Erythropoietins Prior Authorization Criteria

<table>
<thead>
<tr>
<th>Brand</th>
<th>Generic</th>
<th>Dosage Form</th>
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<tbody>
<tr>
<td>Aranesp®</td>
<td>darbepoetin alfa</td>
<td>intravenous or subcutaneous</td>
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<td></td>
<td></td>
<td>injection</td>
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<tr>
<td>Epogen®</td>
<td>epoetin alfa</td>
<td>subcutaneous injection</td>
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<tr>
<td>Procrit®</td>
<td>epoetin alfa</td>
<td>subcutaneous injection</td>
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SUMMARY OF PRIOR AUTHORIZATION CRITERIA

It is the intent of the Erythropoietins Prior Authorization Criteria to ensure that patients who are prescribed erythropoietin therapy are appropriately selected for treatment. The following is a summary of the criteria for approval of the erythropoietin products (erythropoiesis-stimulating agents or ESAs).

Aranesp, Epogen or Procrit - ALL of the following general criteria must be met:

- Prior to starting ESA therapy, the patient’s iron stores should be evaluated, and blood ferritin should be at least 100 ng/mL (nanograms per milliliter) and transferrin saturation should be at least 20%— initial and ongoing ESA therapy should not be administered unless iron stores are maintained; and
- For use in cancer patients, ESA therapy should not be initiated until the Hgb level is approaching or has fallen below 10 g/dL; and
- ESA therapy should not be used to raise the Hgb level above 12 g/dL; and
- The lowest dose of ESAs should be used that will gradually increase Hbg concentration to the lowest level sufficient to avoid the need for red blood cell (RBC) transfusion; and
- Blood pressure is adequately controlled and closely monitored before and during ESA therapy

Aranesp

If the general criteria above are met, Aranesp will be approved for the treatment of anemia:

- Associated with chronic kidney failure (including end-stage renal disease—ESRD) to maintain Hgb levels in the range of 10-12 g/dL; or
- In cancer patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy; or
- In patients with myelodysplastic syndromes to reduce transfusion dependency.

Length of approval:

- Chronic renal failure – 24 weeks
- Anemia secondary to concomitant chemotherapy – 12 weeks
- Myelodysplastic syndrome – 24 weeks
Epogen or Procrit
If the general criteria above are met, Epogen or Procrit will be approved for the treatment of anemia:
- Associated with chronic kidney failure (including end-stage renal disease—ESRD) to maintain Hgb levels in the range of 10-12 g/dL; or
- In cancer patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy; or
- Related to therapy with AZT (zidovudine) in HIV-infected (human immunodeficiency virus) patients; or
- To reduce the need for allogeneic blood transfusion in pre-operative surgery patients who meet all of the following criteria:
  - Scheduled for elective, non-cardiac, non-vascular surgery, and
  - Hgb < 13 g/dL, and
  - Not a candidate for autologous blood transfusion, and
  - High risk for significant perioperative blood loss; or
- Following allogeneic bone marrow transplantation; or
- In patients with myelodysplastic syndromes to reduce transfusion dependency; or
- Of prematurity (birth weight <1500 gm or gestational age <33 weeks, and Hct <33%); or
- Associated with Hepatitis C that is being treated with the combination of ribavirin and interferon alfa or ribavirin and peginterferon, and:
  - Other causes of anemia have been ruled out; and
  - Thyroid function has been assessed and abnormality has been treated appropriately; and
  - Patient has failed to respond (i.e., severe anemia) within two weeks after reducing the dose of Ribavirin by 200 mg/day from the initial dose (NOTE: Use of erythropoietin may be considered prior to dose reduction for the following: 1) documented evidence of cirrhosis, or 2) post liver transplant, or 3) HIV co-infection); and
  - Hgb<10 gm/dL, or patient is symptomatic and has Hgb < 11 g/dL; and
  - Patient does not have uncontrolled hypertension.

Length of approval: for all indications – 24 weeks

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Aranesp (darbepoetin)
Initial and Renewal Evaluation
1. Have the patient’s iron stores been evaluated and BOTH of the following established:
  a) blood ferritin levels are > 100 ng/mL (nanograms per milliliter) and
  b) transferrin saturation is be at least 20%
If yes, continue to 2. If no, deny.

2. Is the patient’s blood pressure adequately controlled and closely monitored?
If yes, continue to 3. If no, deny.

3. Is Aranesp being prescribed for ONE of the following?
   a) anemia associated with chronic renal failure, including ESRD
   b) anemia due to myelodysplastic syndrome, to reduce transfusion dependency
   c) anemia due to chemotherapy for a non-myeloid malignancy
   d) other
If a or b, continue to 4. If c, continue to 5. If d, deny.

4. Is the patient’s hemoglobin level less than 12 g/dL for patients initiating Aranesp therapy or less than or equal to 12 g/dL for patients stabilized on therapy (measured within the previous four weeks)?
If yes, approve for 24 weeks. If no, deny.

5. Is the patient’s hemoglobin level less than 10 g/dL for patients initiating Aranesp therapy or stabilized on therapy (measured within the previous four weeks)?
If yes, continue to 5. If no, deny.

6. Is the patient being concurrently treated with chemotherapy (with or without radiation) (treatment period extends to eight weeks post chemotherapy)?
If yes, approve for 12 weeks. If no, deny.

**Epogen or Procrit (epoetin)**

*Initial and Renewal Evaluation*

1. Have the patient’s iron stores been evaluated and BOTH of the following established:
   a) blood ferritin levels are \( \geq 100 \text{ ng/mL} \) (nanograms per milliliter) and
   b) transferrin saturation is at least 20%
If yes, continue to 2. If no, deny.

2. Is the patient’s blood pressure adequately controlled and closely monitored?
If yes, continue to 3. If no, deny.

3. Is the ESA being prescribed for ONE of the following?
   a) anemia associated with chronic renal failure, including ESRD
   b) anemia due to myelodysplastic syndrome, to reduce transfusion dependency
   c) anemia following allogeneic bone marrow transplantation
   d) anemia resulting from zidovudine treatment of HIV infection
   e) anemia due to chemotherapy for a non-myeloid malignancy
   f) anemia of prematurity
   g) anemia associated with hepatitis C being treated with the combination of ribavirin and interferon alfa or peg interferon
   h) to reduce the need for allogeneic blood transfusion in a surgery patient
   i) other

If a, b, c, or d, continue to 4. If e, continue to 5. If f, continue to 7. If g, continue to 8.
If h, continue to 13. If i, deny

4. Is the patient’s hemoglobin level less than 12 g/dL for patients initiating ESA therapy or less than or equal to 12 g/dL for patients stabilized on therapy (measured within the previous four weeks)?
If yes, approve for 24 weeks. If no, deny.

5. Is the patient’s hemoglobin level less than 10 g/dL for patients initiating ESA therapy or stabilized on therapy (measured within the previous four weeks)?
If yes, continue to 6. If no, deny.

6. Is the patient being concurrently treated with chemotherapy (with or without radiation) (treatment period extends to eight weeks post chemotherapy)?
If yes, approve for 24 weeks. If no, deny.

7. Does the patient have anemia of prematurity associated with BOTH of the following?
   a) birth weight <1500 gm or gestational age <33 weeks and
   b) hematocrit (Hct) <33%
If yes, approve for 24 weeks. If no, deny.

8. Is the patient being treated with a combination of ribavirin and interferon alfa or ribavirin and peginterferon?
If yes, continue to 9. If no, deny.

9. Has the patient failed to respond (i.e., severe anemia) within two weeks after reducing the dose of Ribavirin by 200 mg/day from the initial dose?
[NOTE: Use of erythropoietin may be considered prior to dose reduction for the following: 1) documented evidence of cirrhosis, or 2) post liver transplant, or 3) HIV co-infection]
If yes, continue to 10. If no, deny.

10. Have other causes of anemia been ruled out?
If yes, continue to 11. If no, deny.

11. Has the patient’s thyroid function been assessed and abnormality, if any, been treated appropriately?
If yes, continue to 12. If no, deny.

12. Is the patient’s hemoglobin level less than 10 g/dL, or less than 11 g/dL and patient is symptomatic?
If yes, approve for 24 weeks. If no, deny.

13. Is the patient scheduled for elective, non-cardiac, non-vascular surgery?
If yes, continue to 14. If no, deny.

14. Is the patient at high risk for significant perioperative blood loss?
If yes, continue to 15. If no, deny.

15. Is the patient a candidate for autologous blood transfusion?
If yes, deny. If no, continue to 16.

16. Is the patient’s hemoglobin level less than 13 g/dL?
If yes, approve for 24 weeks. If no, deny.

**CLINICAL BACKGROUND; RATIONALE FOR PRIOR AUTHORIZATION**

Endogenous erythropoietin (EPO) is a glycoprotein hematopoietic growth factor synthesized at the cellular level by cells near the renal tubules in response to changes in the blood oxygen concentration. When a patient is anemic, the ability of the blood to carry oxygen is decreased. An oxygen-sensing protein in the kidney detects the decrease in blood oxygen concentration and induces the production of EPO, which then acts upon the erythroid cell line in the bone marrow to stimulate hematopoiesis, thereby effectively increasing blood hemoglobin (Hgb) concentrations. Suppression of erythropoietin production or suppression of the bone marrow response to erythropoietin results in anemia in several disease processes, including chronic kidney disease (CKD), many types of cancer treatment, other chronic diseases, and use of certain drugs. The severity of anemia is defined by blood Hgb concentration. Normal ranges are 12–16 g/dL in women and 14–18 g/dL in men. Mild anemia is defined as Hgb from 10 g/dL to the lower limit of normal ranges, while moderate anemia is 8-10 g/dL. Severe anemia is defined as Hgb 8 g/dL or below.

Erythropoiesis-stimulating agents (ESAs) are produced using recombinant DNA technologies. They were initially developed as replacement therapy to treat anemia due to endogenous EPO deficiency that commonly occurs in individuals with chronic renal failure (CRF) secondary to CKD. Patients with CRF will become severely anemic, experience severe fatigue, and reduced exercise tolerance unless treated with blood transfusions or an ESA. Partial correction of anemia with ESA treatment results in reduced need for RBC transfusions and enhanced physical functioning.

In cancer, anemia occurs with varying degrees of frequency and severity. It occurs most commonly in genitourinary, gynecologic, lung, and hematologic malignancies. Anemia may be directly related to cancer type or to its treatment. Oncologic anemia occurs by a variety of mechanisms. Poor oral intake or altered metabolism may reduce nutrients (folate, iron, vitamin B₁₂) essential for the red cell production. Antibodies in certain tumor types may cause increased erythrocyte destruction through hemolysis. Tumors may cause blood loss via tissue invasion, for example gastrointestinal bleeding from colon cancer. Other neoplasms, particularly hematologic malignancies (leukemia, lymphoma, multiple myeloma) can invade the bone marrow and disrupt the erythropoietic microenvironment. In more advanced cases, there may be marrow replacement with tumor or amyloid. However, marrow dysfunction can occur, even in the absence of frank
invasion. Inflammatory proteins from interactions between the immune system and tumor cells are thought to cause inappropriately low erythropoietin production and poor iron utilization, as well as a direct suppression of red cell production. The treatment of cancer may also cause anemia. Radical cancer surgery can result in acute blood loss. Radiotherapy and many cytotoxic chemotherapeutic agents cause marrow suppression to some degree. Damage is due to a variety of mechanisms. For example, alkylating agents cause cumulative DNA damage, anti-metabolites damage DNA indirectly, and platinum-containing agents appear to damage erythropoietin-producing renal tubule cells.

RBC transfusion is the traditional approach to quickly ameliorate anemia symptoms. However, it is not risk free, with several potential associated adverse events. The highest adverse event risk (1 per 432 whole blood units) is that for transfusion-related acute lung injury (TRALI). Adverse events due to errors in transfusion (for example, type mismatch) are estimated to occur at a rate of 1 per 5,000–10,000 units of blood transfused. Current transfusion medicine and blood bank practices have significantly reduced the risk of transmissible infections, primarily due to better donor selection and screening for infectious diseases. Estimated risks per unit of blood transfused for transmission of hepatitis B virus (<1 in 400,000), hepatitis C virus (<1 in 1,000,000), human immunodeficiency virus (HIV) (<1 in 1,000,000), and bacterial contaminants (1 per 10,000-100,000) have fallen dramatically since the early 1990s. Therefore, while the initial impetus for commercialization of erythropoietin replacement products was based on reduction in the risks associated with blood transfusion, current practices have mitigated many of those. Nonetheless, blood shortages, transfusion errors, and the risk for alloimmunization and TRALI provide sufficient rationale for the use of ESA therapy in appropriately indicated patients.

Two ESA products have been licensed in the United States. Epoetin alfa is manufactured, distributed and marketed by Amgen, Inc. under the proprietary name Epogen. The same epoetin alfa product manufactured by Amgen, Inc. is also marketed and distributed by Ortho Biotech, LP, a subsidiary of Johnson and Johnson, under the proprietary name Procrit. Under a contractual agreement with Amgen, Ortho Biotech LP has rights to development and marketing of Procrit for any indication other than for the treatment of anemia associated with chronic renal failure in patients on dialysis or use in diagnostic test kits. Epogen and Procrit have identical labeling information for all U.S. Food and Drug Administration (FDA)-approved indications. The other ESA, darbepoetin alfa, is marketed by Amgen solely under the proprietary name Aranesp.

Epoetin alfa has the same amino acid sequence as endogenous erythropoietin, while darbepoetin alfa has two additional oligosaccharide chains; however, the two epoetins and darbepoetin all have pharmacologic actions identical to those of the endogenous hormone; they increase the number of RBCs, and thus the blood concentration of hemoglobin, when given to individuals with functioning erythropoiesis. Both currently marketed ESAs have been approved for use in the treatment of anemia associated with CRF, as well as other indications.

**FDA Labeled indications**

**Chronic Renal Failure**

To support the initial FDA approval of Epogen and Procrit for anemia of CRF, substantial evidence of efficacy was provided predominantly from placebo-controlled and single-arm clinical studies that demonstrated the product sufficiently increased and maintained blood Hgb levels to reduce the need for RBC transfusions. In the clinical development program for Aranesp, evidence of efficacy was provided predominantly from active comparator studies that demonstrated the product increased and maintained Hgb concentrations in a manner similar to that of the comparator. In this development paradigm, blood Hgb concentration served as a form of surrogate for "reduction in the need for RBC transfusions."

At initial approval of epoetin in 1989, the primary objective of treatment was to raise Hgb concentration sufficiently to avoid transfusion, with a target range of 9–10 g/dL in anemic CRF patients. The first National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines in 1997 recommended a Hgb concentration of 11 g/dL, a level that was increased by the second NKF-KDOQI anemia guidelines to 11–13 g/dL. With increased experience in the use of ESAs, it became unclear whether higher Hgb target concentrations, including normalization, would yield additional benefits, in particular in
physical function and improved cardiovascular outcomes. Clinical doubts increased with publication of the first large random controlled trial (RCT) of Hgb normalization in hemodialysis (HD) patients (Normal Hematocrit Cardiac Trial [NHCT]), that showed a trend toward increased mortality risk and significantly increased risk for vascular access thrombosis with ESA treatment to a Hct target of 42%. Subsequently, four published RCTs in HD patients with ESRD and eight in nondialysis patients with CRF found improved physical function at higher Hgb targets but none demonstrated significant improvements in cardiovascular endpoints or mortality.

On the basis of the totality of results, the Epogen and Procrit labels were modified in 1996 to include the results of the NHCT study that showed a higher mortality rate for anemic dialysis patients randomized to a Hct of 42%, compared to a Hct of 30%. Ten years later, the CHOIR study (Correction of Hemoglobin and Outcomes in Renal Insufficiency) reported worse cardiovascular outcomes for anemic CRF patients who were not undergoing dialysis and who were randomized to a Hgb of 13.5 g/dL, compared to a Hgb of 11.3 g/dL. The CREATE study (Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta), also reported in 2006, was a study similar to CHOIR but enrolled fewer patients. CREATE did not demonstrate statistically significant differences in adverse cardiovascular outcomes for the higher Hgb group, but the general trend of the major cardiovascular outcomes was similar to the CHOIR findings.

**Oncology**

The basis of approval for Procrit and Epogen for the expanded indication of treatment of anemia associated with cancer chemotherapy in 1993 was demonstration of a reduction in the proportion of patients transfused during chemotherapy within the second and third months of chemotherapy and epoetin alfa administration. The approval was based on data pooled from six randomized, placebo-controlled, double-blind, clinical trials in a total of 131 anemic cancer patients receiving at least 12 weeks of concurrent chemotherapy who were randomized (1:1) to receive Procrit or placebo subcutaneously for 12 weeks.

The approval of Aranesp for the treatment of anemia associated with cancer chemotherapy was based on demonstration of a significant reduction in the proportion of patients transfused during chemotherapy during week five through the end-of-treatment. Study 980297, a Phase 3, double-blind, placebo-controlled, randomized (1:1) multicenter, multinational study of darbepoetin alfa enrolled 314 anemic patients with previously untreated non-small cell or small cell lung cancer receiving at least 12 weeks of platinum-containing chemotherapy.

Since the first approval of an ESA for treatment of chemotherapy-associated anemia in 1993, additional data became available regarding the increased risks of mortality and of possible tumor promotion from the use of ESAs. Increased mortality has been observed in patients with cancer (BEST, ENHANCE, 20000161, and EPO-CAN-20 studies) when ESA treatment strategies were designed to achieve and maintain Hgb levels above 12 g/dL. In addition, ESA treatment strategies intended to achieve and maintain Hgb levels above 12 g/dL have demonstrated poorer tumor outcomes (BEST, ENHANCE, and DAHANCA studies).

Data from recent clinical trials, consistent with earlier clinical trials presented to ODAC (Oncology Drugs Advisory Committee) in May 2004, led to revised product labeling that includes more expansive and detailed warnings regarding use of ESA treatment strategies that are designed to maintain Hgb levels above 12 g/dL. While the risks of treatment strategies in which ESAs are used to achieve and maintain Hgb levels in excess of that needed to avoid transfusions have been clearly demonstrated to be unacceptable, data from adequate, well-controlled studies employing the recommended doses of ESAs are as yet insufficient to assess effects on survival or tumor promotion. The only data provided to the FDA, which used the recommended dose and medication, was from Amgen Study 20010103 that demonstrated significantly shorter survival in cancer patients receiving ESAs as compared those receiving transfusion support. However, this study was not adequately designed to assess effects on tumor promotion or on thrombotic risks.
Despite these caveats, data from the available body of clinical studies provided sufficient rationale for the FDA to reassess the safety of ESAs in patients with cancer and to re-evaluate the net clinical benefit of ESAs in this setting.

2006-2007 FDA Regulatory Actions
In November 2006, the FDA issued a Public Health Advisory regarding the serious cardiovascular risks evidenced in the CHOIR study and the NHCT study. Subsequently, the FDA received reports of increased risks associated with ESAs used in the treatment of chemotherapy-induced anemia among cancer patients, the use of ESAs among cancer patients not receiving chemotherapy, as well as a report of thrombotic risks among patients receiving an ESA in the perisurgical setting. These data prompted a reassessment of the safety information contained in the ESA product labels and culminated in the approval of revised labels on March 9, 2007.

With respect to dosage information, the reassessment of ESA safety determined that clinical data did not support a specific therapeutic Hgb goal, exclusive of the upper Hgb limit of 12 g/dL. Consequently, the dosage and administration sections of the label revisions deleted references to any specific therapeutic Hgb or Hct "target" range for ESAs. Instead, the label revisions recommended that prescribers use the lowest ESA dose that will gradually increase the Hgb concentration to the lowest level sufficient to avoid the need for RBC transfusion. This recommendation was based, with respect to the use of ESAs among anemic CRF patients, predominantly upon the NHCT and CHOIR study findings as well as the lack of data to support the safety of any specific Hgb or Hct level or range under 12 g/dL. Clinical data were not available to identify specific Hgb or Hct levels that directly correlated with a "reduction in the need for RBC transfusion," the main treatment benefit supporting ESA efficacy. The March 2007 label revision allowed prescribers to use their clinical judgment in determining the "lowest level sufficient to avoid the need for RBC transfusion."

Updated 2007 FDA Recommendations and Considerations for Healthcare Professionals
On November 8, 2007, the FDA released information to update healthcare professionals about revisions to the product labeling for ESAs. These revisions are intended to clarify the evidence for safety and effectiveness and provide more explicit directions and recommendations to prescribers for their use. They are consistent with recommendations made at the May 10, 2007, ODAC and the September 11, 2007, meeting of the CRDAC (Cardiovascular and Renal Drugs Advisory Committee) and the DSRMAC (Drug Safety and Risk Management Advisory Committee). The revised product labeling includes a strengthened Boxed Warning and Warnings, changes to the Indications and Usage, Clinical Experience, and Dosage and Administration sections of the labeling for all ESAs. The changes to the prescribing information for the ESAs (Aranesp, Epogen and Procrit) summarized below expand on the revision made to the labeling and described in a healthcare professional sheet issued in March 2007, and include recommendations made by these FDA Advisory Committees: ODAC, CRDAC and DRSMAC.
Cancer

- ESAs shortened the overall survival and/or time-to-tumor progression in patients with various cancers.
- Risks of shortened survival and tumor progression have not been excluded when ESAs are dosed with the intent to achieve hemoglobin levels <12g/dL.
- Use the lowest dose of (Aranesp/Epogen/Procrit) needed to avoid RBC transfusions. Do not exceed the upper safety limit for hemoglobin levels of 12 g/dL.
- Reduce the ESA dose by 25% when hemoglobin reaches a level needed to avoid transfusion.
- Withhold dosing with an ESA when hemoglobin level exceeds 12 g/dL.
- Restart dosing at 25% below the previous dose when the hemoglobin approaches a level where transfusions may be required.
- Use ESAs only for the treatment of anemia due to concomitant myelosuppressive chemotherapy.
- Discontinue treatment with an ESA following the completion of a course of chemotherapy.
- Use of ESAs in cancer patients have not been demonstrated in controlled clinical trials to improve the symptoms of anemia, quality of life, fatigue, or well-being.

Chronic Renal Failure

- Risks for death and serious cardiovascular events are greater when ESAs are administered to achieve higher target hemoglobin levels (13.5 to 14 g/dL) versus lower hemoglobin levels (10 to 11.3g/dL).
- Dosing should be individualized to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL.
- If a patient is hypo-responsive (hemoglobin levels do not increase or reach the recommended range despite appropriate dose titrations over 12 weeks):
  - Do not administer higher doses and use the lowest dose that will maintain a hemoglobin level to avoid the need for recurrent blood transfusions.
  - Evaluate and treat other causes of anemia, and continue monitoring hemoglobin levels.
  - Follow instructions for dose adjustments.
  - Discontinue ESAs if the patient remains transfusion dependent.

Patient Counseling Information

As part of a risk minimization plan, a patient Medication Guide is currently being developed to better communicate the risks and benefits of ESA use. Physicians and other healthcare professionals should discuss the following with their patients:

- The primary goal of treatment with erythropoiesis stimulating agents (ESA) is to increase the number of RBCs in order to avoid receiving blood transfusions.
- ESAs require at least two weeks of treatment before there is an increase in the number of RBCs and the dose may be adjusted periodically but not more often than every four weeks.
- ESAs increase the chance of blood clots and the risk of dying may be greater in certain circumstances.
- The patient should keep appointments for blood tests so hemoglobin levels can be monitored.
- The patient needs to monitor their blood pressure and to call you if there are any changes outside of the range that has been established for them.
- The patient should call you if they experience any of the following symptoms:
  - Pain and/or swelling in the legs;
  - Worsening in shortness of breath;
  - Increases in blood pressure;
  - Dizziness or loss of consciousness;
  - Extreme tiredness;
  - Blood clots in hemodialysis vascular access ports.
2007 ASCO/ASH Guideline Update on Use of Epoetin and Darbepoetin in Patients with Cancer

The American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) have published their 2007 guideline update on use of ESAs in patients with cancer. Key points of this report are summarized as follows:

“For patients with chemotherapy-associated anemia, the Committee continues to recommend initiating an erythropoiesis-stimulating agent (ESA) as hemoglobin (Hgb) approaches, or falls below, 10 g/dl, to increase Hgb and decrease transfusions. …. Starting doses and dose modifications based on response or lack thereof should follow the package insert. Continuing ESAs beyond 6-8 weeks … does not seem to be beneficial and ESA therapy should be discontinued. … The Committee also cautions against ESA use for patients with cancer who are not receiving chemotherapy, since recent trials report increased thromboembolic risks and decreased survival under these circumstances.”

2007 National Comprehensive Cancer Network Revised Cancer- and Treatment-Related Guidelines

In December 2007, the National Comprehensive Cancer Network (NCCN) released important updates to the NCCN Cancer- and Treatment-Related Anemia Guidelines relating to the use of ESAs, which is summarized as follows:

ESAs are no longer recommended for the treatment of cancer-related anemia associated with solid tumors or hematologic malignancies other than myelodysplastic syndromes (MDS). ESA therapy is an option for patients receiving myelosuppressive chemotherapy who have symptoms of anemia and hemoglobin levels of less than 11 g/dL. ESA therapy should only be considered as an option for patients receiving myelosuppressive chemotherapy without symptoms of anemia if they have hemoglobin levels less than or equal to 10 g/dL and additional risk factors for the development of symptomatic anemia requiring transfusion. When ESAs are administered to patients with cancer receiving myelosuppressive chemotherapy, the drug dosage should be titrated to achieve hemoglobin levels in the range of 10 to <12 g/dL for the purpose of avoiding RBC transfusion. Use of ESAs in patients with cancer receiving myelosuppressive chemotherapy is limited to the period during chemotherapy and for a short period following chemotherapy, usually within six weeks following the end of such therapy. These changes reflect recent evidence indicating decreased survival in patients with cancer receiving ESA therapy and changes made to the product labels of these agents by the FDA.

In order to facilitate shared physician-patient decision-making for those patients with cancer at risk of anemia requiring transfusion who will undergo myelosuppressive chemotherapy, patient counseling regarding the risks and benefits of ESA therapy is recommended.

AZT (Zidovudine)-treated HIV-infected Patients

Efficacy in HIV-infected patients with anemia related to therapy with AZT was demonstrated based on reduction in the requirement for RBC transfusions. Procrit has been studied in four placebo-controlled trials enrolling 297 anemic (hematocrit < 30%) HIV-infected patients who received concomitant therapy with AZT. Procrit therapy resulted in significant increases in hematocrit in comparison to placebo. When examining the results according to the weekly dose of AZT received during month three of therapy, there was a statistically significant reduction in transfusion requirements in patients treated with Procrit compared to placebo treated patients whose mean weekly AZT dose was ≤ 4200 mg/week.

Pre-Operative Surgery Patients

Procrit has been studied in a placebo-controlled, double-blind trial enrolling 316 patients scheduled for major, elective orthopedic hip or knee surgery who were expected to require two or more units of blood and who were not able or willing to participate in an autologous blood donation program. Procrit was also studied in an open-label, parallel-group trial enrolling 145 subjects with a pretreatment hemoglobin level of 10-13 g/dL who were scheduled for major orthopedic hip or knee surgery and who were not participating in an autologous program. Both studies resulted in decreased transfusion rates in the Procrit group than in the control group.
Off-Label Indications
Myelodysplastic Syndromes
Epoetin alfa has been used in a limited number of patients with myelodysplastic syndromes, and is designated an orphan drug by the FDA for this indication. However, it has been associated with relatively limited response.

Anemia of Prematurity
Epoetin alfa is designated an orphan drug by the FDA for anemia of premature neonates, particularly those with pulmonary disease, tachypnea, tachycardia, apnea, and/or impaired growth who may require blood transfusions, which may further suppress endogenous erythropoietin production. Epoetin alfa therapy, combined with iron supplementation, has reduced transfusion requirements and increased hematocrit during the first several weeks of life for carefully selected neonates.

Hepatitis C (HCV)
Standard treatment for HCV involves interferon-based preparation and ribavirin for 24-48 weeks. Anemia is a common adverse effect; interferon causes bone marrow suppression and ribavirin causes hemolysis of RBCs. Ribavirin dose reduction to manage treatment-related anemia may also reduce sustained virologic response (SVR). Small studies have indicated that hematopoietic growth factors may be useful to increase hemoglobin level in people currently being treated with ribavirin, to allow ribavirin to be used without dose reduction and to relieve the fatigue associated with therapy and dramatically improve patients reported quality of life on therapy. The Veteran’s Administration treatment guideline for HVC treatment-related anemia states that maintaining a target ribavirin dose of 80% or more of the original dose is considered reasonable, and erythropoietin therapy may be used for patients who meet the specified criteria.

FDA APPROVED INDICATIONS
The following information is taken from individual drug prescribing information and is provided here as background information only. Not all FDA-approved indications may be considered medically necessary. All criteria are found in the section “Prior Authorization (PA) Criteria for Approval.”

<table>
<thead>
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<th>Products</th>
<th>Indications</th>
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<tr>
<td></td>
<td>Anemia associated with CRF, in patients on dialysis and those not on dialysis</td>
</tr>
<tr>
<td>Darbepoetin alpha [Aranesp]</td>
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<tr>
<td>Epoetin alfa (Erythropoietin, EPO) [EpoGEN]</td>
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<tr>
<td>Epoetin alfa (Erythropoietin, EPO) [Procrit]</td>
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Black Box Warning 1-3

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<thead>
<tr>
<th>WARNING: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR and THROMBOEMBOLIC EVENTS, and INCREASED RISK OF TUMOR PROGRESSION OR RECURRENCE</th>
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**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.

**Cancer:**
- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in patients with breast, non-small cell, lung head and neck, lymphoid, and cervical cancers.
- To decrease these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusion.
- Use ESAs only for treatment of anemia due to concomitant myelosuppressive chemotherapy.
- ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.
- Discontinue following the completion of a chemotherapy course.

For Epogen and Procrit

**Perisurgery:** Epogen and Procrit increased the rate of deep venous thromboses in patients not receiving prophylactic anticoagulation. Consider deep venous thrombosis prophylaxis.

REFERENCES


**Document History Prior Authorization**

Original Client Review, Client Specific Criteria approved by HCSC Corporate Clinical Committee 08/2009
Administrative Action (correction of criteria questions) 10/2010