

**Regence BlueCross BlueShield of Oregon • Regence BlueShield
Regence BlueCross BlueShield of Utah • Regence BlueShield of Idaho
Independent licensees of the Blue Cross and Blue Shield Association**

Medication Policy Manual

Policy No: dru076

Topic: Aranesp[®], darbepoetin

Date of Origin: September 13, 2002

Revised Date: May 9, 2008

Next Review Date: May 2009

Effective Date: September 15, 2008

IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Darbepoetin is long-acting form of epoetin alfa (erythropoietin), a man-made protein that stimulates the production of red blood cells to treat anemia.

Policy/Criteria

I. Most contracts require prior authorization approval of darbepoetin prior to coverage. Darbepoetin may be considered medically necessary for the treatment of:

A. Anemia (hemoglobin less than 12 g/dL), associated with chronic kidney disease (CKD) when:

1. Darbepoetin is prescribed by a nephrologist.

OR

2. There is a diagnosis of Stage 3, 4 or 5 CKD as defined by the National Kidney Foundation.

OR

B. Anemia (hematocrit less than 30%) in AZT-treated HIV infected patients when the dose of AZT is equal to or less than 4,200 mg per week.

OR

C. Anemia of chronic disease (characterized by hemoglobin less than 10 g/dL or hematocrit less than 30%) if:

1. The patient's own erythropoietin levels are equal to or less than 500 mU/ml;

AND

2. Patient's transferrin saturation is at least 20% and ferritin at least 100 ng/mL.

OR

D. Anemia (hemoglobin less than 10 g/dL or hematocrit less than 30%) when prescribed by an oncologist or hematologist for members currently receiving chemotherapy (current is defined as chemotherapy administration within the past 8 weeks).

OR

E. Anemia (characterized by hemoglobin less than 10 g/dL or hematocrit less than 30%) associated with myelodysplastic syndrome (MDS).

II. The dose of darbepoetin may be increased up to a total dose of 4.5 mcg/kg/wk for chemotherapy patients who experience less than a 1.0 g/dL increase in hemoglobin after 6 weeks of therapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence considers darbepoetin to be a self-administered medication or a medication that is administered in the provider office or hospital setting.

B. When prior authorization is approved, darbepoetin may be authorized in doses up to 4.5 mcg/kg/week (or 500 mcg every 3 weeks).

C. Authorization may be reviewed at least once per treatment period or every six months, whichever is less, to confirm that the patient's recent (within the last 60 days) hemoglobin is less than 12 g/dL.

IV. Darbepoetin is considered not medically necessary for all other conditions, including, but not limited to:

A. Any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis.

B. Anemia associated with the treatment of acute and chronic myelogenous leukemias (AML, CML) or erythroid cancers.

C. Anemia of cancer not related to cancer treatment.

D. Any anemia associated only with radiotherapy.

E. Prophylactic use to prevent chemotherapy-induced anemia.

F. Prophylactic use to reduce tumor hypoxia.

G. Patients with erythropoietin-type resistance due to neutralizing antibodies.

Position Summary

- Erythropoietic-stimulating agents (ESAs) increase the risk for death and serious cardiovascular events when administered to target a hemoglobin of greater than 12 g/dL. ^[1]
- A higher incidence of deep venous thrombosis was documented in patients receiving epoetin alfa who were not receiving prophylactic anticoagulation. ^[1]
- These products have not been shown to improve or relieve the symptoms of anemia, nor to improve quality of life in patients with cancer.
- The key safety issues that led to the new black box warnings of 2007 on ESA products were:
 - * Increased risk of thromboembolic events (MI, stroke, DVT, etc.)
 - * Increased risk of death
 - * Tumor progression
- The risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to target a hemoglobin of < 12 g/dL. ^[1]
- Prior to initiation of therapy and during therapy, the patient's iron stores should be evaluated. Transferrin saturation should be at least 20% and ferritin at least 100 ng/mL.
- Blood pressure should be adequately controlled prior to initiation of therapy, and must be closely monitored and controlled during therapy.

Myelodysplastic Syndrome (MDS)

- The actions of darbepoetin are similar to erythropoietin. Both stimulate the production of red blood cells. It is likely that darbepoetin will work in MDS.
- Anemia of MDS is an FDA off-label use. It is not included in the July 2007 CMS Coverage Decision Memorandum for the Use of Erythropoiesis Stimulating Agents in Cancer and Related Neoplastic Conditions. In the final rule CMS declared that MDS is not a neoplastic condition, and therefore exempt from the ruling.

Dialysis and End Stage Renal Disease

- Darbepoetin is FDA approved for the treatment of anemia associated with chronic renal failure, and anemia in patients with non-myeloid cancers where anemia is due to the concomitantly administered chemotherapy. ^[1] The actions of darbepoetin are similar to erythropoietin. Both stimulate the production of red blood cells.
- The benefits of increasing hematocrit values from below 30 percent to 30 to 38 percent in patients undergoing dialysis with darbepoetin include a decrease in the need for transfusion and an improvement in the quality of life, cognitive function, cardiac function, exercise capacity, and immune function. ^[1-23]
- In retrospective studies, the mortality rate among patients with hematocrits below 30 percent was higher than that among patients with hematocrits of 30 to 35 percent. Hematocrits in excess of 35 to 42% were not associated with greater improvements. ^[24-26]
- Retrospective analysis has demonstrated that erythropoietin is associated with a decrease in morbidity and mortality in patients with end-stage renal disease. ^[27]
- Practice guidelines by the National Kidney Foundation for treatment of anemia associated with chronic kidney disease recommend maintaining hematocrit between 33% and 36%. ^[28]
- While uncontrolled observational studies had suggested that improving hemoglobin levels in patients with ESRD with erythropoietins might improve cardiac function, double-blind, randomized controlled trials have not found a causal relationship. ^[66-69]
- Extended dosing schedules (up to every 4 weeks) of epoetin appear to be safe and effective for maintaining hemoglobin in patients with chronic kidney disease. ^[71-72]

Cancer

- Administration of erythropoietin has been shown to increase hemoglobin levels and reduce the numbers of transfusions in patients with non-myeloid malignancies who receive concomitant chemotherapy. ^[29-52,72]
- In several studies, approximately 50% of anemic patients receiving chemotherapy alone required transfusions as compared to approximately 20-25% of patients who received ESAs concurrently with chemotherapy. NNT = 4.9 (95% CI 4.1, 6.1) ^[82]

- Administration of erythropoietins in larger doses less frequently generally results in similar clinical responses. [59,60,72]
- Doses of erythropoietins larger than recommended in the approved product labeling have been studied, but there is no direct useful evidence that these doses improve patient outcomes. [61,72]
- Head-to-head trials between epoetin and darbepoetin generally find little, if any, differences in clinical responses between the two agents. [62-64,72]

Safety

- ESAs increased the risk of death when administered to target a hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for this population.^[1]
- Patients with uncontrolled hypertension should not be treated with darbepoetin alfa; blood pressure should be controlled adequately before initiation of therapy. Blood pressure may rise during treatment of anemia with darbepoetin alfa or epoetin. In darbepoetin alfa clinical trials, approximately 40% of patients with chronic renal failure (CRF) required initiation or intensification of antihypertensive therapy during the early phase of treatment when the hemoglobin was increasing. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with darbepoetin alfa or epoetin.

References

1. Aranesp[®] (darbepoetin alpha) Product Information. Amgen Inc. Thousand Oaks, CA, March 2008..
2. Mahajan S, Boulton H, Gokal R. A trial of subcutaneous administration of darbepoetin alfa once every other week for the treatment of anemia in peritoneal dialysis patients. *J Nephrology* 2004;17(5):687-92.
3. Toto RD, Pichette V, Navarro J, Brenner R, Carroll W, Liu W, Roger S. Darbepoetin alfa effectively treats anemia in patients with chronic kidney disease with de novo every-other-week administration. *Am J Nephrology* 2004;24(4):453-60.

4. Jadoul M, Vanrenterghem Y, Foret M, Walker R, Gray SJ. Darbepoetin alfa administered once monthly maintains hemoglobin levels in stable dialysis patients. *Nephrology Dial Transplant* 2004;19:898-903.
5. Brunkhorst R, Bommer J, Braun J, Haag-Weber M, Gill C, Wagner J, Wagener T, for the German Aranesp Study Group. Darbepoetin alfa effectively maintains hemoglobin concentrations at extended dose intervals relative to intravenous or subcutaneous recombinant human erythropoietin in dialysis patients. *Nephrology Dial Transplant* 2004;19:1224-30.
6. Macdougall IC, Matcham J, Gray SJ for the NESP 960245/246 Study Group. Correction of anemia with darbepoetin alfa in patients with chronic kidney disease receiving dialysis. *Nephrology Dial Transplant* 2003;18:576-81.
7. Vanrenterghem Y, Barany P, Mann JF, Kerr PG, Wilson J, Baker NF, Gray SJ, for the European/ Australian NESP 970200 Study Group. Randomized trial of darbepoetin alfa for treatment of renal anemia at a reduced dose frequency compared with rHuEPO in dialysis patients. *Kidney International* 2002;62:2167-75.
8. Allon M, Kleinman K, Walczyk M, Kaupke C, Messer-Mann L, Olson K, et al. Pharmacokinetics and pharmacodynamics of darbepoetin alfa and epoetin in patients undergoing dialysis. *Clin Pharmacol Ther* 2002;72:546-55.
9. Nissenson AR, Swan SK, Lindberg JS, Soroka SD, Beatey R, Wang C, et al. Randomized, controlled trial of darbepoetin alfa for the treatment of anemia in hemodialysis patients. *Am J Kid Dis* 2002;40:110-8.
10. Eschbach JW, Abdulhadi MH, Browne JK, Delano BG, Downing MR, Egrie JC, et al. Recombinant human erythropoietin in anemic patients with end-stage renal disease: results of a phase III multicenter clinical trial. *Ann Internal Medicine* 1989;111:992-1000.
11. Evans RW, Rader B, Manninen DL. Cooperative Multicenter EPO Clinical Trial Group. The quality of life of hemodialysis recipients treated with recombinant human erythropoietin. *JAMA* 1990;263:825-30.
12. Beusterien KM, Nissenson AR, Port FK, Kelly M, Steinwald B, Ware JE Jr. The effects of recombinant human erythropoietin on functional health and well-being in chronic dialysis patients." *J Am Society Nephrology* 1996;7:763-73.

13. Marsh JT, Brown WS, Wolcott D, Carr CR, Harper R, Schweitzer SV, et al. rHuEPO treatment improves brain and cognitive function of anemic dialysis patients. *Kidney International* 1991;39:155-63.
14. Macdougall IC, Lewis NP, Saunders MJ, Cochlin DL, Davies ME, Hutton RD, et al. Long-term cardio-respiratory effects of amelioration of renal anemia by erythropoietin. *Lancet* 1990;335:489-93.
15. Wizemann V, Kaufmann J, Kramer W. Effect of erythropoietin on ischemia tolerance in anemic hemodialysis patients with confirmed coronary artery disease. *Nephron* 1992;62:161-5.
16. Cannella G, La Canna G, Sandrini M, Gaggiotti M, Nordio G, Movilli E, et al. Reversal of left ventricular hypertrophy following recombinant human erythropoietin treatment of anemic dialyzed uremic patients. *Nephrology Dial Transplant* 1991;6:31-7.
17. Pascual J, Teruel JL, Moya JL, Liano F, Jimenez-Mena M, Ortuno J. Regression of left ventricular hypertrophy after partial correction of anemia with erythropoietin in patients on hemodialysis: a prospective study. *Clin Nephrol* 1991;35:280-7.
18. Zehnder C, Zuber M, Sulzer M, Meyer B, Straumann E, Jenzer HR, et al. Influence of long-term amelioration of anemia and blood pressure control on left ventricular hypertrophy in hemodialyzed patients. *Nephron* 1992;61:21-5.
19. Lundin AP, Akerman MJ, Chesler RM, Delano BG, Goldberg N, Stein RA, et al. Exercise in hemodialysis patients after treatment with recombinant human erythropoietin. *Nephron* 1991;58:315-9.
20. Braumann KM, Nonnast-Daniel B, Boning D, Bocker A, Frei U. Improved physical performance after treatment of renal anemia with recombinant human erythropoietin. *Nephron* 1991;58:129-34.
21. Veys N, Vanholder R, Ringoir S. Correction of deficient phagocytosis during erythropoietin treatment in maintenance hemodialysis patients. *Am J Kid Dis* 1992;19:358-63.
22. Sennesael JJ, Lamote JG, Violet I, Tasse S, Verbeelen DL. Treatment with recombinant human erythropoietin increases antibody titers after hepatitis B vaccination in dialysis patients. *Kidney Int* 1991;40:121-8.

23. Goldberg N, Lundin AP, Delano B, Friedman EA, Stein RA. Changes in left ventricular size, wall thickness, and function in anemic patients treated with recombinant human erythropoietin. *Am Heart J* 1992;124:424-7.
24. Collins A, Ma J, Umen A. Hematocrit as a time-dependent risk factor. *J Am Society Nephrology* 1994;5:429 (abstract).
25. Lowrie EG, Ling J, Lew NL. The anemia of ESRD and related thoughts about iron and EPO therapy. Waltham, Mass.: National Medical Care, August 10, 1995 (memorandum).
26. Besarab A, Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, 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;339:584-90.
27. Tsakiris D. Morbidity and mortality reduction associated with use of erythropoietin. *Nephron* 2000;85(suppl1):2-8.
28. National Kidney Foundation KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease, 2007 Update of Hemoglobin Target. *Am J Kidney Dis.* 2007 Sep;50(3):471-530.
29. Schwartzberg LS, Yee LK, Senecal FM, Charu V, Tomita D, Wallace J, Rossi G. A randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia in patients with breast, lung, or gynecologic cancer. *Oncologist* 2004;9:696-707.
30. Hesketh PJ, Arena F, Patel D, Austin M, D'Avirro P, Rossi G, et al. A randomized controlled trial of darbepoetin alfa administered as a fixed or weight-based dose using a front-loading schedule in patients with anemia who have non-myeloid malignancies. *Cancer* 2004;100:859-68.
31. Vansteenkiste J, Tomita D, Rossi G, Pirker R. Darbepoetin alfa in lung cancer patients on chemotherapy: a retrospective comparison of outcomes in patients with mild versus moderate-to-severe anemia at baseline. *Support Care Cancer* 2004;12:253-62.
32. Kotasek D, Steger G, Faught W, Underhill C, Poulsen E, Colowick AB, et al. for the Aranesp 980291 Study Group. Darbepoetin alfa administered every 3 weeks alleviates anemia in patients with solid tumors receiving chemotherapy; results of a double-blind, placebo-controlled, randomized study. *Eur J Can* 2003;39:2026-34.

33. Hedenus M, Adriansson M, San Miguel J, Kramer MH, Schipperus MR, Juvonen E, et al. for the Darbepoetin Alfa 20000161 Study Group. Efficacy and safety of darbepoetin alfa in anemic patients with lymphoproliferative malignancies: a randomized, double-blind, placebo-controlled study. *Br J Hematol* 2003;122:394-403.
34. Tchekmedyian NS, Kallich J, McDermott A, Fayers P, Erder MH The relationship between psychological distress and cancer-related fatigue. *Cancer* 2003;98:198-203.
35. Smith RE Jr., Tchekmedyian NS, Chan D, Meza LA, Northfelt DW, Patel R, et al. A dose- and schedule-finding study of darbepoetin alpha for the treatment of chronic anemia of cancer. *Br J Cancer* 2003;88:1851-8.
36. Steurer M, Sudmeier I, Stauder R, Gastl G. Thromboembolic events in patients with myelodysplastic syndrome receiving thalidomide in combination with darbepoetin-alpha. *Br J Hematology* 2003;121:101-3.
37. Glaspy JA, Jadeja JS, Justice G, Fleishman A, Rossi G, Colowick AB. A randomized, active-control, pilot trial of front-loaded dosing regimens of darbepoetin-alfa for the treatment of patients with anemia during chemotherapy for malignant disease. *Cancer* 2003;97:1312-20.
38. Vansteenkiste J, Poulsen E, Rossi G, Glaspy J. Darbepoetin alfa: impact on treatment for chemotherapy-induced anemia and considerations in special populations. *Oncology (Huntington)* 2002;16(10 Suppl 11):45-55.
39. Mirtsching B, Charu V, Vadhan-Raj S, Colowick AB, Rossi G, Tomita D, McGuire WP. Every-2-week darbepoetin alfa is comparable to rHuEPO in treating chemotherapy-induced anemia. Results of a combined analysis. *Oncology (Huntington)* 2002;16(10 Suppl 11):31-6.
40. Glaspy JA, Tchekmedyian NS. Darbepoetin alfa administered every 2 weeks alleviates anemia in cancer patients receiving chemotherapy. *Oncology (Huntington)* 2002;16(10 Suppl 11):23-9.
41. Hedenus M, Hansen S, Taylor K, Arthur C, Emmerich B, Dewey C, et al. for the Darbepoetin alfa 990114 Study Group. Randomized, dose-finding study of darbepoetin alfa in anemic patients with lymphoproliferative malignancies. *Br J Hematol* 2002;119:79-86.
42. Vansteenkiste J, Pirker R, Massuti B, Barata F, Font A, Fiegl M, et al. for the Aranesp 980297 Study Group. Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. *J National Cancer Institute* 2002;94:1211-20.

43. Glaspy JA, Jadeja JS, Justice G, Kessler J, Richards D, Schwartzberg L, et al. Darbepoetin alfa given every 1 or 2 weeks alleviates anemia associated with cancer chemotherapy. *Br J Cancer* 2002;87:268-76.
44. Smith RE Jr., Jaiyesimi IA, Meza LA, Tchekmedyian NS, Chan D, Griffith H, et al. Novel erythropoiesis stimulating protein (NESP) for the treatment of anemia of chronic disease associated with cancer. *Br J Cancer* 2001;84(Suppl 1):24-30.
45. Glaspy J, Jadeja JS, Justice G, Kessler J, Richards D, Schwartzberg L, et al. A dose-finding and safety study of novel erythropoiesis stimulating protein (NESP) for the treatment of anemia in patients receiving multicycle chemotherapy. *Br J Cancer* 2001;84 (Suppl 1):17-23.
46. Miller CB, Jones RJ, Piantadosi S, Abeloff MD, Spivak JL, et al. Decreased erythropoietin response in patients with the anemia of cancer. *N Engl J Med* 1990;322:1689-92.
47. Ludwig H, Sundal E, Pecherstorfer M, Leitgeb C, Bauernhofer T, Beinhauer A, et al. Recombinant human erythropoietin for the correction of cancer-associated anemia with and without concomitant cytotoxic chemotherapy. *Cancer* 1995;76:2319-29.
48. Abels R. Erythropoietin for anemia in cancer patients. *Eur J Cancer* 1993;29A(suppl 2):S2-8.
49. Dunphy FR, Harrison BR, Dunleavy TL, Rodriguez JJ, Hilton JG, Boyd JH, et al. Erythropoietin reduces anemia and transfusions after chemotherapy with paclitaxel and carboplatin. *Cancer* 1997;79:1623-8.
50. Plataniias LC, Miller CB, Mick R, Hart RD, Ozer H, McEvelly JM, et al. Treatment of chemotherapy-induced anemia with recombinant human erythropoietin in cancer patients. *J Clin Oncol* 1991; 9:2021-6.
51. Glaspy J, Bukowski R, Steinberg D, Taylor C, Tchekmedyian S, Vadhan-Raj S. Impact of therapy with epoetin alfa on clinical outcomes in patients with non-myeloid malignancies during cancer chemotherapy in community oncology practice. *J Clin Oncol* 1997;15:1218-34.
52. Demetri GD, Kris M, Wade J, Degos L, Cella D. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. *J Clin Oncol* 1998;16:3412-25.

53. Henry DH, Beall GN, Benson CA, Carey J, Cone LA, Eron LJ, et al. Recombinant human erythropoietin in the treatment of anemia associated with human immunodeficiency virus (HIV) infection and zidovudine therapy. Overview of four clinical trials. *Ann Int Med* 1992;117:739-48.
54. Moore RD. Human immunodeficiency virus infection, anemia, and survival. *Clin Inf Dis* 1999;29:44-9.
55. Price TH, Goodnough LT, Vogler WR, Sacher RA, Hellman RM, Johnston MF, et al. The effect of recombinant human erythropoietin on the efficacy of autologous blood donation in patients with low hematocrits: a multicenter, randomized, double-blind, controlled trial. *Transfusion* 1996;36:29-36.
56. De Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. Baseline hemoglobin as a predictor of risk of transfusion and response to Epoetin alfa in orthopedic surgery patients. *Am J Orthopedics* 1996;25:533-42.
57. Weiss G, Goodnough LT. Anemia of Chronic Disease. *N Engl J Med* 2005;352:1011-23.
58. Peeters HR, Jongen-Lavrencic M, Vreugdenhil G, Swaak AJ. Effect of recombinant human erythropoietin on anaemia and disease activity in patients with rheumatoid arthritis and anaemia of chronic disease: a randomized placebo controlled double blind 52 weeks clinical trial. *Ann Rheum Dis* 1996;55:739-44.
59. Canon JL, Vansteenkiste J, Bodoky G, Mateos MV, Bastit L, Ferreira I, et al. Randomized, double-blind, active-controlled trial of every-3-week darbepoetin alfa for the treatment of chemotherapy-induced anemia. *J Natl Cancer Inst.* 2006 Feb 15;98(4):273-84.
60. Steensma DP, Molina R, Sloan JA, Nikcevich DA, Schaefer PL, Rowland KM Jr, et al. Phase III study of two different dosing schedules of erythropoietin in anemic patients with cancer. *J Clin Oncol.* 2006 Mar 1;24(7):1079-89.
61. Justice G, Kessler JF, Jadeja J, Campos L, Weick J, Chen CF, et al. A randomized, multicenter study of subcutaneous and intravenous darbepoetin alfa for the treatment of chemotherapy-induced anemia. *Ann Oncol.* 2005 Jul;16(7):1192-8. Epub 2005 Apr 28.
62. Waltzman R, Croot C, Justice GR, Fesen MR, Charu V, Williams D. Randomized comparison of epoetin alfa (40,000 U weekly) and darbepoetin alfa (200 microg every 2 weeks) in anemic patients with cancer receiving chemotherapy. *Oncologist.* 2005 Sep;10(8):642-50.

63. Senecal FM, Yee L, Gabrail N, Charu V, Tomita D, Rossi G, Schwartzberg L. Treatment of chemotherapy-induced anemia in breast cancer: results of a randomized controlled trial of darbepoetin alfa 200 microg every 2 weeks versus epoetin alfa 40,000 U weekly. *Clin Breast Cancer*. 2005 Dec;6(5):446-54.
64. Reed SD, Radeva JI, Daniel DB, Fastenau JM, Williams D, Schulman KA. Early hemoglobin response and alternative metrics of efficacy with erythropoietic agents for chemotherapy-related anemia. *Curr Med Res Opin*. 2005 Oct;21(10):1527-33.
65. Christodoulakis M, Tsiftsis DD; Hellenic Surgical Oncology Perioperative EPO Study Group. Preoperative epoetin alfa in colorectal surgery: a randomized, controlled study. *Ann Surg Oncol*. 2005 Sep;12(9):718-25. Epub 2005 Jul 28.
66. Levin A, Djurdjev O, Thompson C, Barrett B, Ethier J, Carlisle E, et al. Canadian randomized trial of hemoglobin maintenance to prevent or delay left ventricular mass growth in patients with CKD. *Am J Kidney Dis*. 2005 Nov;46(5):799-811.
67. Parfrey PS, Foley RN, Wittreich BH, Sullivan DJ, Zagari MJ, Frei D. Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. *J Am Soc Nephrol*. 2005 Jul;16(7):2180-9. Epub 2005 May 18.
68. Kirkpantur A, Kahraman S, Yilmaz R, Arici M, Altun B, Erdem Y, et al. The effects of maintenance recombinant human erythropoietin therapy on ambulatory blood pressure recordings: conventional, Doppler, and tissue Doppler echocardiographic parameters. *Artif Organs*. 2005 Dec;29(12):965-72.
69. Ayus JC, Go AS, Valderrabano F, Verde E, de Vinuesa SG, Achinger SG, et al.; Spanish Group for the Study of the Anemia and Left Ventricular Hypertrophy in Pre-dialysis Patients. Effects of erythropoietin on left ventricular hypertrophy in adults with severe chronic renal failure and hemoglobin <10 g/dL. *Kidney Int*. 2005 Aug;68(2):788-95.
70. Sulkowski MS, Dieterich DT, Bini EJ, Brau N, Alvarez D, Dejesus E, et al.; for the HIV/HCV Coinfection Study Group. Epoetin alfa once weekly improves anemia in HIV/hepatitis C virus-coinfected patients treated with interferon/ribavirin: a randomized controlled trial. *J Acquir Immune Defic Syndr*. 2005 Aug 1;39(4):504-6.
71. Provenzano R, Bhaduri S, Singh AK; PROMPT Study Group. Extended epoetin alfa dosing as maintenance treatment for the anemia of chronic kidney disease: the PROMPT study. *Clin Nephrol*. 2005 Aug;64(2):113-23.

72. National Comprehensive Cancer Network (NCCN); Clinical Practice Guidelines in Oncology: Cancer – and Treatment-Related Anemia v.1.2008. Available at: http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf. Accessed on 1/09/2008.
73. Drüeke TB, Locatelli F, Clyne N, Eckarst KU, Macdougall IC, TSakiris D, Burger HU, Scherhag A. Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia. *N Engl J Med*. 2006 Nov 16;355(20):2071-2084. [CREATE trial]
74. Singh AK, Szczech L, Tang KL, et al. Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease. *N Engl J Med*. 2006; 355: 2085-98. [CHOIR trial]
75. Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining Normal Hemoglobin Levels With Epoetin Alfa in Mainly Nonanemic Patients With Metastatic Breast Cancer Receiving First-Line Chemotherapy: A Survival Study. *JCO*. 2005; 23(25): 1-13. [BEST trial]
76. Wright JR, Ung YC, Julian JA, et al. Randomized, Double-Blind, Placebo-Controlled Trial of Erythropoietin in Non-Small-Cell Lung Cancer with Disease-Related Anemia. *JCO*. 2007; 25(9): 1-6.
77. Interim Analysis of DAHANCA 10. Study of the importance of Novel Erythropoiesis Stimulating Protein (Aranesp[®]) for the effect of radiotherapy in patients with primary squamous cell carcinoma of the head and neck. Danish Head and Neck Cancer Group. http://frejacms.au.dk/dahanca/get_media_file accessed March 13, 2007.
78. http://www.clinicalstudyresults.org/documents/company-study_2157_0.pdf, accessed March 13, 2007.
79. Preliminary study analysis of the SPINE trial found at http://download.veritasmedicine.com/PDF/CR004621_ToplineResults.pdf accessed March 16, 2007.
80. Bohlius J, Wilson J, Seidenfeld J, Piper M, Schwarzer G, Sandercock J et al. Erythropoietin or Darbepoetin for patients with cancer. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD003407. DOI: 10.1002/14651858.CD003407.pub4.
81. U.S. Department of Health & Human Services. Centers for Medicare & Medicaid Services. Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N). <http://www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?id=203>. Accessed May 17, 2007.

82. Continuing Reassessment of the Risks of Erythropoiesis-Stimulating Agents (ESAs) Administered for the Treatment of Anemia associated with Cancer Chemotherapy. FDA BRIEFING DOCUMENT May 10, 2007 Oncologic Drugs Advisory Committee. Available at <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4301b2-02-FDA.pdf> accessed May 16, 2007.
83. Rizzo JD, Somerfield MR, Hagerty KL, Seidenfeld J, Bohlius J, Bennett CL, et al. American Society of Clinical Oncology/American Society Of Hematology. 2007 Clinical Practice Guideline Update on the Use of Epoetin And Darbepoetin. *J Clin Oncol*. 2008 Jan 1;26(1):132-49. **AND** *Blood*. 2008 Jan 1;111(1):25-41.

Cross References
Epogen [®] , Procrit [®] , epoetin alfa dru012
<i>Erythropoiesis – Stimulating Agents (ESAs), BlueCross BlueShield Association Medical Policy, #5.01.04, Issue 2/2008.</i>

Codes	Number	Description
HCPCS	J0881	Injection, darbepoetin, (for non-ESRD use), per 1 mcg
HCPCS	J0882	Injection, darbepoetin (for ESRD on dialysis), per 1 mcg

Appendix A: Stages of Chronic Kidney Disease ^[28]

Stage	Description	GFR mL/min/1.73 m ²	Action*
1	Kidney damage with normal or ↑ GFR	≥90	Diagnosis and treatment Treatment of comorbid conditions Slowing progression, CVD risk reduction
2	Kidney damage with mild ↓ GFR	60-89	Estimating progression
3	Moderate ↓ GFR	30-59	Evaluating and treating complications
4	Severe ↓ GFR	15-29	Preparation for kidney transplant therapy
5	Kidney failure	< 15 (or dialysis)	Replacement (if uremia present)

Chronic kidney disease is defined as either kidney damage OR GFR less than 60mL/min/1.73 m² for more than 3months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

* Includes actions from preceding stages.

Abbreviations:

GFR: glomerular filtration rate

CVD: cardiovascular disease