

Erythropoiesis Stimulating Proteins Review

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Erythropoiesis Stimulating Proteins Review

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 due to the effect of concomitantly administered chemotherapy based on studies that have shown a reduction in the need for red blood cell (RBC) transfusions in patients with metastatic, non-myeloid malignancies. <ul style="list-style-type: none"> • Darbepoetin is <u>not</u> indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy. • Darbepoetin is <u>not</u> indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure due to the absence of studies that adequately characterize the impact of darbepoetin on progression-free and overall survival. • Darbepoetin use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.
rHuEPO (Eprex®) ²	Amgen	<ul style="list-style-type: none"> • Treatment of anemia associated with CRF including patients on dialysis and patients not on dialysis. • Treatment of anemia due to the effect of concomitantly administered chemotherapy based on studies that have shown a reduction in the need for RBC transfusions in patients with metastatic, non-myeloid malignancies receiving chemotherapy for a minimum of two months.
rHuEPO (Procrit®) ³	Amgen (distributed by Ortho Biotech)	<ul style="list-style-type: none"> ○ rHuEPO is <u>not</u> indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy. ○ rHuEPO is <u>not</u> indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure due to the absence of studies that adequately characterize the impact of rHuEPO on progression-free and overall survival. ○ rHuEPO is <u>not</u> indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding. ○ rHuEPO use has <u>not</u> been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being. • Treatment of anemia related to therapy with zidovudine in HIV-infected patients. • Treatment of anemic patients (hemoglobin >10 to ≤13 g/dL) who are at risk for perioperative blood loss from elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions.

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

Overview

Anemia is a frequent complication 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.⁴ These conditions can cause anemia by interfering with the production of oxygen-carrying red blood cells (RBCs). Sometimes, as in the case of cancer chemotherapy, anemia can be caused by the treatment itself.

Erythropoietin is a glycoprotein which stimulates RBC production. 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 1000-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 v2.2010 National Comprehensive Cancer Network (NCCN) guidelines state that an increased mortality and tumor progression are associated with Erythropoiesis Stimulating Agents (ESA) therapy.¹¹ Physicians are advised to use the lowest ESA dose to avoid transfusion. In addition, use of ESA is restricted to the treatment of anemia related to myelosuppressive chemotherapy without curative intent. ESAs should be discontinued once the course of chemotherapy has been completed and anemia resolves.

The American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) released joint clinical practice guidelines in 2007 for the use of erythropoiesis stimulating agents (ESAs) in patients with cancer.¹² For patients with chemotherapy-associated anemia, ESA therapy should be initiated as hemoglobin (Hb) approaches, or falls below, 10 g/dL, to increase Hb and decrease need for transfusions. There is no evidence showing increased survival as a result of ESA treatment. Conclusive evidence is lacking that, unless clinical circumstances necessitate earlier treatment, initiating ESAs at Hb levels greater than 10 g/dL neither spares more patients from transfusion nor substantially improves their quality of life. Continuing ESAs beyond six to eight weeks in the absence of response, assuming appropriate dose increase has been attempted, however does not seem to be beneficial in nonresponders. In this instance, ESA therapy should be discontinued. Monitoring iron stores and supplementing iron intake for ESA-treated patients is recommended. ESAs should be used cautiously with chemotherapy or in clinical states associated with elevated risk for thromboembolic complications. ESA use for patients with cancer who are not receiving chemotherapy should be avoided since recent trials report increased thromboembolic risks and decreased survival.

In 2007, Centers for Medicare and Medicaid Services (CMS) issued a memorandum outlining the requirements for reimbursement for rHuEPO and darbepoetin for the non-renal indications.¹³ CMS has announced that erythropoiesis-stimulating agent treatment for the anemia secondary to myelosuppressive anticancer chemotherapy in solid tumors, multiple myeloma, lymphoma, and lymphocytic leukemia is only reasonable and necessary in specific conditions. The Hb level immediately prior to treatment initiation or maintenance treatment should be < 10 g/dL. The starting doses and maintenance dosing schedules should be consistent with the FDA label. ESA treatment duration for each course of chemotherapy includes the eight weeks following the final

dose of myelosuppressive chemotherapy in a chemotherapy regimen.

National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) 2006 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 ≤ 500 mUnits/mL, and who are receiving a dose of zidovudine ≤ 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}

Pharmacology

Recombinant human epoetin alfa (rHuEPO) is a glycoprotein manufactured by recombinant DNA technology that has the same biological effects as endogenous erythropoietin.¹⁷ 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 slows its clearance.^{18,19,20}

Pharmacokinetics^{21,22,23}

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	22.1	42.8	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^{24,25,26}

Contraindications

Darbepoetin and rHuEPO are contraindicated in patients with uncontrolled hypertension and hypersensitivity to any of the components including albumin (human) and mammalian cell-derived products.

Black box warnings

The ESAs have several boxed warnings.

Patients on ESAs are at risk for increased mortality, serious cardiovascular and thromboembolic events, and increased risk of tumor progression or recurrence.

Renal failure patients experienced greater risks for death and serious cardiovascular events when administered ESAs to target higher versus lower Hb levels (13.5 versus 11.3 g/dL; 14 versus 10 g/dL) in two clinical studies. Individualize dosing to achieve and maintain Hb levels within the range of 10 to 12 g/dL.

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 red blood cell transfusion should be used. 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

Patients with chronic renal failure and an insufficient Hb response to ESA therapy may be at even greater risk for cardiovascular events and mortality than other patients. ESAs increased the risks for death and serious cardiovascular events in controlled clinical trials of patients with cancer. These events included myocardial infarction, stroke, congestive heart failure, and hemodialysis vascular access thrombosis. A rate of Hb rise of > 1 g/dL over two weeks may contribute to these risks.

In the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial, 1,432 patients with CKD not on dialysis were randomized to rHuEPO with a target Hb of 13.5 g/dL or 11.3 g/dL.^{27,28} The median study duration was 16 months in the open-label trial. Doses of rHuEPO were initially administered weekly, then extended to once every two weeks with a stable dose. Duration of therapy in the study was up to 36 months or until initiation of renal replacement therapy (RRT). The study was terminated early due to an increased likelihood of patients in the high hemoglobin group experiencing a composite event. The final Hb values were 12.6 g/dL and 11.2 g/dL in the high target and low target groups, respectively. In the intent-to-treat populations, the composite of all-cause death, myocardial infarction (MI), hospitalization for congestive heart failure (CHF) (without renal replacement), and stroke, the primary endpoint, was 125 events in the high target group and 97 events in the low target group (Hazard Ratio (HR)=1.34, 95% Confidence Interval (CI), 1.03 to 1.74; p=0.03). The events that occurred were 65 deaths, 101 CHF hospitalizations, 25 nonfatal MIs, and 23 nonfatal strokes. All-cause mortality did not differ between the groups (p=0.0674). Withdrawal rate in the study was 38.3 percent. Additionally, the patient groups were imbalanced at baseline with more patients being hypertensive (p=0.03) or had coronary artery bypass grafting (p=0.05) in the high target group. These should be taken into consideration when evaluating the results.

A randomized trial enrolling 1,233 hemodialysis patients with ischemic heart disease or CHF evaluated the risks and benefits of rHuEPO therapy to maintain a normalized hematocrit (Hct) at 42 percent (equivalent to approximately 14 g/dL of Hb) compared to maintaining a low Hct of 30 percent (approximately 10 g/dL of Hb).²⁹ The study was terminated early. A trend toward increased mortality was observed in the patients randomized to the high target group (183 deaths and 19 myocardial infarctions) compared to the low target group [150 deaths and 14 myocardial infarctions (HR=1.3; 95% CI 0.9 to 1.9)]. The reason for the increased mortality in the study is unknown. This study was supported by the manufacturer of Epogen.

Cancer patients receiving darbepoetin had more reports of pulmonary emboli, thrombophlebitis, and thrombosis compared to placebo controls.³⁰

In the Trial of Reduced Cardiovascular Events with Aranesp Therapy (TREAT) involving patients with type 2 diabetes, chronic kidney disease (not undergoing dialysis), and anemia, patients (n=2,012) were randomized to darbepoetin alfa or placebo (n=2,026).³¹ Target hemoglobin for the darbepoetin alfa group was approximately 13 g/dL, and patients in the placebo group were allowed rescue darbepoetin alfa if the Hb < 9.0 g/dL. Death or a cardiovascular event occurred in 632 patients (31.4 percent) assigned to darbepoetin alfa and 602 patients (29.7 percent) assigned to placebo (HR for darbepoetin alfa versus placebo, 1.05; 95% CI, 0.94 to 1.17; p=0.41). Death or end-stage renal disease occurred in 652 patients (32.4 percent) assigned to darbepoetin alfa and 618 patients (30.5 percent) assigned to placebo (HR, 1.06; 95% CI, 0.95 to 1.19; p=0.29). Fatal or nonfatal stroke occurred more often in the darbepoetin alfa group (101 patients) than in the placebo group (53 patients) (HR 1.92; 95% CI, 1.38 to 2.68; p<0.001). Red-cell transfusions were administered to 297 patients assigned to darbepoetin alfa and 496 patients assigned to placebo (p<0.001). There was only a modest improvement in patient-reported fatigue in the darbepoetin alfa group as compared with the placebo group.

Increased mortality and/or tumor progression

The erythropoiesis-stimulating agents 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.³² Erythropoiesis-stimulating agents have also been shown to increase the risk of death when administered with a target Hb of 12 g/dL or greater in patients with active malignancy. 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.³³

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.³⁴

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.^{35,36} 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.

The FDA has been reviewing data from a breast cancer trial (PREPARE, n=733) and a cervical cancer trial (GOG-191, n=460).³⁷ In GOG-191, those patients randomized to receive an ESA had a significantly higher rate of potentially life-threatening blood clots (19 percent versus nine percent). Both the PREPARE and GOG-191 studies had higher rates of death and/or tumor progression in patients who received an ESA compared to patients who did not.

Pure red cell aplasia^{38,39,40}

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 ESA and are undergoing treatment for hepatitis C infection with interferon and ribavirin. 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 erythropoietic agents should be withheld.

Hypertension in chronic renal disease patients^{41,42,43}

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.

Other Warnings

ESAs contain 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.

The multi-dose vial formulations of rHuEPO contain the preservative benzyl alcohol. Increased incidence of neurological and other complications have been observed in premature infants receiving benzyl alcohol.

Drug Interactions^{44,45,46}

No formal drug interaction studies have been performed with darbepoetin. No drug interactions have been noted with rHuEPO in clinical trials.

Adverse Effects

CRF patients

Drug	Hypertension (%)	Headache (%)	Myalgia/ Arthralgia (%)	Nausea (%)	Thrombosis Vascular Access	Edema (%)
darbepoetin (Aranesp) ⁴⁷ n=1,801	20	15	9	11	0.22 events per patient year	10
rHuEPO (Epogen, Procrit) ^{48,49} n=200 (placebo n=135)	24 (19)	16 (12)	11 (6)	11 (9)	0.25 events per patient year	9 (10)

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.^{50,51} Studies have not evaluated the effects of darbepoetin when administered to pediatric patients as the initial treatment for the anemia associated with CRF.⁵²

Cancer patients receiving chemotherapy

Drug	Fatigue (%)	Fever (%)	Dizziness (%)	Thrombotic Events (%)	Diarrhea (%)	Edema (%)
darbepoetin (Aranesp) ⁵³ n=873	33	19	14	6.2	22	21
placebo n=221	(30)	(16)	(8)	(4.1)	(12)	(10)
rHuEPO (Epogen, Procrit) ^{54,55} n=63	13	29	5	3.2	21	17
placebo n=68	(15)	(19)	(12)	(11.8)	(7)*	(1)*

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. Statistically significant differences between the placebo and treatment group are indicated with an asterisk (*).

Zidovudine-treated HIV-infected patients

Drug	Fatigue (%)	Pyrexia (%)	Headache (%)	Cough (%)	Diarrhea (%)	Rash (%)
rHuEPO (Epogen, Procrit) ^{56, 57} n=144	25	38	19	18	16	16
placebo n=153	(31)	(29)	(14)	(14)	(18)	(8)

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	Pyrexia (%)	Headache (%)	Injection site reaction (%)	Nausea (%)	Constipation (%)	Vomiting (%)
rHuEPO (Epogen, Procrit) ^{58, 59} 300 units/kg n=112	51	13	25	48	43	22
placebo n=103	(60)	(9)	(22)	(45)	(43)	(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^{60,61,62}

Pharmacokinetic profiles of rHuEPO are similar in both adults and children. There are limited data for ESAs available in neonates.^{63,64,65,66} Both rHuEPO products are FDA-approved for the treatment of anemia in pediatric CRF patients one month of age and older who require dialysis. Additionally, data exist to support the use rHuEPO in pediatric CRF patients three months of age and older who are not undergoing dialysis; patients eight months and older with zidovudine-treated HIV infection; and cancer patients five years and older receiving chemotherapy.

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.^{67,68,69} 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=0.010). 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.

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.⁷⁰

Safety and efficacy of darbepoetin have not been established for pediatric patients with chemotherapy-induced anemia. 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.⁷¹

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 children receiving darbepoetin less than once weekly.⁷² Pediatric patients (age one to 17 years) with CRF receiving or not receiving dialysis were enrolled in an open-label, randomized study.⁷³ 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.⁷⁴ 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.⁷⁵ 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^{76,77,78}

Products in this class are Pregnancy Category C.

Geriatrics^{79,80,81}

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	Target Hb (g/dL)	Starting Dose	Target Hb (g/dL)	Starting Dose	Target Hb (g/dL)	Starting Dose	Target Hb (g/dL)
darbepoetin (Aranesp) ^{82,83}	Dialysis: 0.45 mcg/kg IV or SC once weekly. Not on dialysis: 0.75 mcg/kg SC every two weeks	10-12	--	--	2.25 mcg/kg SC once weekly or 500 mcg SC every three weeks*	sufficient to avoid RBC transfusion	--	--
rHuEPO (Epogen, Procrit) ^{84,85}	Adults: 50-100 units/kg IV or SC three times weekly Pediatrics: 50 units/kg IV or SC three times weekly	10-12	Adults: 100 units/kg IV or SC three times weekly for eight weeks	≤12	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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 2,000, 3,000, 4,000, 10,000, 40,000 units/mL in one mL vials 	<ul style="list-style-type: none"> • 10,000 units/mL in two mL vial • 20,000 units/mL in one mL vial 	--

**Each strength is available as an albumin-containing and an albumin-free solution.

Dosing considerations^{86,87,88}

Prior to and during ESA therapy, patient's 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^{89,90,91}

The dose of darbepoetin should be individualized to maintain Hb levels within the range of 10 to 12 g/dL. When the Hb is increasing and approaching 12 g/dL, the dose of darbepoetin should be reduced by 25 percent. If the Hb continues to increase, darbepoetin should be withheld until the Hb begins to decrease. Reinitiate darbepoetin at 25 percent below the previous dose. If the Hb increases by more than 1 g/dL within a two-week period, darbepoetin dose should be reduced by 25 percent.

If the increase in hemoglobin is less than 1 g/dL over four weeks and iron stores are adequate, the dose of darbepoetin 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 attain a level within the range of 10 to 12 g/dL despite the use of appropriate darbepoetin dose titrations over a 12-week period, do not administer higher doses of darbepoetin and use the lowest dose that will maintain Hb level sufficient to avoid the need for recurrent RBC transfusions. Also, an evaluation and treatment for other causes of anemia should be sought.

For rHuEPO dosing in the patient with CKD, the target Hb should not exceed 12 g/dL.^{92,93} If the Hb is increasing and approaching 12 g/dL or increases by greater than 1 g/dL in any two-week period, the dose of rHuEPO should be reduced by 25 percent. If the Hb continues to rise, rHuEPO should be withheld until the Hb begins to decrease. Therapy with rHuEPO should be restarted with a dose 25 percent less than the previous dose.

If the Hb is less than 10 g/dL and has not increased by 1 g/dL after four weeks of rHuEPO therapy or the Hb decreases below 10 g/dL, then increase the dose by 25 percent. For patients whose Hb does not attain a level within the range of 10 to 12 g/dL despite the use of appropriate rHuEPO 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.

Chemotherapy-related anemia

Therapy with darbepoetin should not be initiated if the Hb is \geq 10 g/dL. For either weekly or every three week dosing schedules, 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, 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.

Therapy with rHuEPO should not be initiated at hemoglobin levels ≥ 10 g/dL. The Hb should be monitored on a weekly basis in patients receiving rHuEPO until Hb becomes stable. The dose of rHuEPO should be titrated for each patient to achieve and maintain the lowest Hb level sufficient to avoid the need for RBC transfusion. 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. It 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. 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, it is unlikely that higher doses will improve response.

FDA-labeled dose conversion of rHuEPO to darbepoetin⁹⁴

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.

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 U 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.⁹⁵ 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.^{96,97,98}

The FDA has provided guidance for administration of the once-weekly dosing regimen for rHuEPO, noting that the initial dose of 40,000 units may be increased to 60,000 units after four doses if, in the absence of RBC transfusion, the Hb level has not increased by at least 1 g/dL.^{99,100}

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/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.^{101,102,103,104,105,106,107,108,109,110,111,112,113,114,115} Retrospective analyses have also evaluated data from patients receiving darbepoetin and rHuEPO for a variety of anemia indications.^{116,117,118,119,120,121,122,123}

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 the symptoms of anemia, quality of life, fatigue, or patient well-being.^{124,125}

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.¹²⁶ 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.¹²⁷ 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 ($p<0.0001$).¹²⁸ 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 anemic lung cancer patients were randomly assigned to receive darbepoetin 2.25 mcg/kg or placebo once weekly.¹²⁹ 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.

Meta-Analyses

Anemia in patients with cancer

A systematic review of 57 clinical trials including 9,353 cancer patients evaluated rHuEPO or darbepoetin for the treatment of anemia.¹³⁰ Both rHuEPO and darbepoetin significantly reduced the risk of RBC transfusion for the treatment or prophylaxis of anemia in cancer patients with or without concurrent chemotherapy (relative risk [RR]=0.64, 95% CI, 0.60 to 0.68) and improved hematologic response (RR=3.43, 95% CI, 3.07 to 3.84). The relative risk of thromboembolic events was significantly increased for rHuEPO or darbepoetin (RR=1.67, 95% CI, 1.35 to 2.06). Effect of therapy with rHuEPO or darbepoetin on overall survival was uncertain.

A systematic review of ESA trials evaluated the rate of venous thromboembolism (VTE) and mortality among patients with cancer.¹³¹ Data were searched from 1985 to January 2008. A total of 51 clinical trials with 13,611 patients had data on mortality and 38 clinical trials with 8,172 patients had information on VTE. Cancer patients on ESAs had an increased risk of VTE (334 VTE events among 4,610 patients treated with ESA versus 173 VTE events among 3,562 control patients; 7.5 percent versus 4.9 percent; relative risk, 1.57; 95% CI, 1.31 to 1.87). Cancer patients treated with ESAs also had an increased risk of mortality (HR 1.10; 95% CI, 1.01 to 1.20).

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 target Hb levels. Darbepoetin and rHuEPO have similar occurrences of adverse effects.

Darbepoetin and rHuEPO product information contain boxed warning regarding risk for increased mortality, serious cardiovascular and thromboembolic events, and increased risk of tumor progression or recurrence.

To reduce cardiovascular 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 and darbepoetin (Aranesp) should not exceed a target hemoglobin of greater than 12 g/dL. Careful

monitoring and appropriate dose adjustments are required to reduce the risk of cardiovascular and thrombotic events.

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