Epoetin and Darbepoetin

ACG: A-0301 (AC)
Link to Codes

MCG Health
Ambulatory Care
27th Edition

Clinical Indications

- Epoetin and darbepoetin (recombinant) may be indicated for **1 or more** of the following(1)(2)(3)(4):
  - Anemia associated with chemotherapy, as indicated by **ALL** of the following[A][B](9)(10)(12):
    - Anemia due to chemotherapy
    - Chemotherapy not being administered in anticipation of cure
    - Chemotherapy to be administered for 2 or more months
    - Hemoglobin 10 g/dL (100 g/L) or less(19)
    - No uncontrolled hypertension
    - Patient has been evaluated and treated for other causes of anemia (eg, iron deficiency, hemolysis, vitamin B12 deficiency).(19)
    - Patient receiving myelosuppressive chemotherapy for metastatic nonmyeloid malignancy(49)
  - Anemia associated with myelodysplastic syndrome, as indicated by **1 or more** of the following[C](9)(10)(50)(52)(53):
    - Initial course, as indicated by **ALL** of the following:
      - Endogenous serum erythropoietin level of 500 International Units per liter (IU/L) or less
      - Hemoglobin of 10 g/dL (100 g/L) or less
      - Less than 10% blasts present in bone marrow[D]
      - No uncontrolled hypertension
      - Normal karyotype (ie, no 5q deletion or other cytogenetic abnormality)[D]
      - Patient has been evaluated and treated for other causes of anemia (eg, iron deficiency, hemolysis, vitamin B12 deficiency).
    - Subsequent course, with favorable response to prior administration of epoetin or darbepoetin
  - Elective surgery, as indicated by **ALL** of the following[E](56)(57)(58):
    - Estimated blood loss of 2 units or more
    - No uncontrolled hypertension
    - Patient has been evaluated and treated for other causes of anemia (eg, iron deficiency, hemolysis, vitamin B12 deficiency).(19)
    - Preoperative hemoglobin greater than 10 g/dL (100 g/L) and less than or equal to 13 g/dL (130 g/L)
    - Replacement for allogeneic transfusion desired
    - Surgical procedure elective, noncardiac, and nonvascular
  - HIV/AIDS and **1 or more** of the following[F]:
    - Initial course, as indicated by **ALL** of the following:
      - Anemia has not improved after 6 months of highly active antiretroviral therapy.
      - Endogenous serum erythropoietin 500 International Units per liter (IU/L) or less
      - Hematocrit less than 30% (0.30)
      - HIV-infected patient receiving zidovudine treatment with dosage 4200 mg/week or less
      - No uncontrolled hypertension
      - Patient has been evaluated and treated for other causes of anemia (eg, iron deficiency, hemolysis, vitamin B12 deficiency).(19)
    - Subsequent course, with favorable response to prior administration of epoetin or darbepoetin
  - Kidney disease and **1 or more** of the following[G][H](62)(63)(64)(65)(66)(67):
    - Initial course, as indicated by **ALL** of the following:
      - Anemia status is **1 or more** of the following(78):

- For adult patient on dialysis, hemoglobin is less than 10 g/dL (100 g/L).(79)(80)(81)
- For adult patient not on dialysis, **ALL** of the following:
  - Hemoglobin is less than 10 g/dL (100 g/L).
  - Rate of hemoglobin decline indicates likelihood of requiring blood transfusion.
  - Therapeutic goal is reduction of blood transfusion-related risks.
- For pediatric patient with chronic kidney disease, hemoglobin is less than 10 g/dL (100 g/L).

- Ferritin prior to therapy 100 ng/mL (mcg/L) or more(82)
- Kidney disease, as indicated by **1 or more** of the following:
  - Chronic kidney disease, not on hemodialysis(83)
  - End-stage renal disease, on hemodialysis
  - Serum creatinine greater than 2 mg/dL (177 micromoles/L)
- No uncontrolled hypertension
- Patient has been evaluated and treated for other causes of anemia (eg, iron deficiency, hemolysis, vitamin B12 deficiency).(19)(84)
- Transferrin saturation prior to therapy 20% or more(82)

- Subsequent course, with favorable response to prior administration of epoetin or darbepoetin

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Evidence Summary

Background

Epoetin and darbepoetin are erythropoiesis-stimulating agents; they are closely related recombinant human proteins similar to erythropoietin that stimulate production of erythrocytes.(1)(2)(3)(4)(5)(6) **(EG 2)**

Criteria

For anemia associated with chemotherapy, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** Systematic reviews of randomized controlled trials and specialty society guidelines indicate that recombinant human erythropoietin is effective in reducing transfusion requirements in cancer patients undergoing chemotherapy, even though increased risks of death and thromboembolic events must always be considered.(11)(12)(45) **(EG 1)** Meta-analyses of patients receiving recombinant human erythropoietin during chemotherapy for lymphoproliferative, lung, and gynecologic malignancies confirmed incremental effectiveness in reducing transfusion requirements, and no significant effects upon either mortality or disease progression.(46)(47) **(EG 1)** A phase III randomized noninferiority study of 2516 patients with stage IV non-small cell lung cancer (all of whom had anemia and were receiving myelosuppressive chemotherapy) compared treatment with either darbepoetin alfa or placebo and found that darbepoetin alfa was noninferior to placebo for overall survival and progression-free survival.(48) **(EG 1)**

For anemia associated with myelodysplastic syndrome, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** A systematic review of 35 studies (6 randomized controlled trials, 18 single-arm investigations, and 11 observational reports) found that erythropoiesis-stimulating agents consistently improved erythroid response rates in up to 75% of patients with anemia due to lower-risk myelodysplastic syndrome. Additionally, several studies showed that patients treated with erythropoiesis-stimulating agents had a reduced need for RBC transfusions and better health-related quality of life with no increased risk of progression to acute myeloid leukemia, when compared with pretreatment condition or placebo. The authors concluded that erythropoiesis-stimulating agents should be considered as first-line treatment for anemia in most patients with myelodysplastic syndrome who lack the 5q deletion.(54) **(EG 1)** Specialty society guidelines state that erythropoiesis-stimulating agents should not be used to treat anemia in patients with malignancy who are not receiving myelosuppressive chemotherapy; one exception is patients with lower-risk myelodysplastic syndrome in order to avoid transfusions.(10)(50)(55) **(EG 2)**

For elective surgery, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** A systematic review and meta-analysis of 12 studies including 1880 adult patients with mild to moderate preoperative anemia (hemoglobin 10 to 12 g/dL (100 to 120 g/L)) undergoing noncardiac surgery found that administration of preoperative recombinant human erythropoietin plus iron reduced the need for RBC transfusion and, when given at higher doses, increased hemoglobin concentration compared with control (ie, no treatment, placebo, or standard of care with or without iron). No difference in adverse events or mortality within 30 days was evident; future well-designed randomized controlled trials were recommended.(56) **(EG 1)**

For HIV/AIDS patients with anemia due to zidovudine, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** An analysis of pooled data from 4 randomized controlled trials with 255 patients with AIDS and zidovudine-related anemia found that for those with serum erythropoietin levels at or below 500 International Units per liter (IU/L), treatment with recombinant human erythropoietin decreased transfusion requirements by 40% and increased hematocrit levels by 3.9 percentage points compared with placebo. However, recombinant human erythropoietin did not provide hematologic benefit for patients with serum erythropoietin levels greater than 500 International Units per liter (IU/L).(59) **(EG 1)**

For kidney disease, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** Systematic reviews and meta-analyses indicate that recombinant human erythropoietin is effective in stimulating erythropoiesis, improving anemia,

increasing health-related quality-of-life measures, and reducing transfusion requirements in patients with chronic kidney disease, whether or not they are receiving dialysis.(61)(62)(63)(64)(68) **(EG 1)** However, patients receiving these agents in controlled clinical trials have experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when the hemoglobin level target is greater than 11 g/dL (110 g/L).(69)(70)(71) **(EG 1)** Meta-analyses investigating the effectiveness of darbepoetin and epoetin for chronic kidney disease confirmed efficacy in reducing transfusion requirements but found no evidence of significant effects on either mortality or quality of life.(41)(72) **(EG 1)** Systematic reviews and randomized trials indicate that erythropoietin administration directed at higher targeted hemoglobin levels in patients with chronic kidney disease also significantly increases risks for hypertension, vascular access thrombosis, and progression of end-stage renal disease.(73)(74)(75)(76)(77) **(EG 1)**

Inconclusive or Non-Supportive Evidence

For allogeneic stem cell transplant, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A randomized controlled trial with 131 patients found that erythropoietin administration significantly improved post-transplant erythroid recovery and hemoglobin restoration while significantly decreasing transfusion requirements, without concomitant worsening of thromboembolic events or other complications; the authors indicated that additional confirmatory study is required.(7) **(EG 1)**

For anemia associated with HIV other than due to zidovudine, evidence demonstrates a lack of net benefit; additional research is recommended. **(RG C1)** A systematic review of randomized controlled trials concluded that erythropoiesis-stimulating agents for this indication do not improve quality of life, increase hemoglobin levels, reduce transfusion requirements, or reduce mortality.(8) **(EG 1)**

For anemia in cancer patients that is not directly related to current myelosuppressive chemotherapy of a nonmyeloid malignancy, evidence demonstrates potential harm that outweighs benefit; additional research is recommended. **(RG C2)** Practice guidelines and systematic reviews with meta-analyses indicate that erythropoiesis-stimulating agents may be ineffective in such settings and may contribute to higher mortality, with the exception of small cell lung cancer, for which there are trials that demonstrate no negative impact on survival or disease progression.(9)(10)(11)(12) **(EG 1)** Safety concerns regarding thromboembolic events,(13) cardiovascular events, tumor progression, and reduced survival(14) or increased mortality(15) have prompted guidelines that specify level of pretreatment hemoglobin,(9)(12) indicate lack of usefulness for myeloid malignancy, and assert lack of usefulness for anemia of cancer related to surgery(16) or related to treatment with radiotherapy alone,(17)(18) or for treatment prior to chemotherapy.(10)(19) **(EG 2)** A meta-analysis concluded that erythropoietin and darbepoetin are not appropriate for managing cancer-related fatigue due to potential for these adverse effects.(20) **(EG 1)**

For anemia caused by ribavirin treatment for hepatitis C, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review and meta-analysis of 4 randomized trials containing 257 patients found that patients who received erythropoietin in response to a drop in hemoglobin had a significantly higher probability of achieving a sustained virologic response as compared with those who underwent a ribavirin dose reduction due to anemia. However, the authors acknowledged that further study is required to determine safety for this indication.(21) **(EG 1)** A subsequent review article found limited data on this subject and indicated that ribavirin dose reduction should remain the primary strategy for anemia management.(22) **(EG 2)**

For aplastic anemia, evidence demonstrates a lack of net benefit; additional research is recommended. **(RG C1)** A systematic review of the use of hematopoietic growth factors as adjunctive therapy to immunosuppression in patients ineligible for transplant found that there was no incremental improvement in mortality, infection rate, hematologic response, or relapse rate up to 5 years.(23) **(EG 1)**

For autologous stem cell transplant, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A randomized study assigned 72 patients undergoing autologous stem cell transplant to no darbepoetin, to darbepoetin every 2 weeks starting on day 28 after transplant, or to darbepoetin plus intravenous iron. Darbepoetin and intravenous iron were each significantly and independently associated with faster achievement of erythrocytic recovery, and were also associated with improved quality-of-life scores, but effects upon transfusion requirements were not significant; larger confirmatory studies are required.(24) **(EG 1)**

For carbon monoxide poisoning, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A randomized controlled study assigned 103 patients with carbon monoxide poisoning to administration of either erythropoietin or saline placebo. After 30 days, those in the active treatment group had significantly improved neurologic outcomes as compared with those in the placebo group, but the authors indicated that further studies are required to assess longer-term outcomes.(25) **(EG 1)**

For cerebrovascular accident, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A trial randomized 522 patients with acute ischemic stroke to either intravenous erythropoietin infusion or placebo. After 90 days, there was no difference between the groups in terms of any neurologic outcomes, but the mortality rate in the erythropoietin group was significantly higher, at 16.4%, as compared with the placebo group, at 9.0%.(26) **(EG 1)** For subarachnoid hemorrhage, a review article found some evidence that erythropoietin may improve both severity and outcome, but the authors concluded that larger confirmatory randomized trials are necessary.(27) **(EG 2)** A meta-analysis and systematic review on the use of erythropoietin in stroke found 3 trials, across which a significantly increased odds ratio of 1.98 was found for mortality; while

erythropoietin significantly increased red cell count, there was no effect observed upon infarct volume.(28) **(EG 1)** A review article indicates that data are sparse as to the therapeutic effectiveness and safety of erythropoietin in stroke.(29) **(EG 2)**

For heart failure, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A meta-analysis of 11 randomized trials found that treatment of anemia in heart failure patients using erythropoiesis-stimulating agents was associated with improvement in quality of life, exercise capacity, and cardiac function, as well as a significant reduction in heart failure-related hospitalizations, but the authors stated that larger confirmatory trials are needed.(30) **(EG 1)** A meta-analysis of 13 randomized studies with 3172 patients found that while administration of erythropoiesis-stimulating agents was associated with subjective improvement in dyspnea and quality of life, there was no significant effect upon either all-cause mortality or rehospitalization; treatment with erythropoiesis-stimulating agents was associated with an increased risk of thromboembolic events.(31) **(EG 1)**

For myocardial ischemia, evidence demonstrates a lack of net benefit; additional research is recommended. **(RG C1)** A meta-analysis and systematic review concluded that short-term use of erythropoietin in the setting of acute myocardial infarction did not improve cardiac function, infarct size, or all-cause mortality.(32) **(EG 1)** A meta-analysis of 11 randomized controlled trials with data for 1564 patients reported that erythropoietin did not decrease infarct size, improve left ventricular ejection fraction, or reduce the risk of cardiovascular events or all-cause mortality.(33) **(EG 1)** A randomized study of 529 patients with acute ST-elevation myocardial infarction who received percutaneous coronary intervention assigned half of the patients to also receive a single bolus of erythropoietin at the time of intervention; after 1 year, there was no difference in occurrence of cardiovascular events between groups.(34) **(EG 1)** Similar lack of effectiveness with respect to infarct size was seen in a randomized study of 56 patients with acute ST-elevation myocardial infarction who received intracoronary instillation of either saline placebo or darbepoetin.(35) **(EG 1)**

For neurodegenerative diseases, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** Experimental observations that erythropoietin is present in the central nervous system and may have a role in neuronal protection and differentiation have led to optimism regarding its therapeutic potential; however, more robust clinical studies are still needed.(36)(37) **(EG 1)**

For postpartum iron deficiency anemia, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A meta-analysis and systematic review found 9 studies that evaluated the use of erythropoietin for postpartum iron deficiency anemia, but there was not sufficient high-quality evidence to make any conclusions as to its effectiveness.(38) **(EG 1)**

For renal transplant, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A randomized controlled trial of 104 patients found that erythropoietin administration peri-transplant did not appear to prevent delayed or slow graft function after transplant.(39) **(EG 1)** A randomized study with 120 patients found positive results with darbepoetin, although the sole comparator was an erythropoietin receptor activator, without use of a true control group.(40) **(EG 1)** A meta-analysis found that the effects of darbepoetin on renal transplant recipients remain uncertain due to limited published evidence.(41) **(EG 1)**

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Footnotes

[A] For anemia associated with chemotherapy, epoetin is administered as a weekly intravenous injection in pediatric patients, or as a once-weekly or thrice-weekly subcutaneous injection in adults.(1)(2) The target hemoglobin should be below 12 g/dL (120 g/L),(42) and the rate of hemoglobin increase should be less than 1 g/dL (10 g/L) every 2 weeks.(1)(2) If there is no response after a total of 8 weeks, the drug should be discontinued.(1)(2) Epoetin should be administered only concurrently with chemotherapy, and it should be discontinued as soon as chemotherapy is completed.(1)(2) [A in Context Link 1]

[B] For anemia associated with chemotherapy, darbepoetin is administered as a subcutaneous injection either once weekly or once every 3 weeks.(3)(43) The rate of hemoglobin increase should be less than 1 g/dL (10 g/L) every 2 weeks.(3) If there is no response after a total of 8 weeks, the drug should be discontinued.(3) Darbepoetin should be administered only concurrently with chemotherapy, and it should be discontinued as soon as chemotherapy is completed.(3) Concomitant iron administration may improve the hematopoietic response.(44) [B in Context Link 1]

[C] For anemia associated with myelodysplastic syndrome, expert consensus guidelines recommend that epoetin be administered as a once-weekly or twice-weekly subcutaneous injection or darbepoetin be administered every 1, 2, or 3 weeks as a subcutaneous injection.(9)(50)(51)(52) [C in Context Link 1]

[D] Risk factors for evolution to acute myelogenous leukemia include percentage of bone marrow blasts, number of cytopenias, chromosome anomalies, and cytogenetic subgroup.(50) [D in Context Link 1, 2]

[E] For elective surgery, epoetin is administered as a subcutaneous injection, either daily for 10 days before surgery, on the day of surgery, and for 4 days after surgery, or as 4 weekly injections beginning 3 weeks before surgery and ending on the day of surgery.(1)(2) [E in Context Link 1]

[F] For HIV/AIDS, epoetin is administered as an intravenous or subcutaneous injection thrice weekly.(1)(2) Response should be evaluated, and dose adjusted if necessary, after 8 weeks and then every 4 to 8 weeks thereafter. If there is no response at the maximum dose, response at higher doses is unlikely.(1)(2) For responding patients, doses should be titrated to maintain the lowest possible hemoglobin below 12 g/dL (120 g/L) consistent with improvement in hemoglobin level and reduction of transfusion requirements.(1)(2) [F in Context Link 1]

[G] For kidney disease, epoetin is administered as a thrice-weekly subcutaneous or intravenous injection, the latter for patients on hemodialysis.(1)(2) Once-monthly doses also have been used successfully for patients not on dialysis.(60)(61) The goals are the lowest possible hemoglobin level for avoiding transfusion and a level below 11 g/dL (110 g/L) if the patient is an adult on dialysis, a level below 10 g/dL (100 g/L) if the patient is an adult not on dialysis, or a level below 12 g/dL (120 g/L) if the patient is a child.(1)(2) The rate of hemoglobin increase should not exceed 1 g/dL (10 g/L) every 2 weeks.(1)(2) Dosage increases should not be made more frequently than monthly.(1)(2) [G in Context Link 1]

[H] For chronic kidney disease, darbepoetin is administered as a single weekly or biweekly subcutaneous or, preferably, intravenous injection for patients on hemodialysis, or as a subcutaneous or intravenous injection every 4 weeks for other patients with chronic kidney disease.(3) The goals are the lowest possible hemoglobin level for avoiding transfusion and a level below 11 g/dL (110 g/L) if the patient is an adult on dialysis, a level below 10 g/dL (100 g/L) if the patient is an adult not on dialysis, or a level below 12 g/dL (120 g/L) if the patient is a child.(3) The rate of hemoglobin increase should not exceed 1 g/dL (10 g/L) every 2 weeks.(3) Dosage increases should not be made more frequently than monthly.(3) [H in Context Link 1]

Codes

HCPCS: J0881, J0882, J0885, J0887, J0888, Q4081, S9537

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