*. 2003 Oct 27;163(19):2395-6; author reply 2396-7.
3. Zhang Y, Thamer M, Stefanik K, Cotter DJ. Does dose matter? *Nephrol Dial Transplant*. 2004 Jun;19(6):1658; author reply 1658-9.
4. Cotter D, To the editor: The December 2006 issue of *NN&I* contained a letter to the editor and excerpts from a position paper attacking our policy paper published in *Health Affairs*. *Nephrology News & Issues*, February 2007, pgs 12 & 17.
5. Mae Thamer; Yi Zhang; Dennis J. Cotter; James Kaufman; Miguel A. Hernán Epoetin Dosing and Dialysis Facility Ownership—Reply *JAMA*, August 22/29, 2007; 298: 862.
6. Thamer M, Zhang Y, Kaufman J, Dong F, Cotter D, Hernan MA In the literature: Dialysis facility ownership and epoetin dosing in patients receiving hemodialysis – the authors respond, *Am J Kid Dis*, 50(4) October 2007 538-541.
7. Cotter D, Thamer, M Zhang, Y To the editor: Exploring Relative Mortality and Epoetin Alfa Dose Among Hemodialysis Patients: A Researcher's Perspective, The Challenge of Analyzing the Effect of Epoetin Dose Levels *Am J Kid Dis*, 2008 accepted.
8. Cotter D, Zhang Y, Thamer M, Kaufman J, Hernan MA Response to "The Effect of Epoetin Dose on Hematocrit " *Kidney Int*. 2008 Sep;74(6):827-8.

MTPPI EPO Presentations to Federal Agencies:

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FDA - Presentation to Drs. Richard Pazdur, Karen Weiss, Dwaine Rieves and staff: Preliminary Epoetin Research Findings, March 07, 2007; Presentation to Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, September 11, 2007. *accessible at:* http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4315s1-03-MTPPI-Cotter_files/frame.htm

CDER Seminar on Epoetin Safety and Product Labeling, February 27, 2009

NIH/NIDDK Seminar Epoetin therapy: Steps to the future, March 12, 2009

CMS - Presentation to Drs. Straube and Phurrough and staff: Preliminary Epoetin Research Findings, April 03, 2007

Congress/GAO - Presentation to Bruce Steinwald and staff, Preliminary Epoetin Research Findings, March 2007; Beneficiary Differences in Medicare Treatment and Payment for Beneficiaries with End-Stage Renal Disease (ESRD) Interview Questions December 16, 2008; Bundling of Epoetin into the ESRD Composite Rate Payment, March 3, 2009

Congress/MedPAC - Presentation to Mark E. Miller, Nancy Ray and staff: Achieving Equity Should Epoetin Become a Component of the ESRD Composite Rate, February 01, 2007; Bundling of Epoetin into the ESRD Composite Rate Payment, March 3, 2009

Congress - The Committee on Ways and Means, Hearing on Patient Safety and Quality Issues in End Stage Renal Disease Treatment, December 6, 2006 *accessible at:* <http://waysandmeans.house.gov/hearings.asp?formmode=view&id=5371> - Staffs of: House The Energy and Commerce Committee and Committee on Ways and Means and Senate Committee on Finance presentation on Seminar on Epoetin Safety and Bundling of Epoetin into the ESRD Composite Rate Payment, March 3, 2009



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- a. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA. 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 Aug 27;339(9):584-90.
- b. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med.* 2006 Nov 16;355(20):2085-98.
- c. Drüeke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, Burger HU, Scherhag A; CREATE Investigators. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med.* 2006 Nov 16;355(20):2071-84.
- d. Szczech LA, Barnhart HX, Inrig JK, Reddan DN, Sapp S, Califf RM, Patel UD, Singh AK. Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. *Kidney Int.* 2008 Sep;74(6):791-8.
- e. Use of Medicare Claims Data to Detect Risk Signals in Anemia Treatment – an Evolving Risk Assessment & Post Market Surveillance Approach, MTPPI Seminar presented to the Office of Oncology Drug Products, the Center for Drug Evaluation and Research, FDA, Presented by MTPPI, Friday, February 27, 2009
- f. Mix TC, Brenner RM, Cooper ME, et al. Rationale--Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT): evolving the management of cardiovascular risk in patients with chronic kidney disease. *Am Heart J.* 2005;149(3):408-13.