



Erythropoiesis Stimulating Proteins

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-approved Indications
darbepoetin (Aranesp®) ¹	Amgen	<ul style="list-style-type: none"> ▪ Treatment of anemia associated with chronic renal failure (CRF) 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. <ul style="list-style-type: none"> – Darbepoetin is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure. – Darbepoetin is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy. – Darbepoetin is not indicated as a substitute for red blood cell (RBC) transfusion in patients who require immediate correction of anemia. – Darbepoetin use has not been demonstrated in controlled clinical trials to improve quality of life, fatigue, or patient well-being.
rHuEPO (Epogen®) ²	Amgen	<ul style="list-style-type: none"> ▪ Treatment of anemia associated with CRF including patients on dialysis and patients not on dialysis to decrease the need for red blood cell (RBC) transfusion. ▪ Treatment of anemia related to therapy with zidovudine ($\leq 4,200$ mg per week) in HIV-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL. ▪ 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. ▪ Indicated to reduce the need for allogenic RBC transfusion among patients with perioperative hemoglobin > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery. <ul style="list-style-type: none"> – rHuEPO is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy. – rHuEPO is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure. – rHuEPO is not indicated as a substitute for red blood cell (RBC) transfusion in patients who require immediate correction of anemia. – rHuEPO is not indicated in patients undergoing cardiac or vascular surgery. – rHuEPO is not indicated for patients who are willing to donate autologous blood pre-operatively. – rHuEPO use has not been demonstrated in controlled clinical trials to improve quality of life, fatigue, or patient well-being.
rHuEPO (Procrit®) ³	Amgen (distributed by Janssen)	<ul style="list-style-type: none"> – rHuEPO is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy. – rHuEPO is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure. – rHuEPO is not indicated as a substitute for red blood cell (RBC) transfusion in patients who require immediate correction of anemia. – rHuEPO is not indicated in patients undergoing cardiac or vascular surgery. – rHuEPO is not indicated for patients who are willing to donate autologous blood pre-operatively. – rHuEPO use has not been demonstrated in controlled clinical trials to improve quality of life, fatigue, or patient well-being.

rHuEPO = recombinant human epoetin alfa; HIV = human immunodeficiency virus

OVERVIEW

Anemia is a frequent complication, affecting over three million Americans, associated with a number of serious diseases, such as chronic kidney disease (CKD), diabetes, heart disease, and cancer, as well as chronic inflammatory conditions like rheumatoid arthritis or inflammatory bowel disease. These conditions can cause anemia by interfering with the production of oxygen-carrying red blood cells (RBCs).⁴ Sometimes, as in the case of cancer chemotherapy, anemia can be caused by the treatment itself.

Erythropoietin is a glycoprotein produced in the kidneys that stimulates RBC production from bone marrow. Erythropoietin acts on the erythroid progenitor cells in the bone marrow to cause late differentiation and maturity of the RBCs.^{5,6,7} Endogenous production of erythropoietin by the kidney is normally regulated by the level of tissue oxygenation. Hypoxia and anemia generally increase the production of erythropoietin, which in turn stimulates erythropoiesis. In normal subjects, plasma erythropoietin levels range from 0.01 to 0.03 units/mL and may increase 100- to 1,000-fold during hypoxia or anemia.⁸ In contrast, patients with CKD have impaired production of erythropoietin, which is the primary cause of their anemia.^{9,10} Anemia in cancer patients may be related to the disease itself or the effect of concomitantly administered chemotherapeutic agents.

The v2.2015 National Comprehensive Cancer Network (NCCN) guidelines state that erythropoiesis stimulating agents (ESAs) are associated with an increased risk of thrombosis, decreased survival, and shortened time to tumor.¹¹ Physicians are advised to use the lowest ESA dose possible to maintain hemoglobin levels (Hb) sufficient to avoid blood transfusions, to prescribe according to FDA guidelines using the REMS program, and to obtain patient consent. ESAs should be discontinued once the course of chemotherapy has been completed and anemia resolves. Use of ESAs is not recommended for the treatment of anemia related to myelosuppressive chemotherapy with curative intent.

The American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) joint clinical practice guidelines for the use of erythropoiesis stimulating agents (ESAs) in patients with cancer were released in 2010.^{12,13} The guidelines stated that, before initiating therapy for anemia in a patient with cancer, consideration should be given to the risks of thromboembolism, the possibility of death, and minimizing ESA use, particularly in patients with malignancy being treated with curative intent. While the FDA label now limits the indication for ESA use to patients receiving chemotherapy for palliative intent, no study has evaluated outcomes of ESA therapy by subgroups defined by chemotherapy intent. Based on the available evidence, the optimal Hb level at which to initiate ESA therapy in patients with chemotherapy-associated anemia and Hb between 10 and 12 g/dL cannot be definitively determined. As a result, the decision to initiate ESA therapy in patients with anemia and Hb between 10 and 12 g/dL should be guided by clinical judgment, consideration of the risks and benefits of ESAs, and patient preferences. When warranted by clinical conditions, RBC transfusion is an option. Because evidence does not exist to support improved effectiveness or safety with alternative starting doses, dose schedules, or dose-modifying schedules, starting and modifying doses should follow the FDA dosing guidelines outlined in the product information of each ESA. ESAs should be discontinued when chemotherapy is concluded. Assuming an appropriate dose increase has been attempted in non-responders as outlined in the FDA-approved label, ESA therapy should be discontinued if there is less than a one to two g/dL increase in Hb or no decrease in transfusion requirements after six to eight weeks of therapy. Non-responders should be investigated for underlying tumor progression, iron deficiency, or other etiologies for anemia.

Hb may be increased to the lowest concentration needed to avoid transfusion and may vary by patient and condition. Since an optimal target Hb concentration cannot be determined based on available literature, reduction of the ESA dose is appropriate when Hb reaches a level sufficient to avoid transfusion or if the Hb increase exceeds one g/dL in any two-week period.

This joint guideline recommends against the use of ESAs for the treatment of anemia associated with malignancy in patients who are not receiving concurrent myelosuppressive chemotherapy, except for patients with lower risk of myelodysplastic syndrome to avoid transfusions.

The ASCO and ASH Update Committee considers all ESAs to be equivalent with respect to effectiveness and safety; this recommendation remains unchanged from the 2007 guideline. National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) updated 2007 guidelines state that each ESA is effective in achieving and maintaining target Hb levels.¹⁴ KDOQI recommends Hb of 11 to 12 g/dL for dialysis or nondialysis patients with CKD with avoidance of Hb levels exceeding 13 g/dL.

Responsiveness to rHuEPO therapy in HIV-infected patients is dependent upon the endogenous serum erythropoietin level prior to treatment. Patients with endogenous serum erythropoietin levels \leq 500 mUnits/mL, and who are receiving a dose of zidovudine \leq 4,200 mg/week, may respond to rHuEPO therapy. Patients with endogenous serum erythropoietin levels $>$ 500 mUnits/mL do not appear to respond to rHuEPO therapy.^{15,16}

In 2011, the Food and Drug Administration (FDA) published a safety communication regarding a more conservative dosing approach to ESAs in patients with CKD due to increased risks of cardiovascular (CV) events. The FDA warned of an increased risk of death, CV events, and strokes in CKD patients when their HB levels were greater than 11 g/dL. However, no clinical trials have been performed which have identified a HB target level or ESA dose that would not increase these risks.¹⁷

Peginesatide (Omontys) is a synthetic ESA approved for the treatment of anemia due to CKD in adult patients on dialysis.¹⁸ Peginesatide was briefly on the market but all lots were voluntarily recalled on February 24, 2013 due to reports of anaphylaxis including three fatal cases.¹⁹ Until further notice, no new or existing patients should receive peginesatide and all health care providers should no longer prescribe it.

PHARMACOLOGY

Recombinant human epoetin alfa (rHuEPO) is a glycoprotein manufactured by recombinant DNA technology that has the same biological effects as endogenous erythropoietin.²⁰ It has a molecular weight of 30,400 daltons and is produced by mammalian cells into which the human erythropoietin gene has been introduced. Epogen and Procrit are identical rHuEPO products that contain the identical amino acid sequence of isolated natural erythropoietin.

Darbepoetin (Aranesp) is an erythropoiesis-stimulating agent similar to rHuEPO. It differs from rHuEPO by having two additional N-glycosylation sites which slow its clearance.^{21,22,23}

PHARMACOKINETICS^{24,25,26}

Chronic Renal Failure Patients

Drug	Adults			Children		
	Half-Life (hours)		SC Bioavailability (%)	Half-Life (hours)		SC Bioavailability (%)
	IV	SC		IV	SC	
darbepoetin (Aranesp)	21	46-70	37	--	--	54
rHuEPO (Epogen, Procrit)	4-13	--	--	4-13	--	--

In patients with chemotherapy-induced anemia, the half-life of subcutaneous darbepoetin is 74 hours. The pharmacokinetic profile of rHuEPO in children and adolescents is similar to adults. Pharmacokinetic profiles for rHuEPO are not available for HIV-positive patients.

CONTRAINDICATIONS/WARNINGS^{27,28,29}

Contraindications

Darbepoetin and rHuEPO are contraindicated in patients with uncontrolled hypertension and hypersensitivity to any of the components. Darbepoetin and rHuEPO are contraindicated in patients with hypersensitivity to albumin (human) and mammalian cell-derived products and in Pure Red Cell Aplasia (PRCA) that begins after treatment with any recombinant-DNA produced erythropoietin protein drugs. rHuEPO from multidose vials contains benzyl alcohol and is contraindicated in neonates, infants, pregnant women, and nursing women. Serious adverse events and death, especially in pediatric patients, has occurred with benzyl alcohol. When rHuEPO therapy is necessary for infants or neonates, use single dose vials. Do not admix with bacteriostatic saline containing benzyl alcohol.

Black Box Warnings

The ESAs have several boxed warnings.

Patients on ESAs are at increased risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence.

Patients with chronic kidney disease experienced greater risks for death, serious adverse CV reactions, and stroke when administered erythropoiesis stimulating agents (ESAs) to target hemoglobin level of greater than 11 g/dL. No trial has identified a hemoglobin target level, darbepoetin or rHuEPO dose, or dosing strategy that does not increase these risks. Use the lowest darbepoetin or rHuEPO dose sufficient to reduce the need for RBC transfusions.

In cancer patients, ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers. To decrease these risks, as well as the risk of serious cardio- and thrombovascular events, the lowest dose needed to avoid RBC transfusion should be used. Because of these risks, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense ESAs to patients with cancer. To enroll in the ESA APPRISE Oncology Program, visit www.esa-apprise.com or call 1-866-284-8089 for further assistance. ESAs should only be used for treatment of anemia due to concomitant myelosuppressive chemotherapy. ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure. ESAs should be discontinued following the completion of a chemotherapy course.

Additionally, rHuEPO (Epogen/Procrit) increased the rate of deep venous thromboses in perisurgical patients not receiving prophylactic anticoagulation. Deep venous thrombosis prophylaxis should be considered for perisurgical patients.

Warnings

Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism

Patients with previous risk factors for thrombosis may be at higher risk for thrombosis with the use of ESAs. Patients should be evaluated for risk factors, such as history of thromboembolism, hypercoagulability, hypertension, heritable mutation, elevated pre-chemotherapy platelet counts, steroid use, prolonged immobilization, recent surgery, multiple myeloma treatments, and use of hormonal agents. The absolute risk of thrombotic events was 7.5 percent in patients using rHuEPO and darbepoetin and 4.9 percent in control patients.³⁰ In clinical trials with patients with CKD comparing higher Hb targets (13 - 14 g/dL) to lower targets (9–11.3 g/dL), ESAs increased the risk of death, myocardial infarction, stroke, congestive heart failure, thrombosis of hemodialysis vascular access, and other thromboembolic events in the groups with higher Hb targets.^{31,32} Using ESAs to treat to a Hb level > 11 g/dL increases the risk of adverse events and has not been shown to provide additional benefit. Use caution with ESAs in patients with coexistent CVD and stroke. Patients with CKD and an insufficient Hb response to ESAs may be at a greater risk for CV adverse effects and mortality than other patients. A rate of Hb rise of > 1 g/dL over a two week period may contribute to these risks.

In clinical trials with patients with cancer, ESAs increased the risk of death and serious CV adverse effects, including myocardial infarction and stroke.

In clinical trials, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and the risk of deep venous thrombosis (DVT) in patients undergoing orthopedic procedures. Cancer patients receiving darbepoetin had more reports of pulmonary emboli, thrombophlebitis, and thrombosis compared to placebo controls.

Increased Mortality and/or Tumor Progression in Patients with Cancer

ESAs resulted in decreased locoregional control/progression-free survival and/or overall survival in patients with metastatic breast cancer receiving chemotherapy, patients with head and neck malignancies receiving radiation therapy, patients with lymphoid malignancy receiving chemotherapy, and advanced non-small cell lung cancer or various malignancies not receiving chemotherapy or radiotherapy. ESAs should be used only to treat anemia that occurs in patients with cancer while they are undergoing chemotherapy and should be stopped when chemotherapy ends.

Because of these risks, prescribers and hospitals must enroll in and comply with the ESA APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe Use of ESAs) Oncology Program to prescribe and/or dispense darbepoetin or rHuEPO to patients with cancer. Additionally, prescribers and patients must provide written acknowledgment of a discussion of the risks associated with these agents.³³

Deep Venous Thrombosis (DVT)

For the patients receiving rHuEPO pre-operatively for reduction of allogenic RBC transfusions, a higher incidence of DVT was documented in patients receiving rHuEPO who were not receiving prophylactic anticoagulation.^{34,35} In the SPINE study, 681 adults not receiving prophylactic anticoagulation and undergoing spinal surgery were randomized to rHuEPO and standard of care or standard of care alone. By duplex imaging or clinical symptoms, the rHuEPO group (4.7 percent) had a higher incidence of DVT than the standard of care group (2.1 percent). Additionally, 12 patients (3.5 percent) receiving rHuEPO

and seven patients (2.1 percent) receiving standard of care had other thrombotic events. Darbepoetin is not approved for this indication.

Increased mortality was observed in a randomized placebo-controlled study of rHuEPO in adult patients who were undergoing coronary artery bypass surgery (seven deaths in 126 patients randomized to rHuEPO versus no deaths among 56 patients receiving placebo). Four of these deaths occurred during the period of study drug administration, and all four deaths were associated with thrombotic events. ESAs are not approved for reduction in allogeneic RBC transfusions in patients scheduled for cardiac surgery.

Hypertension in Chronic Renal Disease Patients^{36,37,38}

Patients with uncontrolled hypertension should not begin therapy with darbepoetin or rHuEPO. Approximately 40 percent of patients with CRF receiving darbepoetin, and approximately 25 percent of patients on dialysis receiving rHuEPO, may require initiation or intensification of antihypertensive therapy during the early phase of treatment when Hb is increasing. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with darbepoetin or rHuEPO. Blood pressure should be closely monitored and carefully controlled in patients receiving ESAs. If blood pressure is difficult to control by pharmacologic or dietary measures, the dose of darbepoetin or rHuEPO should be reduced or withheld.

Seizures

Seizures have been reported in clinical trials involving CRF patients treated with ESAs, particularly during the first 90 days of therapy. Blood pressure and the presence of premonitory neurologic symptoms should be monitored closely during the first several months of therapy.

Pure Red Cell Aplasia^{39,40,41,42,43,44}

Pure red cell aplasia (PRCA) and severe anemia, with and without other cytopenias, have been reported with darbepoetin and rHuEPO. The presence of neutralizing antibodies has been observed. Most cases have been associated with darbepoetin and rHuEPO given subcutaneously in patients with CRF, but PRCA has also been reported in patients receiving darbepoetin and rHuEPO and undergoing treatment for hepatitis C infection with interferon and ribavirin. Although the condition is considered rare, PRCA has been linked to the development of anti-erythropoietin antibodies in patients who received recombinant ESAs. Any patient demonstrating a sudden loss of response to darbepoetin or rHuEPO with severe anemia and low reticulocyte count should be evaluated for the etiology of loss of effect. If anti-erythropoietin antibody-associated anemia is suspected, all recombinant DNA-produced erythropoietic agents (rHuEPO, darbepoetin) should be withheld.

Other Warnings

rHuEPO contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin. Serious allergic reactions have been reported following ESA administration.

REMS Program^{45,46, 47,48,49,50}

The FDA requires that ESAs be prescribed and used under a risk evaluation and mitigation strategy (REMS) program. A medication guide explaining the risks and benefits of ESA therapy must be provided to each patient receiving ESAs. Prescribers and patients must provide written acknowledgement of the risks of ESAs.

The REMS program for ESAs also requires healthcare professionals who prescribe ESAs to patients with cancer to receive education and register with the Assisting Providers and Cancer Patients with Risk Information for the Safe use of ESAs (APPRISE) program. Important points of the education are the risks that ESAs shorten survival and/or increase the risk of tumor progression or recurrence. Prescribers should use the lowest effective dose of ESA to avoid blood transfusion. ESAs should only be used with concomitant myelosuppressive chemotherapy. ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure.

DRUG INTERACTIONS^{51,52,53}

No formal drug interaction studies have been performed with darbepoetin or rHuEPO.

ADVERSE EFFECTS

CRF patients

Drug	Hypertension (%)	Arthralgia (%)	Medical device malfunction (%)	Vascular Access Complication (%)	Edema (%)
darbepoetin (Aranesp) ⁵⁴ n=766	31	nr	nr	8	17
rHuEPO (Epogen, Procrit) ^{55,56} n=148 on dialysis (placebo n=96)	27.7 (12.5)	16.2 (3.1)	8.1 (4.2)	8.1 (4.2)	nr
rHuEPO (Epogen, Procrit) ^{57,58} n=131 not on dialysis (placebo n=79)	13.7 (10.1)	12.2 (7.6)	nr	nr	nr

Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses.

For children with CRF receiving rHuEPO, adverse effects reported are similar to those reported in studies with adults.^{59,60} Studies have not evaluated the effects of darbepoetin when administered to pediatric patients as the initial treatment for the anemia associated with CRF.⁶¹

Cancer Patients Receiving Chemotherapy

Drug	Abdominal Pain (%)	Nausea (%)	Vomiting (%)	Thrombotic Adverse Events (%)	Myalgia (%)	Edema (%)
darbepoetin (Aranesp) ⁶² n=1,203 placebo n=909	13.2 (9.4)	nr	nr	6.1 (4.1)	nr	12.8 (9.7)
rHuEPO (Epogen, Procrit) ^{63,64} n=168 placebo n=165	nr	35 (30)	20 (16)	5 (3)	10 (5)	nr

Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses.

Zidovudine-treated HIV-infected Patients

Drug	Injection Site Irritation (%)	Pyrexia (%)	Urticaria (%)	Cough (%)	Rash (%)
rHuEPO (Epogen, Procrit) ^{65,66} n=144 placebo n=153	7 (4)	42 (34)	3 (1)	26 (14)	19 (7)

Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses.

Surgery Patients

Drug	Chills (%)	Headache (%)	Injection site pain (%)	Nausea (%)	Deep Venous Thrombosis (%)	Vomiting (%)
rHuEPO (Epogen, Procrit) ^{67,68} 300 units/kg n=112 placebo n=103	7 (1)	13 (9)	13 (8)	47 (45)	6 (3)	21 (14)

Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses.

Special Populations

Pediatrics^{69,70,71}

There are limited data for ESAs available in neonates.^{72,73,74,75} Epoetin multidose vials are formulated with benzyl alcohol so do not administer epoetin from multidose vials, or from single-dose vials admixed with bacteriostatic saline containing benzyl alcohol, to neonates or infants. When therapy with epoetin is needed in neonates and infants, use a benzyl alcohol-free formulation.

Pharmacokinetic profiles of rHuEPO are similar in both adults and children. Both rHuEPO products are FDA-approved for the treatment of anemia in pediatric CRF patients one month of age to 16 years who require dialysis and for children with cancer ages five to 18 years for the treatment of anemia due to concurrent myelosuppressive chemotherapy. Additionally, data exist to support the use rHuEPO in patients eight months **to 17 years old with zidovudine-treated HIV infection.**

Safety and effectiveness of rHuEPO have been evaluated in a 16-week, double-blind, randomized trial for the treatment of chemotherapy-induced anemia in 222 pediatric patients ages five to 18 years.^{76,77,78} After week four, patients in the rHuEPO group were significantly more likely than those in the placebo group to remain transfusion-free (38.7 versus 22.5 percent; $p=0.01$). There was no improvement in health-related quality of life with no evidence of effectiveness for fatigue, energy, or strength between the group receiving rHuEPO or placebo. Adverse events were similar between the two groups.

Safety and efficacy of darbepoetin have not been established in the initial treatment of pediatric patients with CKD or in the transition from another erythropoietin to darbepoetin in pediatric CKD patients less than one year of age. Safety and efficacy of darbepoetin have not been established for pediatric patients with chemotherapy-induced anemia.

A study of the conversion from rHuEPO to darbepoetin among pediatric CRF patients over one year of age showed similar safety and efficacy to the findings from adult conversion studies. Safety and efficacy in the initial treatment of anemic pediatric CRF patients, or in the conversion from another erythropoietin to darbepoetin in pediatric CRF patients less than one year of age, have not been established.⁷⁹ Maximum concentration and half-life in pediatric patients with CRF were similar to those obtained in adult CRF patients on dialysis. Following a single subcutaneous dose, the average bioavailability was 54 percent (range: 32 percent to 70 percent), which was higher than that obtained in adult CRF patients on dialysis.⁸⁰

Open-label use of darbepoetin in 33 children with CRF on dialysis has shown to be effective at a dose of 0.5 mcg/kg/week with over 75 percent of children receiving darbepoetin less than once weekly.⁸¹ Pediatric patients (age one to 17 years) with CRF receiving or not receiving dialysis were enrolled in an open-label, randomized study.⁸² Ten patients dropped out, none due to darbepoetin. Patients receiving stable doses of rHuEPO were randomized to either darbepoetin weekly (SC or IV) or to continue on the current rHuEPO regimen. A median weekly dose of darbepoetin 0.41 mcg/kg was required to maintain Hb in the target range. The proportion of patients with Hb values >10 g/dL was 97 percent between weeks eight and 12, and 91 percent between weeks 20 and 24. Adverse effects reported were fever, headache, nasopharyngitis, hypertension, hypotension, cough, and injection site pain. Similar findings were reported in a group of 39 pediatric patients ages 11 to 18 years with CRF.⁸³ Mean darbepoetin dose in the observational, prospective study was 0.63 mcg/kg/week to achieve target Hb of 11 to 13 g/dL.

A randomized, open-label trial compared the efficacy and safety of darbepoetin and rHuEPO in 124 children (age one to 18 years) with CKD.⁸⁴ Patients were receiving stable doses of rHuEPO prior to study entry. Patients were either continued on the stable dose of rHuEPO or switched to darbepoetin and titrated to achieve Hb between 10 to 12.5 g/dL. The adjusted mean change in Hb from baseline was -0.16 g/dL and 0.15 g/dL for rHuEPO and darbepoetin, respectively (95% CI, -0.45 to 1.07). Safety was comparable between the groups.

Pregnancy^{85,86,87}

Products in this class are Pregnancy Category C. Regarding rHuEPO (Epogen/Procrit), single dose vials should be used for pregnant women to avoid the administration of benzyl alcohol.

Geriatrics^{88,89,90}

No differences in overall safety or efficacy of darbepoetin have been observed between older and younger patients in clinical trials involving CRF patients or patients with cancer.

For CKD patients on dialysis and patients undergoing elective surgery, no differences in safety or effectiveness for rHuEPO were observed between geriatric and younger patients in clinical trials. Insufficient numbers of patients age 65 or older were enrolled in clinical studies of rHuEPO for the treatment of anemia associated with pre-dialysis CRF, cancer chemotherapy, and zidovudine-treatment of HIV infection to determine whether they respond differently from younger subjects.

DOSAGES

Drug	CRF		Zidovudine-treated HIV-infected Patients	Chemotherapy-associated Anemia in Cancer Patients		Surgery
	Starting Dose		Starting Dose	Starting Dose	Target Hb (g/dL)	Starting Dose
darbepoetin (Aranesp) ⁹¹	Dialysis: 0.45 mcg/kg IV or SC once weekly or 0.75 mcg/kg every two weeks	Not on dialysis: 0.45 mcg/kg IV or SC every four weeks	--	2.25 mcg/kg SC once weekly or 500 mcg SC every three weeks*	sufficient to avoid RBC transfusion	--
rHuEPO (Epogen, Procrit) ^{92,93}	Dialysis: Adults: 50-100 units/kg IV or SC three times weekly Pediatrics: 50 units/kg IV or SC three times weekly	Not on dialysis Adults: 50-100 units/kg IV or SC three times weekly	Adults: 100 units/kg IV or SC three times weekly	Adults: 150 units/kg SC three times weekly or 40,000 units SC once weekly* Pediatrics: 600 units/kg IV weekly (max 40,000 units weekly)*	sufficient to avoid RBC transfusion	Adults: 300 units/kg SC daily for ten days prior to surgery, day of surgery and four days after surgery OR 600 units/kg once weekly starting three weeks prior to, and on day of surgery

Some patients have been treated successfully with darbepoetin given SC every two weeks.

*Discontinue when chemotherapy completed.

Availability

Drug	Single Dose Vials	Multiple Dose Vials	Prefilled Syringe and SureClick Autoinjectors
darbepoetin (Aranesp) ⁹⁴	150 mcg/0.75 mL vial 25, 40, 60, 100, 200, 300, 500 mcg/mL in one mL vials	--	25 mcg/0.42 mL, 40 mcg/0.4 mL, 60 mcg/0.3 mL, 100 mcg/0.5 mL, 150 mcg/0.3 mL, 200 mcg/0.4 mL, 300 mcg/0.6 mL, 500 mcg/1 mL
rHuEPO** (Epogen, Procrit) ^{95,96}	2,000, 3,000, 4,000, 10,000, 40,000 units/mL in one mL vials	10,000 units/mL in two mL vial 20,000 units/mL in one mL vial	--

*Contains preservative

**All formulations of rHuEPO contain albumin

Dosing Considerations^{97,98,99}

Prior to and during ESA therapy, patients' iron stores, including transferrin saturation and serum ferritin, should be evaluated. Transferrin saturation should be at least 20 percent, and ferritin should be at least 100 ng/mL. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels that will adequately support erythropoiesis stimulated by ESA.

Hb should be monitored weekly until it has stabilized and the maintenance dose has been established.

Chronic Renal Failure^{100,101,102}

The dose of ESA should be individualized to maintain Hb levels sufficient to reduce the need for RBC transfusion. Do not increase the dose of ESA more than once per four weeks; however, reductions in ESAs may occur more frequently.

For patients with CKD on dialysis, darbepoetin or rHuEPO therapy may be initiated when Hb is less than 10 g/dL. When the Hb is increasing and approaching 11 g/dL, the dose of darbepoetin or rHuEPO should be reduced by 25 percent. If the Hb continues to increase, darbepoetin or rHuEPO should be withheld until the Hb begins to decrease. Reinitiate darbepoetin or rHuEPO at 25 percent below the previous dose. If the Hb increases by more than 1 g/dL within a two-week period, darbepoetin or rHuEPO dose should be reduced by 25 percent or more.

If the increase in hemoglobin is less than 1 g/dL over four weeks and iron stores are adequate, the dose of darbepoetin or rHuEPO may be increased by approximately 25 percent of the previous dose. Further increases may be made at four-week intervals until the specified Hb is obtained. Increases in dose should not be made more frequently than once a month.

For patients whose Hb does not adequately respond despite the use of appropriate ESA dose titrations over a 12-week period, do not administer higher doses and use the lowest dose that will maintain a hemoglobin level sufficient to avoid the need for recurrent RBC transfusions. Evaluate for other causes of anemia, and continue to monitor response.

For patients with CKD not on dialysis, darbepoetin or rHuEPO therapy may be initiated when Hb is less than 10 g/dL and the rate of Hb decline indicates that a RBC transfusion is likely and the goal is to reduce the risk of alloimmunization and/or other RBC transfusion-related risks. If Hb exceeds 10 g/dL, reduce or interrupt the dose of ESA and use the lowest dose of ESA sufficient to reduce the need for RBC transfusion.

Chemotherapy-related Anemia

Therapy with darbepoetin or rHuEPO should only be initiated if the Hb is <10 g/dL and if there is a minimum of two additional months of planned chemotherapy. The dose of darbepoetin or rHuEPO should be titrated for each patient to achieve and maintain the lowest Hb level sufficient to avoid the need for RBC transfusion.

For either weekly or every three week dosing schedules of darbepoetin, the dose should be adjusted for each patient to maintain the lowest Hb level sufficient to avoid RBC transfusion. If the rate of Hb increase is more than 1 g/dL per two-week period or when the Hb reaches a level needed to avoid transfusion, the dose should be reduced by 40 percent of the previous dose. If the Hb exceeds a level needed to avoid RBC transfusion, darbepoetin should be temporarily withheld until the Hb approaches

a level where RBC transfusions may be required. Therapy should be reinitiated at a dose 40 percent below the previous dose.

For patients receiving weekly administration, if there is less than a 1 g/dL increase in Hb after six weeks of therapy and Hb remains less than 10 g/dL, the dose of darbepoetin should be increased up to 4.5 mcg/kg. Discontinue darbepoetin if after eight weeks of therapy there is no response as measured by Hb levels or if transfusions are still required. Discontinue darbepoetin following the completion of a chemotherapy course.

Reduce rHuEPO dose by 25 percent when Hb reaches a level needed to avoid RBC transfusion or increases > 1 g/dL in any two-week period. rHuEPO should be withheld when Hb exceeds a level needed to avoid RBC transfusion. rHuEPO should be restarted at 25 percent below the previous dose when the Hb approaches a level where RBC transfusions may be required. rHuEPO should be discontinued following the completion of chemotherapy course. After the initial four weeks of rHuEPO, if the Hb increases by less than 1 g/dL and remains < 10 g/dL, increase rHuEPO dose to 300 units/kg three times per week in adults or 60,000 units weekly in adults or 900 units/kg (maximum of 60,000 units) weekly in children. If after eight weeks of rHuEPO therapy there is no response as measured by Hb levels, or if RBC transfusions are still required, discontinue rHuEPO.

Zidovudine-treated HIV-infected Patients

Prior to beginning rHuEPO, it is recommended that the endogenous serum erythropoietin level be determined (prior to transfusion). Available evidence suggests that patients receiving zidovudine with endogenous serum erythropoietin levels greater than 500 mUnits/mL are unlikely to respond to therapy with rHuEPO.

If Hb exceeds 12 g/dL, rHuEPO dose should be discontinued until the Hb is less than 11 g/dL. The rHuEPO dose should be reduced by 25 percent when treatment is resumed.

If a satisfactory response is not seen within eight weeks of therapy, rHuEPO dose can be increased by 50 to 100 units/kg three times weekly. Response should be evaluated every four to eight weeks, and the dose adjusted accordingly by 50 to 100 units/kg increments three times weekly. If a patient has not responded to rHuEPO 300 units/kg three times weekly for eight weeks, discontinue rHuEPO.

Dose Conversions

FDA-labeled Dose Conversion of rHuEPO to darbepoetin for Patients with CKD on Dialysis¹⁰³

Previous weekly rHuEPO (Epogen/Procrit) dose (units)	Equivalent weekly darbepoetin (Aranesp) dose in adults (mcg)	Equivalent weekly darbepoetin (Aranesp) dose in pediatric patients with CRF (mcg)
< 1,500	6.25	available data are insufficient to determine
1,500 to 2,499	6.25	6.25
2,500 to 4,999	12.5	10
5,000 to 10,999	25	20
11,000 to 17,999	40	40
18,000 to 33,999	60	60
34,000 to 89,999	100	100
> 90,000	200	200

Darbepoetin is administered once weekly for patients who received rHuEPO two to three times per week and once every two weeks for those who received rHuEPO once weekly; the same route of administration should be maintained. For patients with CKD not on dialysis, the above table does not accurately reflect the once monthly administration of darbepoetin.

Clinical study results suggest that greater relative potency differences are seen between rHuEPO and darbepoetin alfa when the dosing intervals are longer and when rHuEPO dose requirements are higher. Although 200 units of rHuEPO contains the same peptide mass as 1 mcg of darbepoetin alfa, a fixed ratio of 200:1 does not necessarily predict an appropriate dose conversion between the two drugs across the entire spectrum of dose ranges. When converting patients with CRF from rHuEPO to darbepoetin alfa, dosing should be based on relevant clinical data. Appropriate guidance for conversion of patients with CKD from rHuEPO to darbepoetin alfa is provided in the approved package insert for darbepoetin alfa (Aranesp). In patients who are prescribed darbepoetin alfa, either by conversion from rHuEPO or as de novo treatment, therapy should begin according to recommendations in the package insert; after which, doses should be titrated individually according to each patient's hemoglobin response.¹⁰⁴ Retrospective chart analyses have shown that the two most commonly used doses, rHuEPO (Epogen/Procrit) 40,000 units weekly and darbepoetin (Aranesp) 200 mcg every two weeks, result in similar hematologic outcomes with the higher Hb targets.^{105,106,107}

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class for the FDA-approved indications used in the outpatient setting. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Several comparative trials between rHuEPO and darbepoetin have been performed in an open-label manner in a variety of types of anemia.^{108,109,110,111,112,113,114,115,116,117,118,119,120,121,122} Retrospective analyses have also evaluated data from patients receiving darbepoetin and rHuEPO for a variety of anemia indications.^{123,124,125,126,127,128,129,130}

Use of erythropoiesis-stimulating agents in anemic patients with HIV that have been treated with zidovudine have not been demonstrated in controlled clinical trials to improve quality of life, fatigue, or patient well-being.^{131,132}

Chronic Renal Failure

rHuEPO (Epogen/Procrit) three times weekly versus darbepoetin (Aranesp) once weekly

A randomized, double-blind, noninferiority study was conducted to determine whether darbepoetin is as effective as rHuEPO for the treatment of anemia in 507 hemodialysis patients when administered at a reduced dosing frequency.¹³³ Patients receiving rHuEPO therapy were randomized to continue rHuEPO administered IV three times weekly or change to darbepoetin administered IV once weekly. The dose of darbepoetin or rHuEPO was individually titrated to maintain Hb concentrations within -1 to +1.5 g/dL of patients' baseline values and within a range of 9 to 13 g/dL. Mean changes in Hb levels from baseline to the evaluation period (weeks 21 to 28) were 0.24 g/dL in the darbepoetin group and 0.11 g/dL in the rHuEPO group. This difference was not statistically significant or clinically relevant despite the reduced frequency of darbepoetin administration. The safety profile of darbepoetin was similar to that of rHuEPO, and no antibody formation to either treatment was detected.

Chemotherapy-induced Anemia

rHuEPO (Epogen/Procrit) versus placebo

In a randomized, double-blind, placebo-controlled clinical trial, the effects of rHuEPO on transfusion requirements, hematopoietic parameters, quality of life (QoL), and safety in anemic cancer patients receiving nonplatinum chemotherapy were assessed.¹³⁴ Three hundred seventy-five patients with solid or nonmyeloid hematologic malignancies and Hb levels less than or equal to 10.5 g/dL, or between

10.5 and 12 g/dL after a Hb decrease of at least 1.5 g/dL per cycle since starting chemotherapy, were randomized to rHuEPO 150 to 300 units/kg or placebo three times per week for 12 to 24 weeks. The primary endpoint was proportion of patients transfused; secondary endpoints were change in Hb and QoL. The protocol was amended before unblinding to prospectively collect and assess survival data 12 months after the last patient completed the study. Active treatment with rHuEPO significantly decreased transfusion requirements compared to placebo (24.7 versus 39.5 percent, respectively; $p=0.0057$) and increased Hb (2.2 versus 0.5 g/dL, respectively; $p<0.001$). Improvement of all primary cancer- and anemia-specific quality of life (QoL) domains, including energy level, ability to do daily activities, and fatigue, were significantly ($p<0.01$) greater for rHuEPO patients. Adverse events were comparable between groups.

A double-blind, placebo-controlled trial with 344 patients with anemia after receiving chemotherapy evaluated the efficacy of rHuEPO 40,000 units SC weekly for 16 weeks. The mean increase in Hb was 0.9 g/dL for placebo and 2.8 g/dL for rHuEPO ($p<0.0001$).¹³⁵ Increases of ≥ 2 g/dL in Hb were observed in 31.7 and 72.7 percent of the placebo and rHuEPO groups, respectively ($p<0.0001$). Transfusions of RBCs occurred significantly less frequently in the rHuEPO group than with placebo (25.3 versus 39.6 percent in placebo group, $p=0.005$), and total transfused units were significantly lower in the active treatment group also (127 versus 256 units in placebo group, $p<0.0001$). The average QoL scores were similar between the groups. Patients who experienced an increase in Hb in either group had improvements in mean change in Functional Assessment of Cancer Therapy (FACT) fatigue score from baseline which was significantly greater than nonresponders ($p=0.006$).

darbepoetin (Aranesp) versus placebo

In a multicenter, double-blind, placebo-controlled trial, 320 patients with lung cancer and anemia were randomly assigned to receive darbepoetin 2.25 mcg/kg or placebo once weekly.¹³⁶ By 12 weeks, patients receiving darbepoetin required about half as many blood transfusions (27 versus 52 percent, $p<0.001$) and nearly a third fewer units of blood (0.67 versus 1.92, $p<0.001$). Hematopoietic response, defined as a 2 g/dL rise in Hb or reaching a Hb of 12 g/dL, occurred more frequently in treatment patients (66 versus 24 percent, $p<0.001$). Treated patients also had more improvement in fatigue scores (56 versus 44 percent, $p=0.019$) than patients receiving placebo. With regard to QoL, 56 percent of the patients in the darbepoetin group and 44 percent in the placebo group had an improvement in the FACT-fatigue cancer chemotherapy score ($p=0.052$). Adverse events were similar in each group.

SUMMARY

Based on available evidence, darbepoetin (Aranesp) and rHuEPO (Epogen/Procrit) appear to have comparable safety and efficacy in reducing the need for RBC transfusions in the treatment of chemotherapy-induced anemia in patients with cancer. In the patients with CRF on dialysis or pre-dialysis, darbepoetin (Aranesp) and rHuEPO (Epogen/Procrit) are effective in achieving and maintaining Hb levels sufficient to avoid RBC transfusions. Darbepoetin (Aranesp) and rHuEPO (Epogen/Procrit) have similar occurrences of adverse effects when used according to their labeling.

Darbepoetin (Aranesp) and rHuEPO (Epogen/Procrit) product information contain boxed warnings regarding risk for increased mortality, serious CV and thromboembolic events, and increased risk of tumor progression or recurrence.

To reduce risk, use the lowest dose of rHuEPO (Epogen/Procrit) and darbepoetin (Aranesp) that will gradually increase the hemoglobin concentrations to a level sufficient to avoid the need for RBC transfusion. Additionally, therapy with rHuEPO (Epogen/Procrit) and darbepoetin (Aranesp) for CKD should not exceed target hemoglobin of greater than 11 g/dL.

All peginesatide (Omontys) lots were voluntarily recalled on February 24, 2013 due to safety concerns involving anaphylaxis.

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