Therapeutic Class Overview
Erythropoiesis-Stimulating Agents

Therapeutic Class

- **Overview/Summary:** The erythropoiesis-stimulating agents (ESAs) currently available are darbepoetin alfa (Aranesp®), epoetin alfa (Epogen®, Procrit®) and peginesatide (Omontys®).[1-4] There is no generic ESA is currently available in the United States. All ESAs are approved by the Food and Drug Administration (FDA) for the treatment of anemia in patients with chronic kidney disease; however, peginesatide is only approved for use in patients on dialysis. Darbepoetin alfa and epoetin alfa are also indicated for the treatment of anemia in cancer patients receiving chemotherapy. Moreover, epoetin alfa products are also FDA-approved for the treatment of anemia due to zidovudine therapy in patients with human immunodeficiency virus infection as well as to reduce the need for allogeneic blood transfusion in anemic patients who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery.[1-5] Both epoetin alfa and darbepoetin alfa are manufactured via recombinant deoxyribonucleic acid technology and have similar biological effects as endogenous erythropoietin.[6] Although darbepoetin alfa has identical pharmacological actions, the additional carbohydrate chains prolong its elimination half-life by two- to three-fold compared to epoetin alfa. Because of this, darbepoetin alfa is dosed less frequently compared to epoetin alfa. Peginesatide is structurally distinct from epoetin alfa and darbepoetin alfa in that it is a synthetic dimeric peptide that is bound to polyethylene glycol (PEG) and structurally unrelated to the recombinant products. Because of its synthetic structure, peginesatide may have a low risk of neutralizing antibody development and reduced risk of red blood cell aplasia.[7] Furthermore, by being attached to PEG, the half-life of peginesatide is prolonged, allowing for once-monthly dosing compared to biweekly or more frequent dosing with epoetin alfa and darbepoetin alfa.[1-4] Though not FDA-approved, ESAs have been used to treat refractory anemia in patients with myelodysplatic syndrome.[5,8,9] For the management of anemia with ESA therapy in patients with chronic kidney disease, the hemoglobin target range is generally between 11 and 12 g/dL, as recommended by the Kidney Disease Outcome Quality Initiative practice guidelines.[10-12] In June 2011, the FDA released more conservative recommendations for using the ESAs in patients with anemia of chronic kidney disease as a result of data showing that using ESAs to target a hemoglobin level of >11 g/dL increased the risk cardiovascular events without providing any additional benefit to patients. More information regarding the use of ESAs and hemoglobin targets is expected to be provided by currently ongoing and future clinical trials in patients with chronic kidney disease.[13]

Table 1. Current Medications Available in Therapeutic Class[1-4]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Darbepoetin alfa (Aranesp®)	Treatment of anemia associated with chronic kidney disease, including patients on dialysis and patients not on dialysis*, treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy	Single-dose vial (polysorbate solution or albumin solution): 25 µg/mL 40 µg/mL 60 µg/mL 100 µg/mL 150 µg/0.75 mL 200 µg/mL 300 µg/mL 500 µg/mL Single-dose prefilled syringe and single-dose autoinjector (polysorbate solution or albumin solution):	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		25 µg/0.42 mL 40 µg/0.4 mL 60 µg/0.3 mL 100 µg/0.5 mL 150 µg/0.3 mL 200 µg/0.4 mL 300 µg/0.6 mL 500 µg/mL	
Epoetin alfa (Epogen®, Procrit®)	Treatment of anemia associated with chronic kidney disease, including patients on dialysis and patients not on dialysis, treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy, treatment of anemia due to zidovudine administered at ≤ 4200 mg/week in human immunodeficiency virus-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL, reduce the need for allogeneic red blood cell transfusions among patients with perioperative hemoglobin > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery	Multi-dose vial (preserved solution): 10,000 units/mL 20,000 units/mL Single-dose vial (preservative-free solution): 2,000 units/mL 3,000 units/mL 4,000 units/mL 10,000 units/mL 40,000 units/mL	-
Peginesatide (Omontys®)	Treatment of anemia due to chronic kidney disease in adult patients on dialysis	Multi-dose vial (preserved solution): 10 mg/mL 20 mg/mL Single-dose pre-filled syringe (preservative-free solution): 1 mg/ 0.5 mL 2 mg/ 0.5 mL 3 mg/ 0.5 mL 4 mg/ 0.5 mL 5 mg/ 0.5 mL 6 mg/ 0.5 mL Single-dose vial (preservative-free solution): 2 mg/ 0.5 mL 3 mg/ 0.5 mL 4 mg/ 0.5 mL 5 mg/ 0.5 mL	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		6 mg/ 0.5 mL	

*To elevate or maintain the red blood cell level (as manifested by hematocrit or hemoglobin levels) and to decrease the need for transfusions in these patients.

Evidence-based Medicine

- Clinical trials evaluating darbepoetin alfa and epoetin alfa in the treatment of their respective Food and Drug Administration-approved indications have not consistently demonstrated "superiority" of one agent over another.
- In a study of adult patients with chronic kidney disease by Nissenson et al, the mean changes in hemoglobin levels from baseline to the evaluation period were similar between the darbepoetin alfa (0.16 to 0.09 g/dL) and epoetin alfa treatment groups (0.00 to 0.06 g/dL). The difference between treatments was 0.16 g/dL (95% confidence interval [CI], -0.06 to 0.38; *P* value not reported).[14]
- In a study by Vanrenterghem and colleagues in which patients with chronic kidney disease on dialysis were randomized to receive darbepoetin alfa or epoetin alfa, the mean change in hemoglobin was 0.05 g/dL in the darbepoetin alfa group compared to 0.00 g/dL in the epoetin alfa treatment (difference, 0.05 g/dL; 95% CI, -0.14 to 0.24; *P* values not reported). No statistically significant differences in the mean change in hemoglobin levels from baseline, the primary endpoint were reported. In addition, in both studies there were no differences in safety profiles and no antibodies detected to either treatment.[15]
- The Agency for Healthcare Research and Quality (AHRQ) performed a meta-analysis of 57 randomized controlled studies, seven of which directly compared epoetin alfa to darbepoetin alfa in patients diagnosed with malignant disease that were anemic or at risk for anemia from chemotherapy and/or radiotherapy or the underlying malignant disease. Of the endpoints evaluated, the AHRQ found that the evidence did not demonstrate any clinically significant differences between epoetin alfa and darbepoetin alfa with regard to hemoglobin response, transfusion reduction and thromboembolic events. Of the other endpoints evaluated, it was determined that the evidence was not sufficient for conclusions on effects of either epoetin alfa or darbepoetin alfa on quality of life, tumor response and progression, survival or adverse outcomes.[16]
- Studies evaluating the safety and efficacy of peginesatide have not been published outside of the prescribing information. Peginesatide was compared to epoetin alfa or beta in two randomized, multi-center, open-label studies. In Study 1, the mean change in hemoglobin values were similar between peginesatide (-0.09 g/dL) and epoetin (-0.24 g/dL) over weeks 29 to 36, the primary endpoint. The least squares mean change between treatments was -0.15 g/dL (95% CI, -0.30 to -0.01). In Study 2 the mean change in hemoglobin from baseline, was similar between peginesatide (-0.07 g/dL) and epoetin therapy (-0.17 g/dL). The least squares mean change between treatments was 0.1 g/dL (95% CI, -0.05 to 0.26). In both studies, the proportion of patients receiving blood transfusions was similar between treatments. Furthermore, the composite safety endpoint of death, myocardial infarction, stroke or serious adverse events of congestive heart failure, unstable angina or arrhythmia occurred in 22.8% of patients receiving peginesatide compared to 24.45% of patients receiving epoetin (hazard ratio, 0.95; 95% CI, 0.77 to 1.17).[4]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Darbepoetin alfa and epoetin alfa are considered equally effective in the treatment of anemia associated with chronic kidney disease and concomitant chemotherapy.[10,17]
  - Iron status, including serum iron, serum ferritin and transferrin saturation, should be monitored and corrected prior to and throughout treatment with erythropoiesis-stimulating agents (ESAs).[10,17,18]
  - For patients with anemia of chronic kidney disease who are not on dialysis, the Food and Drug Administration (FDA) recommends that ESA treatment can be considered when the hemoglobin level is <10 g/dL, and the dose should be reduced or interrupted when hemoglobin exceeds 10 g/dL. For patients with anemia of chronic kidney disease currently on

dialysis, ESA treatment should be initiated when the hemoglobin level is <10 g/dL, and the dose should be reduced or interrupted when hemoglobin approaches or exceeds 11 g/dL.[13]
    - The European Renal Best Practice position statement recommends using a lower hemoglobin target range of 10 to 12 g/dL in chronic kidney disease patients with type 2 diabetes not yet receiving dialysis.[12]
    - The use of ESAs in cancer patients should be reserved only in those who are receiving concomitant myelosuppressive chemotherapy. ESAs should not be used when the anticipated outcome from the chemotherapy is a cure. ESAs can be initiated in patients with chemotherapy-associated anemia and a hemoglobin level of <10 g/dL.[17,19]
- Other Key Facts:
    - The ESAs are only available as branded agents.
    - Due to the increased risks of tumor progression and deaths associated with ESA use in patients with malignancies, the FDA approved a risk evaluation and mitigation strategy (REMS) on February 16, 2010, to ensure the appropriate use of all ESAs in cancer patients. As part of the REMS, prescribers must be enrolled and receive training through the ESA Assisting Providers and Patients with Risk Information for the Safe Use of ESAs (APPRISE) Oncology program in order to prescribe and dispense ESAs to cancer patients. This requirement does not apply to prescribers who use ESAs in patients with non-malignancy conditions.[1-3]
    - Peginesatide (Omontys®) was approved by the Food and Drug Administration in March 2012 for the treatment of anemia due to chronic kidney disease in adult patients on dialysis. In patients with anemia due to chronic kidney disease who were not receiving dialysis, a higher incidence of cardiovascular events was reported with peginesatide compared to darbepoetin alfa; therefore, peginesatide is not approved in this patient population.

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Therapeutic Class Review
Erythropoiesis-Stimulating Agents

Overview/Summary

Erythropoietin is a naturally occurring glycoprotein hormone that stimulates the production and maturation of erythrocytes in the bone marrow.[1] Erythrocytes, or red blood cells, are responsible for transporting oxygen from the lungs to the peripheral tissues. Erythropoietin is primarily produced and released into the bloodstream by the kidneys. Renal production of erythropoietin is stimulated when the renal oxygen sensor is triggered by hypoxia or low tissue oxygen.[2,3]

There are currently three erythropoiesis-stimulating agents (ESAs) available in the United States including epoetin alfa (Epogen®, Procrit®), darbepoetin alfa (Aranesp®) and peginesatide (Omontys®). Both epoetin alfa and darbepoetin alfa are manufactured via recombinant deoxyribonucleic acid technology in Chinese hamster ovary cells and have similar biological effects as endogenous erythropoietin.[4] Darbepoetin alfa differs from epoetin alfa in that it is genetically modified to contain two additional carbohydrate chains.[4] Although darbepoetin alfa has identical pharmacological actions, the additional carbohydrate chains prolong its elimination half-life by two- to three-fold compared to epoetin alfa. Due to the prolonged half-life, darbepoetin alfa is dosed less frequently compared to epoetin alfa.[5] Peginesatide is structurally distinct from epoetin alfa and darbepoetin alfa in that it is a synthetic dimeric peptide that is bound to polyethylene glycol (PEG) and structurally unrelated to the recombinant products. Because of its synthetic structure, peginesatide is believed to have a low risk of neutralizing antibody development and reduced risk of red blood cell aplasia compared to the recombinant products.[6] Furthermore, by being attached to PEG, the half-life of peginesatide is prolonged, allowing for once-monthly dosing compared to biweekly or more frequent dosing with epoetin alfa and darbepoetin alfa.[7-11]

All three ESAs are approved for the treatment of anemia associated with chronic kidney disease; however, peginesatide is only indicated for adult patients who are on dialysis. Both epoetin alfa and darbepoetin alfa are also approved for anemia due to chemotherapy. Furthermore, the epoetin alfa products have additional FDA-approved indications for the treatment of anemia related to therapy with zidovudine in human immunodeficiency virus-infected patients as well as anemic patients who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions.[7-11] For the treatment of anemia of chronic kidney disease, epoetin alfa is recommended to be administered three times a week, darbepoetin alfa is recommended to be administered once weekly and peginesatide is indicated for once-monthly dosing. For the treatment of anemia in cancer patients receiving chemotherapy, epoetin alfa should be dosed three times weekly or once weekly and darbepoetin alfa should be dosed once weekly or once every three weeks. All ESAs are contraindicated in patients who have uncontrolled hypertension. The prescribing information for darbepoetin alfa states it is contraindicated in patients with a known hypersensitivity to the active substance or any of the excipients, while epoetin alfa products more specifically state a contraindication in patients with a known hypersensitivity to mammalian cell-derived products. Furthermore, the epoetin alfa products are contraindicated in patients with a known hypersensitivity to human albumin as they contain albumin; however, Darbepoetin alfa is available as an albumin-containing solution and a polysorbate solution without albumin. Due to the ESAs containing albumin, there is a theoretical risk of transmitting viral diseases and Creutzfeldt-Jakob disease to patients who receive them, although no cases of transmission of either have been identified with albumin.[7-11]

According to the National Kidney Foundation, anemia is defined as a deficiency in circulating red blood cells and should be diagnosed when the hemoglobin is <13.5 g/dL in adult males and <12.0 g/dL in adult females.[12] Anemia is a common manifestation of chronic kidney disease and is thought to be due to the decrease in functioning renal mass, leading to a decrease in erythropoietin production by the kidney.[13] Anemia may decrease a patient's quality of life by causing fatigue, reduced exercise capacity, decreased cognition and impaired immunity. Moreover, left ventricular hypertrophy and maladaptive cardiomyopathy may be a result of anemia increasing the workload on the heart. These cardiovascular effects increase

the risk of death from heart failure or ischemic heart disease.[14] Based on the recommendations from the Kidney Disease Outcome Quality Initiative (K/DOQI) Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease, the hemoglobin level at which ESA therapy should be initiated as well as the hemoglobin target during therapy should be based on the individual patient, potential benefits (including improvement in quality of life and avoidance of transfusion) and potential harms of therapy (including the risk of life-threatening adverse events). Generally speaking, the guidelines recommend that patients with chronic kidney disease, both dialysis and nondialysis, receiving ESA therapy have a hemoglobin target range of 11 to 12 g/dL, and the hemoglobin levels should not exceed 13 g/dL. This recommendation is based on clinical studies demonstrating that patients with a hemoglobin ≥13 g/dL do not have improvements in survival, hospitalization or left ventricular hypertrophy and may in fact be more prone to excessive adverse cardiovascular events compared to individuals with lower hemoglobin targets.[12,15]

In June 2011, the FDA released more conservative recommendations for using the ESAs in patients with anemia of chronic kidney disease resulting from data showing that using ESAs to target a hemoglobin level of >11 g/dL increased the risk cardiovascular events, without providing any additional benefit to patients. For patients with anemia of chronic kidney disease who are not on dialysis, ESA treatment can be considered when the hemoglobin level is <10 g/dL, and the dose should be reduced or interrupted when hemoglobin exceeds 10 g/dL. For patients with anemia of chronic kidney disease currently on dialysis, ESA treatment should be initiated when the hemoglobin level is <10 g/dL, and the dose should be reduced or interrupted when hemoglobin approaches or exceeds 11 g/dL.[16] The Black Box Warnings for all three products reflect the recent recommendations. The K/DOQI guidelines state that the available ESAs are each effective in achieving and maintaining hemoglobin targets, and preference of one agent over another is not provided. [12,15] A position statement by the European Renal Best Practice on anemia in chronic kidney disease suggests a hemoglobin target range of 10 to 12 g/dL in type 2 diabetic patients not receiving dialysis. This recommendation is based on a clinical study that found type 2 diabetic patients with chronic kidney disease are at an increased risk of fatal and non-fatal stroke when receiving ESA therapy with a hemoglobin target of 13 g/dL.[17,18]

Both epoetin alfa and darbepoetin alfa also carry Boxed Warnings regarding shortened survival and increased risk of tumor progression or recurrence in patients with breast, non-small cell lung, head and neck, lymphoid and cervical cancers. Furthermore, the warnings emphasize to use ESAs only for the treatment of anemia due to concomitant myelosuppressive chemotherapy and to discontinue ESAs following completion of a chemotherapy course. Moreover, ESAs should not be initiated in cancer patients receiving myelosuppressive therapy when the anticipated outcome is curative. To further ensure appropriate use of ESAs in cancer patients, hospitals and prescribers wishing to prescribe and dispense ESAs to cancer patients must now be enrolled in a prescriber training and certification program called Assisting Providers and Patients with Risk Information for the Safe Use of ESAs (APPRISE) Oncology program. Prescribers are required to counsel patients on the risks of ESAs and obtain a written acknowledgement from the patients prior to dispensing ESAs. This program does not apply to providers and patients using ESAs for non-cancer indications.[7-10]

Though not FDA-approved, epoetin alfa is used off-label to treat anemia associated with various conditions including but not limited to anemia due to hepatitis C therapy, anemia of prematurity and anemia associated with myelodysplastic syndrome.[19,20] The National Comprehensive Cancer Network clinical practice guidelines on myelodysplastic syndrome recommends the use of ESAs to treat refractory anemia in patients with low-risk disease and whose serum erythropoietin levels are <500 units/L. The guidelines suggest darbepoetin alfa has comparable if not greater efficacy compared to epoetin alfa.[21]

Medications

Table 1. Medications Included Within Class Review[8-11]

Generic Name (Trade name)	Medication Class	Generic Availability
Darbepoetin alfa (Aranesp®)	Erythropoietin agent	-
Epoetin alfa (Epogen®, Procrit®)	Erythropoietin agent	-
Peginesatide (Omontys®)	Erythropoietin agent	-

Indications

Table 2. Food and Drug Administration Approved Indications[8-11]

Indication	Darbepoetin alfa	Epoetin alfa	Peginesatide
Treatment of anemia associated with chronic kidney disease, including patients on dialysis and patients not on dialysis	a	a *	
Treatment of anemia due to chronic kidney disease in adult patients on dialysis			a
Treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy	a	a	
Treatment of anemia due to zidovudine administered at ≤ 4200 mg/week in human immunodeficiency virus-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL		a	
Reduce the need for allogeneic red blood cell transfusions among patients with perioperative hemoglobin > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery		a	

*To elevate or maintain the red blood cell level (as manifested by hematocrit or hemoglobin levels) and to decrease the need for transfusions in these patients.

Although not Food and Drug Administration approved for this indication, both darbepoetin alfa and epoetin alfa have been used in the treatment of anemia associated with myelodysplastic syndrome. Darbepoetin alfa has also been used off-label in the treatment of anemia associated with malignancy. Epoetin alfa has been used off-label for anemia associated with the following conditions: chronic disease, congestive heart failure, critically ill patients, epidermolysis bullosa, multiple myeloma, porphyria, prematurity, puerperium, radiation treatment, rheumatoid arthritis, sickle cell disease, thalassemia and treatment with ribavirin and interferon alfa in hepatitis C-infected patients. Additional off-label uses for epoetin alfa include athletic enhancement, sexual dysfunction, transfusional iron overload and uremic pruritus.[19,20]

Pharmacokinetics

The pharmacokinetics of darbepoetin alfa and epoetin alfa were studied in cancer patients and patients with chronic kidney disease. Patients with cancer received subcutaneous darbepoetin alfa or epoetin alfa, whereas patients with chronic kidney disease received intravenous or subcutaneous treatment. The elimination half-life of darbepoetin alfa and epoetin alfa was similar in both pediatric and adult patients with chronic kidney disease.[8-10]

Table 3. Pharmacokinetics[8-11]

Generic Name	Bioavailability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Darbepoetin alfa	Adult, 37*; children, 54*	Not reported	(% not specified)	Not reported	Intravenous, 21*; subcutaneous, adults with cancer, 74; adults on dialysis, 46; adults not on dialysis, 70
Epoetin alfa	Not reported	Not reported	(% not specified)	Not reported	Intravenous, 4 to 13*†; subcutaneous, 40‡
Peginesatide	46	Not reported	(% not specified)	Not reported	Intravenous, healthy adults, 25 patients on dialysis, 48 subcutaneous, healthy adults, 53

*Chronic kidney disease patients.
†Chronic kidney disease patients; approximately 20% longer than healthy adults.
‡Cancer patients.

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the erythropoiesis-stimulating agents (ESAs) in their respective Food and Drug Administration (FDA)-approved indications are listed in Table 4.[7,22-36] There are several clinical studies comparing the efficacy of epoetin alfa to darbepoetin alfa for the treatment of anemia due to chronic kidney disease or myelosuppressive chemotherapy.

Two non-inferiority studies comparing epoetin alfa to darbepoetin alfa in the treatment of anemia of chronic kidney disease demonstrated no difference in efficacy between the two agents. In a study of adult patients with chronic kidney disease by Nissenson et al, the mean changes in hemoglobin levels from baseline to the evaluation period were similar between the darbepoetin alfa (0.16 to 0.09 g/dL) and epoetin alfa (0.00 to 0.06 g/dL) groups (difference, 0.16 g/dL; 95% confidence interval [CI], -0.06 to 0.38; *P* value not reported). In a second study by Vanrenterghem and colleagues (N=522) of patients with chronic kidney disease on dialysis, the mean change in hemoglobin was 0.05 g/dL in the darbepoetin alfa group compared to 0.00 g/dL in the epoetin alfa treatment (difference, 0.05 g/dL; 95% CI, -0.14 to 0.24; *P* values not reported). No statistically significant differences in the mean change in hemoglobin levels from baseline, the primary endpoint were reported. In addition, in both studies there were no differences in safety profiles and no antibodies detected to either treatment.[23,24]

The Agency for Healthcare Research and Quality (AHRQ) performed a meta-analysis of 57 randomized controlled studies, seven of which directly compared epoetin alfa to darbepoetin alfa in patients diagnosed with malignant disease that were anemic or at risk for anemia from chemotherapy and/or radiotherapy or the underlying malignant disease. Of the endpoints evaluated, the AHRQ found that the evidence did not show any clinically significant differences between epoetin alfa and darbepoetin alfa with regard to hemoglobin response, transfusion reduction and thromboembolic events. Of the other endpoints evaluated, it was determined that the evidence was not sufficient for conclusions on effects of either epoetin alfa or darbepoetin alfa on quality of life, tumor response and progression, survival or adverse outcomes.[7]

Darbepoetin alfa is not FDA-approved for the treatment of anemia in patients with human immunodeficiency virus who are receiving zidovudine therapy or for the reduction of allogeneic blood transfusions in surgery patients and there are no comparative studies between the erythropoiesis-stimulating agents for these two indications. Darbepoetin alfa and epoetin alfa have been used off-label in the treatment of anemia associated with myelodysplastic syndrome. There are currently no clinical studies directly comparing the efficacy of darbepoetin alfa to epoetin alfa in this non-FDA approved indication; however, a meta-analysis of 30 studies found that there was no difference in hemoglobin response between darbepoetin alfa and epoetin alfa therapies.[38]

To date, studies demonstrating the safety and efficacy of peginesatide have not been published outside of the prescribing information. Peginesatide was evaluated in two randomized, multi-center, open-label studies compared to epoetin alfa or beta. In Study 1, patients taking intravenous epoetin one to three times per week were randomized to continue current epoetin therapy or switch to intravenous peginesatide once-monthly. The mean change in hemoglobin values were similar between peginesatide (-0.09 g/dL) and epoetin (-0.24 g/dL) over weeks 29 to 36, the primary endpoint. The least squares mean change between treatments was -0.15 g/dL (95% CI, -0.30 to -0.01). Patients in Study 2 were receiving intravenous or subcutaneous administration of epoetin one to three times per week and were randomized to continue current treatment or switch to peginesatide once-monthly via their baseline administration route. The mean change in hemoglobin from baseline, the primary endpoint, was similar between peginesatide (-0.07 g/dL) and epoetin therapy (-0.17 g/dL). The least squares mean change between treatments was 0.1 g/dL (95% CI, -0.05 to 0.26). In both studies, the proportion of patients receiving blood transfusions was similar between treatments. Furthermore, the composite safety endpoint of death, myocardial infarction, stroke or serious adverse events of congestive heart failure, unstable angina or arrhythmia occurred in 22.8% of patients receiving peginesatide compared to 24.45% of patients receiving epoetin (hazard ratio, 0.95; 95% CI, 0.77 to 1.17).[11]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Anemia Associated With Chronic Kidney Disease, Including Patients on Dialysis and Patients Not on Dialysis				
Locatelli et al[22] Darbepoetin alfa 0.45 µg/kg SC once-weekly vs epoetin alfa 50 units/kg SC twice weekly Study drug dose was adjusted by 25% of the starting dose as necessary to achieve a hemoglobin increase of ≥1 g/dL from baseline and to maintain hemoglobin levels within a range of 11 to 13 g/dL.	MC, OL, RCT Adult patients diagnosed with CKD not yet receiving dialysis and ESA-naïve 12 weeks before first planned study dose, a hemoglobin <11 g/dL, adequate iron stores (serum ferritin ≥100 µg/L), serum Vitamin B_{12} levels and folate levels above the lower limit of the normal range, and a creatinine clearance of <30 mL/minute	N=166 24 weeks	Primary: Proportion of patients achieving a hemoglobin response during the 24-week treatment period, (increase in hemoglobin of ≥1 g/dL from baseline and a hemoglobin level of ≥11 g/dL) Secondary: Time to achieve a hemoglobin response, hemoglobin level over time, dose of study drug at the time of hemoglobin response and at week 24, number of patients receiving blood transfusions and adverse events	Primary: Ninety-three percent (95% CI, 87 to 97) of patients in the darbepoetin alfa group and 92% (95% CI, 78 to 98) of patients in the epoetin alfa group achieved a hemoglobin response (*P* value not reported). Secondary: In both groups, the median time to achieve a hemoglobin response was seven weeks (three to 25 weeks). The mean hemoglobin level after four weeks of therapy was 1.38 g/dL (95% CI, 1.21 to 1.55) in the darbepoetin alfa group and 1.40 g/dL (95% CI, 1.07 to 1.72) in the epoetin alfa group (*P* value not reported). Mean changes in hemoglobin was similar between the two groups up to 24 weeks (*P* value not reported). At the time of hemoglobin response, the median weekly weight-adjusted dose of darbepoetin alfa was 0.46 µg/kg (0.3 to 2.3), and the corresponding dose of epoetin alfa was 100 units/kg (range of 75 to 175). Both doses were nearly identical to those at the beginning of the study. At week 24, median study drug doses had decreased to 0.34 µg/kg (range of 0.00 to 1.30) in patients receiving darbepoetin alfa and to 56.9 units/kg (range of 19.0 to 250.0) in patients receiving epoetin alfa (*P* values not reported). Three patients in the darbepoetin alfa group and two patients in the epoetin alfa group required blood transfusions (*P* value not reported). Safety profiles were similar between the two groups. Adverse events were reported in 107 patients (83%) in the darbepoetin alfa group and in 24 patients (65%) in the epoetin alfa group; most were mild to moderate in nature (*P* value not reported). The most commonly reported adverse events in darbepoetin alfa and epoetin alfa groups were hypertension (32 and 22%, respectively) and peripheral edema (13 and 11%, respectively) (*P* values not reported).

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				There were six reported deaths in the study, 4% in the darbepoetin alfa group and 3% in the epoetin alfa group (*P* value not reported).
Nissenson et al[23] Darbepoetin alfa IV once-weekly (initial dose was based on the total weekly dose of epoetin alfa at the time of randomization [200 units of epoetin alfa=1 µg of darbepoetin alfa]) vs epoetin alfa IV TIW After a 4-week screening and baseline period, patients were randomized to continue epoetin alfa IV TIW or change to darbepoetin alfa IV once-weekly (plus placebo two times weekly). Study drug was adjusted to maintain hemoglobin levels within -1.0 to 1.5 g/dL) of their baseline values and within a range of 9 to 13 g/dL.	DB, MC, NI, RCT Adult patients with CKD, clinically stable on HD for ≥12 weeks, stable on IV epoetin alfa therapy TIW for ≥8 weeks, a mean baseline hemoglobin level of 9.5 to 12.5 g/dL and a transferrin saturation of ≥20% or greater	N=504 28 weeks	Primary: Mean change in hemoglobin levels from baseline to evaluation periods Secondary: Percentage of hemoglobin values within the target range (-1.0 to 1.5 g/dL of baseline and nine to 13 g/dL), hemoglobin levels necessitating a dose change, within-patient variance in hemoglobin levels, dose of study drug and adverse events	Primary: The mean changes in hemoglobin levels from baseline to the evaluation period were similar between the darbepoetin alfa (0.16 to 0.09 g/dL) and epoetin alfa (0.00 to 0.06 g/dL) groups, with a difference of 0.16 g/dL (95% CI, -0.06 to 0.38; *P* value not reported). Secondary: The 95% CI of the ratio between darbepoetin alfa and epoetin alfa included one, indicating no statistically significant difference between treatments in each of the secondary endpoints (actual values and *P* values not reported). In the darbepoetin alfa group, 69% of patients had a dose change during the titration period, and 44% changed dose during the evaluation period. In epoetin alfa-treated patients, 73 and 49% had dose changes during the titration and evaluation periods, respectively (*P* values not reported). At least one adverse event was reported in 93% of patients in the darbepoetin alfa group and 99% of patients in the epoetin alfa group. The most frequently reported adverse events included nausea (29% for darbepoetin alfa; 27% for epoetin alfa), upper respiratory infection (27% for both groups) and hypertension (28% for darbepoetin alfa; 24% for epoetin alfa) (*P* values not reported). Nine patients (5%) in the darbepoetin alfa group and 23 patients (7%) in the epoetin alfa group died during the study or within 30 days of the last dose of study drug (*P* value not reported). Deaths were reported by the study investigators as unrelated to study drug.
Vanrenterghem et al[21] Darbepoetin alfa (initial dose was based on the total weekly dose of epoetin alfa at the time of randomization [200 units of epoetin alfa=1 µg of	MC, OL, RCT Patients ≥18 years with CKD, clinically stable on HD or PD for ≥6 months, stable on	N=522 52 weeks	Primary: The mean change in hemoglobin from baseline to evaluation period	Primary: The mean change in hemoglobin from baseline to evaluation period was 0.05 g/dL (SD, 0.80) in the darbepoetin alfa group and 0.00 g/dL (SD, 0.87) in the rHuEPO group for a difference of 0.05 g/dL (95% CI, -0.14 to 0.24; *P* values not reported). Secondary:

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darbepoetin alfa]) vs rHuEPO After a 4-week screening and baseline period, patients were randomized to continue rHuEPO at current dose or change to darbepoetin alfa using the same route but at a reduced frequency (i.e., weekly or every other week). Study drugs were adjusted to maintain hemoglobin levels within -1.0 to 1.5 g/dL) of their baseline values and within a range of 9 to 13 g/dL.	rHuEPO IV therapy given one, two or three times weekly for ≥3 months, a mean baseline hemoglobin of 9.5 to 12.5 g/dL and a serum ferritin of >100 µg/L		Secondary: Proportion of patients necessitating a dose change, within-subject variance of hemoglobin, proportion of patients in the target (-1.0 to 1.5 g/dL of baseline and 9 to 13 g/dL) and therapeutic ranges (9 to 13 g/dL) and adverse events	The ratios (95% CI) between darbepoetin alfa and rHuEPO for each of the secondary endpoints were as follows: proportion of patients necessitating a dose change, within-subject variance of hemoglobin, 0.794 (0.476 to 1.325); proportion of patients in the target ranges, 1.030 (0.855 to 1.242) and therapeutic ranges, 1.036 (0.993 to 1.081) (*P* values not reported). The 95% CI included 1 in all secondary endpoints, demonstrating no significant differences between the treatment groups. At least one adverse event was reported in 96% of patients in the darbepoetin alfa group and 95% of patients in the rHuEPO group. The three most commonly reported adverse events were hypotension (39% for darbepoetin alfa; 38% for rHuEPO), myalgia (34% for darbepoetin alfa; 36% for rHuEPO) and hypertension (30% for darbepoetin alfa, 28% for rHuEPO) and those with the largest reported rates between the groups were pruritus (14% for darbepoetin alfa; 5% for rHuEPO) and back pain (10% for darbepoetin alfa; 16% for rHuEPO) (*P* values not reported). There were 52 deaths during the study, 12% of patients (41/346) in the darbepoetin alfa treatment group compared to 6% (11/173; 6%) (*P*=0.062). All deaths were reported by the study investigators as unrelated to study drug.
Anemia Associated With Concomitant Chemotherapy in Patients With Metastatic, Non-myeloid Malignancies				
Bohlius et al[25] Darbepoetin alfa (no minimal dose was required) or epoetin alfa IV or SC ≥300 units/kg body weight per week for at least four weeks vs placebo or no treatment	MA of 57 RCTs Patients diagnosed with malignant disease, using clinical and histological/ cytological criteria, regardless of type or stage of the disease or previous therapy, anemic or at risk	N=9,353 >20 weeks	Primary: Hematological response, patients receiving red blood cell transfusions, number of red blood cell units transfused per patient and overall survival Secondary: Tumor response	Primary: Hematological response occurred in 1,364 of 2,486 participants in the epoetin alfa/darbepoetin alfa groups compared to 286 of 1,821 participants in the control groups (RR, 3.43; 95% CI, 3.07 to 3.84; *P* value not reported). The RR of red blood cell transfusions was significantly reduced in the epoetin alfa/darbepoetin alfa groups compared to the control group (RR, 0.64; 95% CI, 0.60 to 0.68; *P* value not reported). On average, participants in the epoetin alfa or darbepoetin alfa group received one unit of blood less than the control group (WMD, -1.05; 95% CI, -1.32 to -0.78; *P* value not reported). Overall survival demonstrated a HR of 1.08 (95% CI, 0.99 to 1.18) in favor of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	for anemia from chemotherapy and/or radiotherapy or the underlying malignant disease		(complete response), changes in quality of life including cancer-related fatigue and adverse events	placebo or no treatment, but the effect is uncertain (*P* value not reported). Secondary: The overall estimate of tumor response showed a RR of 1.12 (95% CI, 1.01 to 1.23) in favor of ESAs but the effect is uncertain (*P* value not reported). The results show an overall positive effect on quality of life from epoetin alfa, which seems unlikely to be due to chance. The size of this effect is impossible to speculate on using the method of analysis employed. What was noted was that for participants with baseline hemoglobin below 12 g/dL, hematological response was observed more often in participants receiving epoetin alfa or darbepoetin alfa (RR, 3.43; 95% CI, 3.07 to 3.84; *P* value not reported). For adverse events, the RR for thromboembolic complications was increased in patients receiving epoetin alfa or darbepoetin alfa compared to placebo (RR, 1.67, 95% CI, 1.35 to 2.06). The RR to develop hypertension for ESA-treated participants was increased by 24% (RR, 1.24; 95% CI, 1.00 to 1.54). The RR of developing thrombocytopenia was not increased in the ESA-treated participants (RR, 1.13; 95% CI, 0.08 to 1.60). Overall 21 events of skin rash, irritations or pruritus in the ESA group (N=395) and 11 cases in the control group (N=280) were reported resulting in a RR of 1.17 (95% CI, 0.63 to 2.18). There was no evidence for significant differences in seizures between the groups compared (RR, 1.19; 95% CI, 0.33 to 4.35; *P* values not reported).
Bohlius et al[26] Darbepoetin alfa IV or SC (no minimal dose was required) or epoetin alfa IV or SC (no minimal dose was required) vs	MA of 53 RCTs with at least 100 patients in each study Patients with a diagnosis of malignant disease receiving chemotherapy and/or radiation	N=13,933 8 to 52 weeks	Primary: Mortality during the active study period and overall survival (defined as death from any cause between date of randomization and date of the last available	Primary: During the active study period, more deaths occurred in the ESA group (865 of 7,634 patients) compared to the placebo group (665 of 6,699 patients; HR, 1.17; 95% CI, 1.06 to 1.30; *P*=0.0025). Among patients undergoing chemotherapy, mortality rate between the two treatment groups was similar during the active study period, 605 of 5,676 patients in the ESA group died, compared to 490 of 4,765 patients in the placebo group (HR, 1.10; 95% CI, 0.98 to 1.24; *P*=0.1212). During the follow-up period, 2,643 of 7,634 cancer patients in the ESA group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo or no treatment	therapy or no therapy		follow-up) in all cancer patients and in those on chemotherapy Secondary: Not reported	died, compared to 2,350 of 6,299 patients in the placebo group (HR, 1.06; 95% CI, 1.00 to 1.12; *P*=0.0464). Survival rate during the follow-up period among patients receiving chemotherapy was not significantly different between the two groups (HR, 1.04; 95% CI, 0.97 to 1.11; *P*=0.2634). Secondary: Not reported
Seidenfeld et al[7] Darbepoetin alfa (no minimal dose was required) vs epoetin alfa IV or SC ≥300 units/kg body weight per week for at least four weeks or darbepoetin alfa or epoetin alfa vs observation (alone or with placebo)	MA of 59 RCT Patients diagnosed with malignant disease and undergoing treatment with chemotherapy or radiotherapy	N=6,531 ≤16 weeks	Primary: Hematological response, rate of transfusion and thromboembolic events Secondary: Quality of life, tumor response and progression, survival and adverse events	Primary: Although a MA on hematological response was not performed due to differences in the definition of response, five of six trials comparing darbepoetin alfa to epoetin alfa showed no statistically significant difference between these agents. For rates of transfusion, trials comparing darbepoetin alfa to epoetin alfa showed no statistically significant difference between these agents (RR, 1.10; 95% CI, 0.93 to 1.29; *P* value not reported). For thromboembolic events, trials comparing darbepoetin alfa to epoetin alfa showed no statistically significant difference between these agents (RR, 0.86; 95% CI, 0.61 to 1.21; *P* value not reported). Secondary: The evidence is not sufficient for conclusions on effects of either epoetin alfa or darbepoetin alfa on quality of life, tumor response and progression, survival or adverse events other than thromboembolic events (*P* values not reported). Trials did not completely or consistently report quality of life results. Overall, quality of life measures tended to favor treatment with epoetin alfa or darbepoetin alfa. However, the degree of change varied widely across studies, and not all positive changes were statistically significant (*P* values not reported). The limited evidence available (five studies, N=688) does not suggest that

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				ESAs improve solid tumor response to a concurrent course of cancer therapy (*P* values not reported). Of 40 (N=8,249) RCTs reporting on survival, only seven (N=2,188) were actually designed to assess effects on survival (progression-free or overall). No studies designed to test survival used epoetin alfa or darbepoetin alfa as currently recommended; rather, all seven trials sought to maintain hemoglobin levels >12 g/dL. Analysis of mortality in all 40 trials showed no overall benefit of darbepoetin alfa or epoetin alfa on survival (*P* value not reported). For other adverse events, reporting is incomplete, representing less than one-third of patients. Studies did not use consistent definitions of events and severity. Overall, adverse events were more frequent with epoetin alfa or darbepoetin alfa than control, but pooled results did not show statistically significant differences.
Glaspy et al[27] Darbepoetin alfa 200 µg once-every 2 weeks vs epoetin alfa 40,000 units once-weekly For both treatment arms, a 50% dose escalation was permitted at week 5 if the hemoglobin increase was <1 g/dL. Study drug was withheld if a patient's hemoglobin >13 g/dL at any time and was reinstated at 75% of the previously	MC, OL, RCT Adult patients with a diagnosis of nonmyeloid malignancy with ≥8 weeks of planned chemotherapy, anemia (hemoglobin ≤11 g/dL), adequate renal and liver function and the ability to provide written informed consent	N=1,220 18 weeks	Primary: Incidence of red blood cell transfusion from week five to end of treatment period Secondary: Transfusion requirements over the entire treatment period, proportion of patients achieving a hemoglobin ≥11 g/dL, those who subsequently maintained	Primary: Twenty-one percent (95% CI, 17 to 24) of patients in the darbepoetin alfa group received a red blood cell transfusion between week five and the end of the treatment period compared to 16% (95% CI, 12 to 19) of patients in the epoetin alfa group (*P* value not reported). Noninferiority was concluded due to the upper 95% CI limit of the difference between groups (10.8%) being below the pre-specified noninferiority margin of 11.5%. Secondary: Twenty-seven percent (95% CI, 24 to 31) of patients in the darbepoetin alfa group received a red blood cell transfusion over the entire treatment period compared to 22% (95% CI, 19 to 26) of patients in the epoetin alfa group (*P* value not reported). Noninferiority was concluded due to the upper 95% CI limit of the difference between groups being below the pre-specified noninferiority margin of 11.5%. Eighty percent (463 patients) of patients achieved target hemoglobin level of ≥11 g/dL in the darbepoetin alfa group compared to 86% (487 patients) of patients in the epoetin alfa group (*P* values not reported). Of these patients, 341 (74%) in the darbepoetin alfa group and 389 (80%) in the epoetin group

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administered dose after the hemoglobin concentration decreased to ≤12 g/dL.			hemoglobin levels in the target range (11 to 13 g/dL), mean hemoglobin change from baseline, HRQOL and adverse events	maintained hemoglobin level in the target range (*P* value not reported). In both groups, the mean hemoglobin levels improved from approximately 10.2 g/dL at baseline to 11.8 g/dL by the end of the treatment period (*P* value not reported). No differences were observed between the two groups for any of the other HRQOL assessments (fatigue, anemia, emerge, daily activity and overall health) (*P* values not reported). The safety profiles of darbepoetin alfa and epoetin alfa were similar with no differences observed between groups. Cardiovascular and thromboembolic events were reported in 6% of patients the darbepoetin alfa group and 7% of patients in the epoetin alfa group. The death rates were 11% in the darbepoetin alfa group and 14% in the epoetin alfa group (*P* values not reported).
Case et al[28] Darbepoetin alfa at recommended doses vs epoetin alfa at recommended doses The majority of patients in the darbepoetin alfa arm received dosages of 200 µg every other week (93%) while the others received 100 µg weekly or 300 µg every other week. In the epoetin alfa arm most patients received a dosage of 40,000 units weekly (86%),	RETRO Patients with a gynecologic malignancy (cervical, ovarian endometrial, or vaginal) receiving chemotherapy with ≥1 agent in a single outpatient setting who had chemotherapy-induced anemia (hemoglobin <10 g/dL), and had received at least 2 doses of either darbepoetin alfa or epoetin alfa	N=123 Duration not specified	Primary: Transfusion rates Secondary: Change in hemoglobin after receiving ≥2 doses of each agent and dosage and frequency of administration of each agent	Primary: Twenty-one patients in the in the darbepoetin alfa group received a transfusion compared to 12 patients in the epoetin alfa group (*P*=0.05). Secondary: The mean change in hemoglobin after receiving ≥2 doses was 2.5 g/dL for the darbepoetin alfa group and 2.3 g/dL for the epoetin alfa group; the difference was not statistically significant (*P* value not reported). Patients in the epoetin alfa group did receive an increased number of respective ESA (5.7 for darbepoetin alfa and 8.1 for epoetin alfa; *P*=0.001).

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with the remainder receiving 60,000 units weekly.				
Pashos et al[29] Darbepoetin alfa initiated at 500 µg (frequency not specified) vs epoetin alfa initiated at 40,000 units (frequency not specified) The mean dose per injection observed in the study was 488 µg for darbepoetin alfa and 41,979 units for epoetin alfa.	MC, OS, PRO Adult patients with malignant disease who have received at least two doses of darbepoetin alfa or epoetin alfa	N=540 ≤16 weeks	Primary: Patient-specific treatment duration, darbepoetin alfa and epoetin alfa utilization and cumulative cost, change in hemoglobin levels from baseline at weeks four, eight, 12 and 16, percentage of patients requiring blood transfusions between day 28 and the end of study, number of units of packed red blood cells transfused per patient Secondary: Not reported	Primary: The average treatment duration was 61.8 days in the darbepoetin alfa group and 60.9 days in the epoetin alfa group (*P*=0.888). The epoetin alfa-to-darbepoetin alfa dose ratio was 169:1. Patients in the epoetin alfa group had a greater increase in hemoglobin levels from baseline through week 12 compared to patients in the darbepoetin alfa group (0.6 vs 0.1 g/dL, respectively; *P*=0.032). The mean cumulative epoetin alfa cost per patient was significantly lower than the cumulative darbepoetin alfa cost per patient ($4,261 vs $8,643, respectively; *P*=0.0001). Cost was calculated based on May 2009 wholesale acquisition costs of $4.94/µg for darbepoetin alfa and $0.014/unit for epoetin alfa. Fewer patients receiving epoetin alfa required a blood transfusion between day 28 and the end of study (13.9%) compared to darbepoetin alfa (22.5%; *P*=0.026). The number of units of red blood cell transfused per patient was also lower in the epoetin alfa group than the darbepoetin alfa group (0.4 vs 0.7, respectively; *P*=0.02). Secondary: Not reported
Anemia Associated With Therapy of Zidovudine in Human Immunodeficiency Virus-Infected Patients To Elevate or Maintain the Red Blood Cell Level and to Decrease the Need for Transfusions in These Patients				
Henry et al[30] rHuEPO 100 to 200 units/kg IV or SC TIW	MA of 4 DB, MC, RCTs Patients 18 to 75	N=297 ≤12 weeks	Primary: Changes in hematocrit, transfusion	Primary: Patients whose serum endogenous erythropoietin level was ≤500 IU/L and received rHuEPO had significantly greater increases in hematocrit from baseline compared to the placebo group (mean change, 4.6 vs 0.5,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo IV or SC TIW Dosing was to continue for 12 weeks or until a hematocrit of ≥38% (without a transfusion in the previous four weeks) was achieved. Results were evaluated based on patients' endogenous erythropoietin levels (low: ≤500 IU/L or high: >500 IU/L).	years of age with a diagnosis of AIDS (based on CDC criteria), a performance status of 0, 1 or 2 according to the system of Miller et al[31], a hematocrit of ≤30% and dependant on transfusions and at least a 15% decline in hematocrit since the initiation of zidovudine therapy		requirements, quality of life and adverse events Secondary: Not reported	respectively; *P*=0.0002; mean difference, 3.9; 95% CI, 1.8 to 6.0). Of patients whose serum endogenous erythropoietin level was >500 IU/L, there were no significant differences in changes in hematocrit from baseline between the rHuEPO group and the placebo group (mean change, 3.2 vs 2.2, respectively; *P*>0.2; mean difference, 0.9; 95% CI, -2.1 to 3.9). Patients with low serum endogenous erythropoietin level and received rHuEPO had significantly lower transfusion requirements compared to the placebo group (mean units per patient, 3.19 vs 5.34 units, respectively; *P*=0.003; mean difference, -1.88; 95% CI, -3.18 to -0.58). Of patients with high serum endogenous erythropoietin levels, there were no significant differences in transfusion requirements between the rHuEPO group and the placebo group (mean units per patient, 9.35 vs 8.83, respectively; *P* value not reported; mean difference, 0.22; 95% CI, -1.28 to 1.72). In patients with low serum endogenous erythropoietin levels, there were no significant differences in the overall quality of life score between the rHuEPO and placebo groups (mean change, 0.92 vs -5.33, respectively; *P*=0.13). Scores for patients with high erythropoietin levels were not reported. No significant differences in the incidence or severity of adverse events (i.e. pyrexia, fatigue, headache and cough) were observed between the rHuEPO and placebo groups (*P* values not reported). Two patients in the placebo group and four in the rHuEPO group died during the study (*P* value not reported). Secondary: Not reported
Treatment of Anemic Patients (Hemoglobin >10 to <13 g/dL) at High Risk for Perioperative Blood Loss From Elective, Noncardiac, Nonvascular Surgery to Reduce the Need for Allogeneic Blood Transfusions				
Faris et al[32] Group 1:	DB, MC, RCT Adult patients	N=200 4 weeks	Primary: Percentage of patients who	Primary: Significantly fewer patients in the rHuEPO treatment groups required transfusions compared to those in the placebo group (Group 1, 17%; Group

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rHuEPO 100 units/kg/day SC vs Group 2: rHuEPO 300 units/kg/day SC vs Group 3: placebo SC daily The study drugs were administered for 15 consecutive days, beginning 10 days before the operation and extending through to the fourth postoperative day. Patients were also stratified into two groups based on the pre-treatment hemoglobin levels.	scheduled to have a major orthopedic procedure in which transfusion of ≥2 units of whole blood or red blood cells is usually required during or after the procedure, who could not or did not choose to donate autologous blood preoperatively and, if female, had been postmenopausal for ≥1 year, were sterile or were using a reliable method of birth control and had had a negative pregnancy test immediately before being enrolled in the study		were transfused and the number of units of blood that each patient received Secondary: Change in erythroid parameters and adverse events	2, 25%; Group 3, 54%; *P*≤0.001 for both rHuEPO groups compared to placebo). There was no significant difference between the two rHuEPO groups (*P* value not reported). The mean number of units transfused for each patient was significantly lower in the rHuEPO groups compared to the placebo group (Group 1, 0.37±0.96; Group 2, 0.58±1.15; Group 3, 1.42±1.67; *P*<0.01 for both rHuEPO groups compared to placebo). There was no significant difference between Groups 1 and 2 (*P*>0.05). In those patients who had a baseline hemoglobin level of 10 to 13 g/dL, rHuEPO significantly reduced the proportion of patients who received a red-blood-cell transfusion compared to placebo (14% in Group 1, 39% in Group 2 and 78% in Group 3; *P*≤0.009 for both rHuEPO groups compared to the placebo group). For patients who had a baseline hemoglobin level of ≥13 g/dL, similar trend was seen among the treatment groups (14% in Group 1, 11% in Group 2 and 36% in Group 3; *P*=0.03 for both rHuEPO groups compared to the placebo group). Secondary: Adverse events were reported in 97% of patients in Group 1, 92% in Group 2 and 93% in Group 3. Nine percent of patients in Group 3 reported depression, compared to 0% of patients in Group 1 (*P*<0.05). Ten percent of patients in Group 3 reported chest pain, compared to 1% of patients in Group 2 (*P*<0.05) and 2% of patients in Groups 1 and 2 combined (*P*<0.05). Reports of thrombotic and vascular events were not significantly different between the rHuEPO and placebo groups (*P*=0.40).
deAndrade at al[33] Epoetin alfa 100 units/kg SC daily vs	DB, MC, PC, PG Adult patients scheduled for elective orthopedic surgery of the hip or knee,	N=316 6 weeks	Primary: Risk of transfusion Secondary: Mean number of units transfused	Primary: Overall, 11% of patients receiving epoetin alfa 100 units/kg, 11% of patients receiving epoetin alfa 300 units/kg and 23% of patients receiving placebo underwent allogeneic red blood cell transfusions (*P* values not reported). For patients in stratum 2, (hemoglobin >10 to ≤13 g/dL) patients who received epoetin alfa experienced significantly less transfusions compared to placebo (16 vs 45%, respectively; *P*=0.024).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
epoetin alfa 300 units/kg SC daily vs placebo SC daily The study drugs were administered for 15 consecutive days, beginning 10 days before the operation and extending through to the fourth postoperative day. Patients were stratified based on their entry hemoglobin level (stratum 1: hemoglobin ≤10 g/dL, stratum 2: hemoglobin >10 to ≤13 g/dL and stratum 3: hemoglobin >13 g/dL).	in good general health with no clinically significant abnormal lab values, expected to require ≥2 units of blood without having participated in a preoperative autologous donation program, a hemoglobin level ≤15 g/dL, and a serum iron to TIBC ≥15% and a serum ferritin level ≥50 ng/mL		per patient, hemoglobin, hematocrit and reticulocyte levels and adverse events	Secondary: Overall, the mean number of units transfused per person was significantly lower in patients treated with epoetin alfa compared to patients treated with placebo (*P*=0.0278). For patients in stratum 2, the mean number of units transfused was 1.140±1.432 in the placebo group compared to 0.420±0.945 in the epoetin alfa 100 units/kg group (*P*=0.0180) and 0.450±1.207 in the epoetin alfa 300 units/kg group (*P*=0.0229). The mean hemoglobin, hematocrit and reticulocyte levels were higher in the epoetin alfa-treated patients than in the placebo-treated patients through post-surgery day seven for patients in stratum 2 (*P* values not reported). In stratum 2, significantly greater increases in mean hemoglobin and reticulocyte counts were noted with both epoetin alfa groups compared to the placebo group (*P*=0.0001 for both). Epoetin alfa was safe and well tolerated. The incidence of adverse events was similar across treatment groups and across baseline hemoglobin strata. Most commonly reported adverse events were: pyrexia, nausea and constipation.
Christodoulakis et al[34] Epoetin alfa 150 units/kg SC daily vs epoetin alfa 300 units/kg SC daily vs control group Patients received treatment beginning 10 days before	OL Adult patients undergoing elective colorectal surgery for resectable colorectal cancer with a hemoglobin level >9 and <12 g/dL	N=223 Duration not specified	Primary: Need for blood transfusions Secondary: Effects on hematocrit, hemoglobin and reticulocyte count	Primary: Patients in the 300 units/kg epoetin alfa group required significantly fewer transfusion units compared to the control patients, both perioperatively (0.81±1.22 [0 to 5] vs 1.34±1.59 [0 to 7], respectively; *P*=0.016) and postoperatively (0.87±1.21 [0 to 4] vs 1.35±1.58 [0 to 7], respectively; *P*=0.023). The epoetin alfa 150 units/kg group was not significantly different from the control group (perioperatively, 1.19±1.46 [0 to 7] and postoperatively, 1.10±1.42 [0 to 7]; *P* values not reported). Secondary: Mean hematocrit levels were significantly higher in the 150 units/kg epoetin alfa group than in the control group at day -1 (*P*=0.031) and at day +15 (*P*=0.030); however, the 300 units/kg epoetin alfa group obtained significantly higher mean hematocrit levels than the 150 units/kg group (*P*=0.031 and *P*=0.030, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
surgery until the day after surgery.				Significantly greater increase in hemoglobin concentrations were seen with the epoetin alfa groups compared to the control group (*P*<0.004 for both epoetin alfa groups vs control). Reticulocyte and white blood cell counts in both the 150 and 300 units/kg epoetin alfa groups were significantly lower compared to the control group at baseline (day -10; *P*<0.05), but there were no other significant differences in hematological values at any time point (*P* values not reported).
Goldberg et al[35] Epoetin alfa 300 units/kg SC daily for 10 days prior to surgery, on the day of surgery and for four days postoperatively vs epoetin alfa 600 units/kg SC once per week for three weeks prior to surgery and on the day of surgery	MC, OL, PG, RCT Adult patients scheduled for major elective orthopedic surgery involving hip or knee replacement, in good general health, not enrolled in a preoperative autologous donation program prior to surgery, provided informed consent, had a hemoglobin level ≥10 to ≤13 g/dL, a serum iron to TIBC ratio ≥0.20 and a serum ferritin ≥50 ng/mL	N=145 Duration not specified	Primary: Mean change in hemoglobin and absolute reticulocyte counts from prestudy to presurgery Secondary: Proportion of patients transfused, mean change in hemoglobin and reticulocyte counts presurgery to postsurgery day one, total units transfused per patient, reasons for transfusion and safety	Primary: Mean change in hemoglobin from prestudy to presurgery in the epoetin alfa 600 units/kg group was 1.44±1.03 g/dL compared to 0.73±0.87 g/dL in the epoetin alfa 300 units/kg group (95% CI, 0.3786 to 1.0326; *P* value not reported). Mean change in absolute reticulocyte counts from prestudy to presurgery in the epoetin alfa 600 units/kg group was 0.110±0.069x10^6 cells/mm^3 compared to 0.170±0.070x10^6 cells/mm^3 in the epoetin alfa 300 units/kg group (95% CI, -0.1515 to 0.0326; *P* value not reported). Secondary: The proportion of patients transfused in the epoetin alfa 600 units/kg group was 16% (11 patients) compared to 20% (14 patients) in the epoetin alfa 300 units/kg group (95% CI, -16.44 to 8.88; *P* value not reported). Mean change in hemoglobin from presurgery to postsurgery day one in the epoetin alfa 600 units/kg group was -2.94±1.43 g/dL, compared to -2.30±1.30 g/dL in the epoetin alfa 300 units/kg group (95% CI, -1.0393 to -0.2374; *P* value not reported). Mean change in absolute reticulocyte counts from presurgery to postsurgery day one was -0.05±0.05x10^6 cells/mm^3 in both the epoetin alfa 600 units/kg and epoetin alfa 300 units/kg groups (95% CI, -0.0845 to 0.0848; *P* value not reported). The mean number of units of allogeneic blood transfused per patient was 0.33±0.87 in the epoetin alfa 600 units/kg group compared to 0.30±0.64 in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				epoetin alfa 300 units/kg group (95% CI, -0.2526 to 0.3277). Anemia (hemoglobin <9 g/dL) was the most common reason for transfusion which accounted for 68.8% of all transfusions. At least one adverse event was reported in 96% of patients in the epoetin alfa 600 units/kg group compared to 99% in the epoetin alfa 300 units/kg group (*P* value not reported). The most commonly reported adverse events included constipation, pyrexia and nausea. One death was reported in the epoetin alfa 600 units/kg group although it was reported to be unlikely related to the drug. Four patients (5%) in the epoetin alfa 600 units/kg group reported thrombotic/vascular events, and none were reported in the 300 units/kg group; all were reported to be unrelated to the study drug.
Feagan et al[36] Low-dose group: Epoetin alfa 20,000 units SC weekly vs High-dose group: epoetin alfa 40,000 units SC weekly vs placebo SC weekly Therapy was initiated four weeks prior to surgery. The total possible dose was 160,000 units in the high-dose group and 80,000 units in the low-dose group.	DB, MC, PG, RCT Adult patients undergoing total hip joint arthroplasty, had a hemoglobin level 9.8 to 13.7 g/dL and did not donate blood preoperatively	N=201 Duration not specified	Primary: Allogeneic transfusion Secondary: Change in reticulocyte count and hemoglobin concentration, thromboembolic events and adverse events	Primary: The percent of patients who received an allogeneic transfusion in each of the groups was as follows: 11.4% (five of 44 patients) in the high-dose group and 22.8% (18 of 79 patients) in the low-dose group, compared to 44.9% (35 of 78 patients) in the placebo group (*P*=0.001 and *P*=0.003, respectively, for epoetin groups compared to the placebo group). Secondary: Mean reticulocyte counts significantly increased in the high-dose group ($58.8x10^9$ cells/L) compared to the low-dose group ($37.0x10^9$ cells/L; *P*=0.003) and the placebo group ($1.8x10^9$ cells/L; *P*<0.001). Mean hemoglobin levels increased in the high-dose group (1.95 g/dL) and low-dose group (1.72 g/dL), whereas little changes occurred in the placebo group (0.12 g/dL; *P*<0.001). Occurrences of thrombotic events (DVT/PE) occurred in the two patients in the high-dose group, five patients in the low-dose group and six patients in the placebo group (*P* value not reported). The proportion of patients who experienced any serious adverse event was similar in the three study groups: 8.5% in the placebo group, 3.5% in the low-dose group and 6.5% in the high-dose group (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
The study drug was withheld if hemoglobin was ≥150 g/L, if systolic blood pressure was ≥200 mm Hg or if the diastolic blood pressure was ≥105 mm Hg.				
Treatment of Anemia Associated with Myelodysplastic Syndrome (Non-Food and Drug Administration Approved Indication)				
Ross et al[37] Darbepoetin alfa SC or IV or epoetin alfa or epoetin beta* SC or IV vs placebo or no treatment	MA of 59 OS, RCT, RETRO Patients with myelodysplastic syndrome with an average baseline hemoglobin level 8.4 g/dL and baseline serum erythropoietin level 374 units/L	N=2,106 1 to 104 weeks	Primary: Percentage of patients with hemoglobin response using the IWGc[†] Secondary: Transfusion, quality of life measured by changes on FACT[‡]-Fatigue and LASA, adverse events	Primary: In four controlled studies (N=172), 27.3% of patients in the epoetin group had a hemoglobin response, compared to 6.7% of patients in the placebo group (OR, 5.2; 95% CI, 2.5 to 10.8; *P* value not reported). In 46 non-controlled studies (N=1,508) using epoetin alfa or epoetin beta, the hemoglobin response rate was 32.1% (95% CI, 26.3 to 37.9). The hemoglobin response rate with darbepoetin alfa in three non-controlled studies (N=102) was 48.1% (95% CI, 25.2 to 70.9). Secondary: Fewer patients treated with epoetin required transfusions compared to patients treated with placebo in the controlled studies (77.8 vs 90.4%; OR, 0.3; 95% CI, 0.1 to 1.6; *P* value not reported). In non-controlled studies, 62.4% of epoetin-treated patients and 45.9% of darbepoetin alfa-treated patients required transfusion. There was insufficient data to assess quality of life. No adverse events were observed to reach a statistically significant odds ratio in the controlled studies.
Moyo et al[38] Epoetin alfa in IWGc studies vs epoetin alfa in non-IWGc studies	MA of 30 trials Patients with myelodysplastic syndrome, with >74% of patients having refractory anemia or	N=1,314 Duration not specified	Primary: Hemoglobin response rates Secondary: Not reported	Primary: The hemoglobin response rate was 57.6% (95% CI, 45.1 to 70.0) in 589 patients receiving epoetin alfa in IWGc studies and 31.6% (95% CI, 24.9 to 38.4) in 336 patients in non-IWGc studies (*P*<0.001). There was no significant difference in the hemoglobin response rate between epoetin alfa and darbepoetin alfa. The hemoglobin response rate in the darbepoetin alfa group was 59.4% (95% CI, 49.0 to 69.9), compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
or darbepoetin alfa in non-IWGc studies Dosing regimens not specified for all treatment groups.	refractory anemia with ringed sideroblasts			57.6% (95% CI, 45.1 to 70.0) in the epoetin alfa group (*P*=0.8282). Secondary: Not reported

*Agent not available in the United States.
†International Working Group criteria are a uniform set of criteria for assessing erythroid response in myelodysplastic syndrome in clinical trials.
‡ Fatigue=Functional Assessment of Cancer Therapy-Fatigue= scores ranging from 0 to 52, with higher scores indicating less fatigue.
Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, NI=noninferiority, OL=open-labeled, PC=placebo controlled, OS=observational study, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective
Miscellaneous abbreviations: AIDS=acquired immunodeficiency syndrome, CDC=Centers for Disease Control, CI=confidence interval, CKD=chronic kidney disease, ESA=erythropoiesis-stimulating agent, DVT=deep vein thrombosis, FACT-Fatigue=Functional Assessment of Cancer Therapy-Fatigue, HD=hemodialysis, HR=hazard ratio, HRQOL=health-related quality of life, IU=international unit, IV=intravenous, IWGc= International Working Group criteria, LASA=Linear Analogue Self-Assessment, OR=odds ratio, PD=peritoneal dialysis, PE=pulmonary embolism, rHuEPO=recombinant human erythropoietin, RR=relative risk, SC=subcutaneous, SD=standard deviation, TIBC=total iron-binding capacity, TIW=three times a week, WMD=weighted mean difference

Table 5. Special Populations[8-11]

Generic Name	Population and Precaution					
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk	Others
Darbepoetin alfa	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in pediatric cancer patients and chronic renal failure patients less than one year of age have not been established.	Patients with chronic kidney disease not yet receiving dialysis may require lower maintenance doses. Patient maintenance dose should be individualized.	Not reported	C	Unknown	Safety and efficacy in patients with underlying hematologic diseases have not been established.
Epoetin alfa	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in pediatric patients less than one month of age have not been established.*	Patient maintenance dose should be individualized.	Not reported	C	Unknown	Safety and efficacy in patients with a known history of seizure disorders or underlying hematologic diseases have not been established.
Peginesatide	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Patient maintenance dose should be individualized.	Not reported	C	Unknown	None

Generic Name	Population and Precaution					
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk	Others
	Safety and efficacy in children have not been established.					

*Benzyl alcohol, found in multi-dose preserved formulations, has been reported to be associated with an increased incidence of neurological and other complications in premature infants, which are sometimes fatal.[8-11]

Adverse Drug Events

The most commonly reported adverse events with erythropoiesis-stimulating agents (ESAs) include hypertension, headache and fever. Seizures and thromboembolic events have also been reported in patients receiving ESAs. A potential for immunogenicity exists with these agents and has been documented in post-marketing reports. The following table presents the most common (occurring ≥5%) adverse events reported with ESAs.[8-11]

Table 6. Adverse Drug Events (%)[8-11]

Adverse Event	Darbepoetin alfa	Epoetin alfa	Peginesatide
Cardiovascular			
Angina pectoris or cardiac chest pain	8	-	-
Cardiac arrhythmias or cardiac arrest	8	-	-
Chest pain, unspecified	7	7	-
Congestive heart failure	5	-	-
Hypertension	20	10 to 24	13.2
Hypotension	20	-	10.9 to 14.2
Thrombosis vascular access	6	-	-
Thrombotic events	6.2	3 to 10	-
Central Nervous System			
Anxiety	-	2 to 11	-
Dizziness	7 to 14	5 to 21	-
Fatigue	9 to 33	9 to 25	-
Fever	7 to 19	29 to 51	12.2
Headache	12 to 15	10 to 19	15.4
Insomnia	-	13 to 21	-
Dermatological			
Access hemorrhage	7	-	-
Access infection	6	-	-
Clotted access	-	7	-
Injection site pain/reaction	6	7 to 29	-
Pruritus	6	14 to 22	-
Rash	7	16	-
Skin pain	-	4 to 18	-
Gastrointestinal			
Abdominal pain	10	-	-
Constipation	5 to 18	42 to 53	-
Diarrhea	14 to 22	6 to 21	18.4
Dyspepsia	-	7 to 11	-
Nausea	11	11 to 58	17.4
Vomiting	14	8 to 29	15.3

Adverse Event	Darbepoetin alfa	Epoetin alfa	Peginesatide
Musculoskeletal			
Arthralgia	9 to 13	11	10.7
Back pain	7	-	10.9
Limb pain	8	-	-
Muscle spasm	17	-	15.3
Myalgia	8	-	-
Pain in extremity	-	-	10.9
Respiratory			
Bronchitis	5	-	-
Congestion	-	15	-
Cough	9	18	15.9
Dyspnea	10	-	18.4
Shortness of breath	-	13 to 14	-
Upper respiratory infection	15	11	-
Other			
Arteriovenous fistula site complication	-	-	16.1
Asthenia	5	7 to 13	-
Death	6	-	-
Dehydration	5	-	-
Edema	21	6 to 17	-
Fluid overload	6	-	-
Hyperkalemia	-	-	11.4
Infection*	24	-	-
Influenza like symptoms	6	-	-
Paresthesia	-	11	-
Peripheral edema	10	-	-
Urinary tract infection	-	3 to 12	11

- Event not reported or incidence ≤5%.
*Infection includes sepsis, bacteremia, pneumonia, peritonitis and abscess.

Contraindications

Table 7. Contraindications[8-11]

Contraindication	Darbepoetin alfa	Epoetin alfa	Peginesatide
Allergy to active ingredient	a	a	-
Neonates, infants, pregnant women, and nursing mothers	-	a *	-
Pure red blood cell aplasia (PRCA) that begins after treatment with erythropoietin protein drugs	a	a	-
Uncontrolled hypertension	a	a	a

*Procrit from multi-dose vials contains benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients. When therapy is needed in neonates and infants, use single-dose vials; do not admix with bacteriostatic saline containing benzyl alcohol

Black Box Warning for Darbepoetin alfa[8]

WARNING
Increased mortality, serious cardiovascular and thromboembolic events, stroke and increased risk of tumor progression or recurrence: *Chronic renal failure*: · In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a

WARNING
hemoglobin level of greater than 11 g/dL. · No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks. · Use the lowest darbepoetin alfa dose sufficient to reduce the need for red blood cell (RBC) transfusions. *Cancer*: · Erythropoiesis-stimulating agents 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 transfusions. · Because of these risks, prescribers and hospitals must enroll in and comply with the erythropoiesis-stimulating agents APPRISE Oncology Program to prescribe and/or dispense darbepoetin alfa to patients with cancer. To enroll in the erythropoiesis-stimulating agents APPRISE Oncology Program, visit www.esa-apprise.com or call 1-866-284-8089 for further assistance. · Use erythropoiesis-stimulating agents only for treatment of anemia due to concomitant myelosuppressive chemotherapy. · Erythropoiesis-stimulating agents are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure. · Discontinue following the completion of a chemotherapy course.

Black Box Warning for Epoetin alfa[9,10]

WARNING
Increased mortality, serious cardiovascular and thromboembolic events, stroke and increased risk of tumor progression or recurrence: *Chronic renal failure*: · In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL. · No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks. · Use the lowest epoetin alfa dose sufficient to reduce the need for red blood cell (RBC) transfusions. *Cancer*: · Erythropoiesis-stimulating agents 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 transfusions. · Because of these risks, prescribers and hospitals must enroll in and comply with the erythropoiesis-stimulating agents APPRISE Oncology Program to prescribe and/or dispense epoetin alfa to patients with cancer. To enroll in the erythropoiesis-stimulating agents APPRISE Oncology Program, visit www.esa-apprise.com or call 1-866-284-8089 for further assistance. · Use erythropoiesis-stimulating agents only for treatment of anemia due to concomitant myelosuppressive chemotherapy. · Erythropoiesis-stimulating agents are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.

WARNING
· Discontinue following the completion of a chemotherapy course. Perisurgery: · Epoetin alfa increased the rate of deep venous thromboses in patients not receiving prophylactic anticoagulation. Consider deep venous thrombosis prophylaxis.

Black Box Warning for Peginesatide[11]

WARNING
Increased mortality, serious cardiovascular and thromboembolic events, stroke and increased risk of tumor progression or recurrence: *Chronic renal failure*: · In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL. · No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks. · Use the lowest peginesatide dose sufficient to reduce the need for red blood cell (RBC) transfusions.

Warnings/Precautions

Table 8. Warnings and Precautions[8-11]

Contraindication	Darbepoetin alfa	Epoetin alfa	Peginesatide
Dialysis management; patients may require adjustments in dialysis prescriptions after initiating erythropoietin treatment.	a	a	a
Hypertension; reduce or withdraw therapy if blood pressure becomes difficult to control	a	a	a
Increased mortality and/or increased risk of tumor progression or recurrence in patients with cancer	a	a	a
Increased mortality, myocardial infarction, stroke, and thromboembolism	a	a	a
Increases the risk of seizures in patients with chronic kidney disease. Closely monitor patients during the first several months following the initiation of treatment.	a	a	-
In order to prescribe and distribute this product in patients with cancer, prescribers and hospitals must enroll and comply with ESA APPRISE Oncology Program requirements.	a	a	-
Laboratory monitoring for transferring saturation and serum ferritin prior to and during treatment.	a	a	a
Lack or loss of hemoglobin response; initiate a search for causative factors and follow dose recommendation for patients with insufficient response to therapy.	a	a	a
Product contains albumin, a derivative of human blood. There is an extremely remote risk for transmission of viral diseases.	-	a	-

Pure red blood cell aplasia; withhold treatment and evaluate for neutralizing antibodies to erythropoietin	a	a	-
Serious allergic reactions may occur.	a	a	-

Drug Interactions
There are no specific drug interactions reported with the use of the erythropoietin agents.[8-11]

Dosage and Administration
In order to ensure effective erythropoiesis, evaluate iron stores prior to and during therapy with erythropoiesis-stimulating agents (ESAs). The majority of patients will eventually require supplemental iron therapy. In addition, after administration of an ESA, the hemoglobin should be monitored routinely until it has stabilized and the maintenance dose has been established. Once stabilized, the hemoglobin should be monitored at regular intervals.[8-11]

In order to prescribe and/or dispense ESAs to cancer patients, prescribers must be enrolled in the ESA Assisting Providers and Patients with Risk Information for the Safe Use of ESAs (APPRISE) Oncology program. Moreover, prescribers and patients must provide written acknowledgement of a discussion of the risks associated with these agents.[8-11]

Table 9. Dosing and Administration[8-11]

Generic Name	Adult Dose	Pediatric Dose	Availability
Darbepoetin alfa	Anemia associated with chronic kidney disease for patients on dialysis: Initial, 0.45 µg/kg IV or SC once-weekly or 0.75 µg/kg SC once-every two weeks; maintenance, dose should be individualized to maintain hemoglobin levels that do not exceed 11 g/dL Anemia associated with chronic kidney disease for patients not on dialysis: Initial, 0.45 µg/kg IV or SC once-every four weeks; maintenance, dose should be individualized to maintain hemoglobin levels that do not exceed 10 g/dL Anemia associated with concomitant chemotherapy in patients with metastatic, non-myeloid malignancies based on studies that have shown a reduction in the need for red blood cell transfusions: Initial, 2.25 µg/kg SC once-weekly or 500 µg SC once every three weeks; maintenance, dose should be individualized to maintain the lowest hemoglobin level sufficient to avoid red blood	Safety and efficacy in pediatric cancer patients and chronic renal failure patients less than one year of age have not been established.	Single-dose vial (polysorbate solution or albumin solution): 25 µg/mL 40 µg/mL 60 µg/mL 100 µg/mL 150 µg/0.75 mL 200 µg/mL 300 µg/mL 500 µg/mL Single-dose prefilled syringe and single-dose autoinjector (polysorbate solution or albumin solution): 25 µg/0.42 mL 40 µg/0.4 mL 60 µg/0.3 mL 100 µg/0.5 mL 150 µg/0.3 mL 200 µg/0.4 mL 300 µg/0.6 mL 500 µg/mL

Generic Name	Adult Dose	Pediatric Dose	Availability
	cell transfusion		
Epoetin alfa	Anemia associated with chronic kidney disease, including patients on dialysis and patients not on dialysis: Initial, 50 to 100 units/kg IV or SC TIW; maintenance, dose should be individualized to maintain hemoglobin levels that do not exceed 11 mg/dL (dialysis) or 10 g/dL (non-dialysis) Anemia associated with concomitant chemotherapy in patients with metastatic, non-myeloid malignancies based on studies that have shown a reduction in the need for red blood cell transfusions: Initial, 150 units/kg SC TIW or 40,000 units SC weekly; maintenance, dose should be individualized to maintain the lowest hemoglobin level sufficient to avoid red blood cell transfusion Anemia associated with therapy of zidovudine in human immunodeficiency virus-infected patients to elevate or maintain the red blood cell level (as manifested by hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients: Initial, 100 units/kg IV or SC TIW for eight weeks*; maintenance, dose should be individualized to maintain desired response Treatment of anemic patients (hemoglobin >10 to <13 g/dL) at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions: 300 units/kg/day SC for 10 days before surgery, on the day of surgery and for four days after surgery; alternative dosing	Anemia associated with chronic kidney disease, including patients on dialysis and patients not on dialysis: Initial, 50 units/kg IV or SC TIW; maintenance, dose should be individualized to maintain hemoglobin levels between 10 and 12 g/dL Anemia associated with concomitant chemotherapy in patients with metastatic, non-myeloid malignancies based on studies that have shown a reduction in the need for red blood cell transfusions: Initial, 600 units/kg IV weekly; maintenance, dose should be individualized to maintain the lowest hemoglobin level sufficient to avoid red blood cell transfusion Safety and efficacy in pediatric patients less than one month of age have not been established.†	Multi-dose vial (preserved solution): 10,000 units/mL 20,000 units/mL Single-dose vial (preservative-free solution): 2,000 units/mL 3,000 units/mL 4,000 units/mL 10,000 units/mL 40,000 units/mL

Generic Name	Adult Dose	Pediatric Dose	Availability
	schedule is 600 units/kg SC once-weekly, at 21, 14 and seven days before surgery, with a fourth dose on the day of surgery		
Peginesatide	Treatment of anemia due to chronic kidney disease in adult patients on dialysis: Initial, 0.04 mg/kg IV or SC once- monthly; maintenance, dose should be individualized to maintain the lowest hemoglobin level sufficient to avoid red blood cell transfusion	Safety and efficacy in children have not been established.	Multi-dose vial (preserved solution): 10 mg/mL 20 mg/mL Single-dose pre-filled syringe (preservative-free solution): 1 mg/ 0.5 mL 2 mg/ 0.5 mL 3 mg/ 0.5 mL 4 mg/ 0.5 mL 5 mg/ 0.5 mL 6 mg/ 0.5 mL Single-dose vial (preservative-free solution): 2 mg/ 0.5 mL 3 mg/ 0.5 mL 4 mg/ 0.5 mL 5 mg/ 0.5 mL 6 mg/ 0.5 mL

IV=intravenously, SC=subcutaneously, TIW=three times a week
*For adult patients with serum erythropoietin levels <500 units/mL receiving a dose of zidovudine ≤4,200 mg/week.
†Benzyl alcohol, found in multi-dose preserved formulations, has been reported to be associated with an increased incidence of neurological and other complications in premature infants, which are sometimes fatal.[8-11]

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
National Kidney Foundation Kidney Disease Outcome Quality Initiative: **Kidney Disease Outcome Quality Initiative Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease (2006)[12], Update of Hemoglobin Target (2007)[15]**	Recommendations for anemia in chronic kidney disease in adults · Hemoglobin testing should be carried out in all patients with chronic kidney disease, regardless of disease stage or cause. · Anemia testing of hemoglobin levels should be measured at least annually. · Diagnosis of anemia should be made when hemoglobin reaches <13.5 g/dL in adult males and <12.0 g/dL in adult females. · Selection of the hemoglobin target and level at which erythropoiesis-stimulating agent (ESA) therapy is initiated in the individual patient should include consideration of potential benefits (including improvement in quality of life and avoidance of transfusion) and potential harms (including the risk of life threatening adverse events). · In dialysis and nondialysis patients with chronic kidney disease receiving ESA therapy, the selected hemoglobin target should generally be in the range of 11 to 12 g/dL. · Hemoglobin levels should be monitored at least monthly in patients receiving ESA therapy.

Clinical Guideline	Recommendations
	· The initial ESA dose and dose adjustments should be determined by the patient's hemoglobin level, the hemoglobin target, the observed rate of increase in hemoglobin level and clinical circumstances. · ESA doses should be decreased, but not necessarily withheld, when a downward adjustment of hemoglobin level is needed. · Scheduled ESA doses that have been missed should be replaced at the earliest possible opportunity. · ESA administration in ESA-dependent patients should continue during hospitalization. · Hypertension, vascular access occlusion, inadequate dialysis, history of seizures or compromised nutritional status are not contraindications to ESA therapy. · The route of ESA administration should be determined by the stage of disease, treatment setting, efficacy, safety and class of ESA used. · Convenience favors subcutaneous administration of ESAs in non-hemodialysis patient and intravenous administration in hemodialysis patients. · The disease stage, treatment setting, efficacy considerations, and class of ESA should determine frequency of administration. · Convenience favors less frequent administration, particularly in non-hemodialysis patients. · Iron status tests should be performed every month during initial ESA treatment and at least every three months during stable ESA treatment or in patients receiving hemodialysis not treated with an ESA. · Results of iron status tests, hemoglobin level and ESA dose should be interpreted together to guide iron therapy. · Sufficient iron should be administered to generally maintain the following indices of iron status during ESA therapy: o Hemodialysis: serum ferritin >200 ng/mL, transferrin saturation >20% or reticulocyte hemoglobin content >29 pg/cell. o Nondialysis-dependent and peritoneal dialysis-dependent: serum ferritin >100 ng/mL and transferrin saturation >20%. · There is insufficient evidence to recommend routine administration of intravenous iron if the serum ferritin level is >500 ng/mL. When the ferritin level is >500 ng/mL, decisions regarding intravenous iron administration should take into consideration response to ESAs, hemoglobin, transferrin saturation and the patient's clinical status. · Androgens should not be used as an adjuvant to ESA treatment in anemic patients with chronic kidney disease. · There is insufficient evidence to recommend the use of L-carnitine or vitamin C (ascorbate) as adjuvants to ESA treatment in the management of anemia in patients with chronic kidney disease. · Patients with anemia and chronic kidney disease should undergo evaluation for specific causes of hyporesponse whenever the hemoglobin level is inappropriately low for the ESA dose administered. Such conditions include, but are not limited to: o A significant increase in the ESA dose requirement to maintain a certain hemoglobin level. o A significant decrease in hemoglobin at a constant ESA dose. o A failure to increase the hemoglobin to > 11 g/dL despite an ESA dose equivalent to epoetin alfa >500 units/kg/week. · Evaluation for antibody-mediated pure red cell aplasia is recommended when a patient receiving ESA therapy for more than four weeks develops

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	each of the following: o Sudden rapid decrease in hemoglobin at the rate of 0.5 to 1.0 g/dL/week OR requirement of red blood cell transfusions at the rate of approximately one to two times per week. AND o Normal platelet and white blood cell counts. AND o Absolute reticulocyte count <10,000/µL. Clinical practice recommendations for anemia in chronic kidney disease in children · In the pediatric patient, diagnosis of anemia should be made and further evaluated whenever the observed hemoglobin level is less than the fifth percentile of normal when adjusted for age and sex. · Selection of the hemoglobin target and selection of the hemoglobin level at which ESA therapy is initiated in the individual pediatric patient should include consideration of potential benefits (including improvement in quality of life, school attendance, performance and avoidance of transfusion) and potential harms (including the risk of life-threatening adverse events). · In pediatric dialysis and nondialysis patients with chronic kidney disease receiving ESA therapy, the selected hemoglobin target should generally be in the range of 11 to 12 g/dL and should not be >13 g/dL. · In pediatric patients, the route of administration should be determined by the disease stage, treatment setting, efficacy considerations, the class of ESA used and the anticipated frequency of and pain of administration. · In pediatric patients, the frequency of administration should be determined by the disease stage, treatment setting, efficacy considerations and class of ESA; consideration should be given to the anticipated frequency of and pain of administration of each agent and their potential effects on the child and family. · Sufficient iron should be administered to maintain the following indices of iron status during ESA treatment: o Hemodialysis: serum ferritin >100 ng/mL and transferrin saturation >20%.
European Renal Best Practice: **Anemia Management in Patients with Chronic Kidney Disease: A Position Statement by the Anemia Working Group of European Renal Best Practice (2009)[14], Update Following the TREAT Study (2010)[39]**	· Hemoglobin levels defining a diagnosis of anemia is <13.5 g/dL in adult males and <12.0 g/dL in adult females. · In general, hemoglobin target range in patients with chronic kidney disease should be 11 to 12 g/dL; hemoglobin should not exceed 13 g/dL. · During ESA therapy in patients with chronic kidney disease, iron status should be monitored with transferrin saturation and serum ferritin levels. Transferrin saturation should be maintained at >20% and serum ferritin should be maintained at 100 ng/mL in nondialysis patients and 200 ng/mL in dialysis patients. · Epoetin delta* has the same amino acid sequence as endogenous epoetin and epoetin alfa but is synthesized in human cells. Its pharmacokinetics and pharmacodynamics are similar to epoetin alfa and therefore should be administered similarly to epoetin alfa. · Continuous erythropoiesis receptor activator*, a modified recombinant human erythropoietin, has a considerably longer half-life than other ESAs and should be dosed once every two weeks for anemic correction and once every four weeks for maintenance of hemoglobin levels. The safety and tolerability of continuous erythropoiesis receptor activator are similar

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	to that of other ESAs. · Biosimilars of epoetin alfa can only be administered intravenously and should not be used in exchange of the original ESA or other ESAs without physician's approval. · Suspected antibody-mediated pure red cell aplasia should be carefully evaluated. Retreatment with ESAs may be considered in patients with a history of pure red cell aplasia if anti-epoetin antibodies are no longer detectable. · Iron replacement therapy should be used first-line in patients with chronic kidney disease who are or may be iron-deficient. Replete iron stores prior to initiating ESA therapy. · Iron should be administered to patients with chronic kidney disease during ESA therapy in order to reach and maintain the desired hemoglobin target with the lowest ESA doses. · Consider ESA therapy when hemoglobin levels are consistently <11 g/dL when all other causes of anemia have been excluded. · Start ESAs at a low dose to avoid exceeding the hemoglobin target. Dose adjustments should be made gradually to avoid an increase in hemoglobin of >2 g/dL per month. · A lower hemoglobin target range of 10 to 12 g/dL is reasonable in nondialysis patients with type 2 diabetes. The patient's involvement is important in making a decision on the desired hemoglobin level. · The risks and benefits of blood transfusion should be considered carefully, especially for patients who are eligible for kidney transplantation. · In diabetic patients with ischemic heart disease or a history of stroke, the benefit of reduced need for coronary revascularization procedures and transfusion should be carefully weighed against an increased risk of stroke recurrence when using ESAs. Use the lowest possible ESA doses to reach the hemoglobin target. · In patients with a history of cancer, the risk of tumor recurrence and related death should be considered prior to starting ESA therapy. Use the lowest possible ESA doses to reach the hemoglobin target. · The use of high ESA doses should be carefully evaluated, especially in patients who do not respond to treatment as expected or in whom the worsening of anemia is linked to non-renal factors.
National Comprehensive Cancer Network: **Cancer- and Chemotherapy Induced Anemia Clinical Practice Guidelines in Oncology (2013)**[40]	<u>ESA therapy in cancer-related anemia</u> · Use ESAs only to treat anemia due to concomitant myelosuppressive chemotherapy in cancer patients. · Discontinue ESAs after the completion of chemotherapy when anemia resolves, which is usually within six to eight weeks after the last chemotherapy cycle. · ESAs should only be administered to cancer patients with informed patient consent under the risk evaluation and mitigation strategy program required by the Food and Drug Administration (FDA), which consists of providing Medication Guides to patients and enrolling in a provider assistance program. <u>Special categories in considering ESA use</u> · ESA therapy should not be used in patients who are receiving chemotherapy when the anticipated treatment outcome is curative, such as primary and adjuvant chemotherapy. · ESA therapy or red blood cell transfusion is recommended in patients receiving palliative care.

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	· For the remainder of patients experiencing anemia on myelosuppresive chemotherapy without other identifiable causes of anemia ESA therapy or red blood cell transfusion is recommended. · In patients with chronic kidney disease and malignancies, the use of ESAs can be considered with regard to indications and dosing adjustments for this patient population. · The hemoglobin threshold for treating and dosing with ESAs is different for chemotherapy-induced anemia and chronic kidney disease. · Healthcare providers prescribing ESAs for patients with cancer must enroll in the ESA APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe use of ESAs) Oncology Program. <u>ESA therapy: administration and response assessment</u> · Epoetin alfa and darbepoetin alfa are equivalent in efficacy and safety. · The recommended initial dosing of epoetin alfa includes 150 units/kg subcutaneously three times weekly and 40,000 units subcutaneously once- weekly. Other dosing schedules may be considered including an extended dosing of 80,000 units subcutaneously every two weeks and a dose of 120,000 units subcutaneously every three weeks. · For darbepoetin alfa, the recommended dosing includes 2.25 µg/kg subcutaneously once-weekly or 500 µg subcutaneously once every three weeks. <u>ESA therapy: response assessment and dose titration</u> · Treatment with ESAs is required for at least two weeks before there is an increase in red blood cells. · Hemoglobin levels should be measured weekly until they are stabilized. · A 25 to 40% reduction in ESA doses (individualization may be needed) should occur if hemoglobin increases by ≥1 g/dL in two weeks or if hemoglobin reaches a level sufficient to avoid blood transfusion. · If hemoglobin increases by <1 g/dL after four weeks of epoetin alfa therapy or six weeks of darbepoetin alfa therapy, the ESA doses should be titrated up. Epoetin alfa dose should be increased from 150 units/kg three times weekly or 40,000 units once-weekly to 300 units/kg three times weekly or 60,000 units once-weekly, respectively. If darbepoetin alfa is used, the dose should be increased from 2.25 µg/kg once weekly to 4.5 µg/kg once weekly. · Iron supplementation may be considered to improve patient response to ESA therapy. · Treatment response should be reevaluated after eight to nine weeks of therapy. ESA therapy should be discontinued in patients who have no response despite iron supplementation, and blood transfusion should be considered. · ESAs should be discontinued when chemotherapy is completed and anemia has resolved, usually within six weeks of chemotherapy completion. <u>Iron monitoring and supplementation</u> · Prior to initiating ESA therapy, patients should receive iron studies including serum iron, total iron binding capacity and serum ferritin to rule out absolute iron deficiency, which may be treated with oral iron therapy. · “Functional” iron deficiency often occurs with continued ESA therapy, and iron supplementation is usually required. It is recommended that

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	intravenous iron products be used (without ESAs) for repletion in cancer patients with an absolute iron deficiency (ferritin <30 ng/mL, transferrin saturation <15%) or in patients receiving ESAs who have functional iron deficiency (ferritin ≤800 ng/mL, transferrin saturation <50%).
American Society of Hematology/ American Society of Clinical Oncology: **American Society of Clinical Oncology/ American Society of Hematology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients With Cancer (2010)**[41]	· Each patient with cancer should be thoroughly assessed to rule out other causes of anemia (iron, folate and B12 deficiency). Consideration should be given to minimize the use of ESAs in patients with high risk of thromboembolic events and the possibility of death, especially in patients undergoing chemotherapy with curative intent. · Based on current literature comparing the efficacy of epoetin alfa and darbepoetin alfa in patients with chemotherapy-induced anemia, these agents are equivalent with respect to effectiveness and safety. · To decrease transfusion, epoetin alfa and darbepoetin alfa are both recommended as treatment options for patients with chemotherapy-induced anemia and a hemoglobin <10 g/dL. Blood transfusion is also an option depending upon the severity of the anemia or clinical circumstances. · An optimal hemoglobin level at which to initiate ESA therapy in patients with anemia and a hemoglobin level between 10 and 12 g/dL cannot be definitively determined. In these patients, initiation of ESA therapy should be determined by clinical judgment, taking into consideration the risks and benefits of ESAs and patient preferences. · Due to clinical data published regarding the increased risk of thromboembolism with epoetin alfa and darbepoetin alfa therapy, risks (i.e. history of thromboses, surgery and prolonged immobilization or limited activity) should be evaluated, and caution should be used with these products. Blood transfusion is also an option when warranted by clinical conditions. · The FDA-approved starting dose of epoetin alfa is 150 units/kg three times a week or 40,000 units once-weekly subcutaneously. The FDA-approved starting dose of darbepoetin alfa is 2.25 µg/kg once-weekly or 500 µg once every three weeks subcutaneously. Dose adjustments should follow the FDA-approved product labeling. There is a lack of data supporting greater effectiveness with the use of alternative starting doses and different dose titration schedules. · ESAs should be discontinued in patients who have failed to respond (<1 to 2 g/dL increase in hemoglobin or no decrease in transfusion requirements) after six to eight weeks of therapy. These patients should be evaluated for underlying tumor progression, iron deficiency or other etiologies for anemia. · Epoetin alfa or darbepoetin alfa should be titrated to the lowest hemoglobin levels needed to avoid transfusions, which may vary by patient and disease condition. An optimal hemoglobin target cannot be determined by the available literature. To avoid excessive ESA exposure, reducing the ESA dose is appropriate when hemoglobin reaches a level sufficient to avoid transfusion or when hemoglobin increases more than 1 g/dL in two weeks. · To help reduce the need for ESA therapy, baseline and periodic iron studies (i.e., iron, total iron binding capacity, transferring saturation, ferritin levels) should be performed and iron repletion should be instituted when indicated. There is inadequate evidence to specify the optimal timing, frequency or testing regimen for monitoring iron status. There is also insufficient evidence to use intravenous iron as standard of care.

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	· ESAs should not be used for the treatment of anemia in patients with malignancies who are not receiving concurrent myelosuppressive chemotherapy. An exception to this recommendation is the use of ESAs in patients with low-risk myelodysplastic syndrome to avoid transfusion. · For patients with myeloma, non-Hodgkin's lymphoma or chronic lymphocytic leukemia, initiate treatment with chemotherapy and/or corticosteroids and observe hematological outcomes through tumor reduction before considering ESA therapy. If hemoglobin fails to increase following chemotherapy, the use of epoetin alfa or darbepoetin alfa in these patients should follow the recommendations outlined above. Particular caution should be exercised in the use of ESAs concomitant with chemotherapeutic agents and diseases where risk of thromboembolic complications is increased. Blood transfusion is also a therapeutic option.
The Human Immunodeficiency Virus Medicine Association of the Infectious Diseases Society of America: **Guidelines for the Management of Chronic Kidney Disease in Human Immunodeficiency Virus-Infected Patients (2005)**[42]	· All patients at the time of human immunodeficiency virus diagnosis should be assessed for existing kidney disease with a screening urine analysis for proteinuria and a calculated estimate of renal function. · Use of ESAs should be considered in patients with hemoglobin levels that are 2 g/dL less than the lower limit of normal; the hemoglobin target range is between 11 and 12 g/dL. · ESA therapy is an appropriate treatment option for patients with symptomatic mild or moderate anemia (hemoglobin level that is ≥2 g/dL below the lower limit of normal).
American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. **Practice Guidelines for Perioperative Blood Transfusion and Adjuvant Therapies (2006)**[43]	· Literature supports the use of ESAs in reducing the volume of allogeneic blood transfused per patient as well as reducing the number of patients requiring such transfusion in selected populations (e.g., renal insufficiency, anemia of chronic disease, refusal of transfusion). · It is recommended that ESAs be administered when possible to reduce the need for allogeneic blood in selected patient populations (*e.g.*, renal insufficiency, anemia of chronic disease, refusal of transfusion). It is recognized that ESA therapy is perceived as being expensive and requires time (in weeks) to induce a significant increase in hemoglobin concentration.
National Comprehensive Cancer Network: **Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (2011)**[21]	Treatment of related anemia · ESAs have been used safely in improving symptomatic anemia in patients with myelodysplastic syndrome. Treatment should aim for a target hemoglobin of ≤12 g/dL. · Patients with normal cytogenetics, with <15% marrow blasts and serum erythropoietin levels of ≤500 units/L tend to respond well to ESA therapy compared to those with high serum erythropoietin levels. · A typical epoetin dose is 40,000 to 60,000 units once to three times a week subcutaneously in patients with myelodysplastic syndrome. Patients generally respond within six to eight weeks of treatment. A more prompt response may be seen by initiating ESAs at a higher dose. · If patient responds to ESA treatment, the dose of ESA may be continued, but attempts should be made to decrease the dose to tolerance. · Iron repletion should be verified before initiating ESA therapy. · The addition of a colony stimulating factor should be considered in

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	patients who do not respond to ESAs alone. After the addition of colony stimulating factor, if no response occurs within six to eight weeks, then treatment should be discontinued. · ESA use is not recommended in patients with serum erythropoietin levels >500 units/L since these patients tend to have very low response rate to ESA therapy. · Darbepoetin alfa has a similar or possibly higher hemoglobin response rate compared to epoetin.

*Product not available in the United States.

Conclusions

The three erythropoiesis-stimulating agents (ESAs) available in the United States include darbepoetin alfa (Aranesp®), epoetin alfa (Epogen®, Procrit®) and peginesatide (Omontys®). All three agents are Food and Drug Administration (FDA)-approved for the treatment of anemia associated with chronic kidney disease; however, peginesatide is only indicated for patients who are currently on dialysis. Both epoetin alfa and darbepoetin alfa are also approved for the treatment anemia due to the effect of concomitantly administered chemotherapy in patients with metastatic, non-myeloid malignancies. Furthermore, epoetin alfa is approved for the treatment of anemia related to therapy with zidovudine in human immunodeficiency virus-infected patients as well as the treatment of anemic patients who are at risk for perioperative blood loss from elective, noncardiac, nonvascular surgery.[8-11] Both darbepoetin alfa and epoetin alfa have been used off-label for the treatment of anemia associated with myelodysplastic syndrome.[19,20] Peginesatide has been evaluated in adult patients with anemia of chronic kidney disease who are not on dialysis; however, a higher incidence of cardiovascular events was reported with peginesatide compared to darbepoetin alfa. Therefore, it has not been approved for use in this population.[11]

The three ESAs have similar pharmacological actions but differ in their elimination half-lives. Due to the additional carbohydrate chain on the darbepoetin alfa molecule, its half-life is prolonged two- to three-fold, allowing it to be dosed less frequently than epoetin alfa.[5] For the treatment of anemia associated with chronic kidney disease, the recommended frequency of administration of epoetin alfa is three times weekly while darbepoetin alfa is given once weekly.[8-10] Peginesatide is a pegylated synthetic peptide that is administered once monthly and is not structurally similar to erythropoietin. This may reduce the risk of antibody formation and incidence of pure red cell dysplasia.[11] Clinical trials comparing the efficacy of the epoetin alfa and darbepoetin alfa for the treatment of anemia associated with chronic kidney disease as well as anemia due to the concomitant chemotherapy have demonstrated no differences between the agents.[23-25] To date, there are no published studies comparing these agents for the other FDA-approved indications or against peginesatide. Current practice guidelines for anemia of chronic kidney disease, such as the National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI), and the American Society of Hematology/American Society of Clinical Oncology (ASH/ASCO) guideline for the use of epoetin alfa and darbepoetin alfa in patients with cancer do not specify a preferred agent. The K/DOQI guideline states that each of the agents are effective at achieving and maintaining target hemoglobin levels, and the ASH/ASCO guideline states that based on available data, these agents should be considered equivalent with respect to effectiveness and safety.[10,13,39] If a patient switches from epoetin alfa or darbepoetin alfa to peginesatide, the instructions on dosage conversion are provided in the product labeling for peginesatide.[11]

The ESAs are commonly used for the treatment of anemia associated with chronic kidney disease to improve quality of life and reduce the need for transfusions. According to the K/DOQI Anemia Guidelines, ESAs are critical in the management of anemia of chronic kidney disease. The K/DOQI guidelines recommend a hemoglobin target range of 11 to 12 g/dL (not to exceed 13 g/dL) in dialysis and nondialysis patients with chronic kidney disease receiving ESA therapy. In June 2011, the FDA released new recommendations for using the ESAs in patients with anemia of chronic kidney disease as a result of data demonstrating that using ESAs to target a hemoglobin level of > 11 g/dL increased the risk cardiovascular events, without providing any additional benefit to patients. For patients with anemia of

chronic kidney disease who are not on dialysis, ESA treatment can be considered when the hemoglobin level is <10 g/dL, and the dose should be reduced or interrupted when hemoglobin exceeds 10 g/dL. For patients with anemia of chronic kidney disease currently on dialysis, ESA treatment should be initiated when the hemoglobin level is <10 g/dL, and the dose should be reduced or interrupted when hemoglobin approaches or exceeds 11 g/dL.[16] The Black Box Warnings on all three products were updated to reflect the FDA recommendations. Due to the increased risk for mortality and tumor progression associated with ESA therapy in patients with malignancies, the FDA warns that ESAs should be reserved for those who are receiving concomitant myelosuppressive chemotherapy and only when the chemotherapy is not intended to be curative.

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