Erythropoiesis Stimulating Proteins Review

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FDA-Approved Indications

Drug	Manufacturer	FDA-approved Indications
darbepoetin (Aranesp®)[1]	Amgen	• 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 concomitantly administered chemotherapy
rHuEPO (Epogen®)[2]	Amgen	• 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 concomitantly administered chemotherapy • Treatment of anemia related to therapy with zidovudine in HIV-infected patients • Treatment of anemic patients (hemoglobin >10 to ≤13 g/dL) scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions
rHuEPO (Procrit®)[3]	Amgen (distributed by Ortho Biotech)	

- rHuEPO is recombinant human epoetin alfa
- HIV is human immunodeficiency virus

Overview

Anemia is a frequent complication associated with a number of serious diseases. In fact, anemia of chronic disease is the second most common form of anemia worldwide. Those at greatest risk are people with 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). Sometimes, as in the case of cancer and chemotherapy, anemia can be caused by the treatment itself.

Erythropoietin is a glycoprotein which stimulates RBC production. Erythropoietin acts on the erythroid progenitors in the bone marrow to cause late differentiation and maturity of the RBCs.[4,5,6] 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.[7] In contrast, patients with CKD have impaired production of erythropoietin, which is the primary cause of their anemia.[8,9] Anemia in cancer patients may be related to the disease itself or the effect of concomitantly administered chemotherapeutic agents. Supplementation with exogenous erythropoietin corrects the anemia resulting from these and other diseases.

Optimal hemoglobin (Hb) for patients with chemotherapy-induced anemia is ≤12 g/dL, and treatment is recommended when the patient is symptomatic with Hb <10 g/dL or considered when Hb is between 10 to 11 g/dL with symptoms.[10] The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend Hb of ≥11 g/dL for patients with CKD with avoidance of Hb levels exceeding 13 g/dL.[11]

Centers for Medicare and Medicaid Services (CMS) has issued a memorandum outlining the requirements for reimbursement for rHuEPO and darbepoetin recently for the non-renal indications.[12] CMS has "determined 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 under specified conditions."

Pharmacology

Recombinant human epoetin alfa (rHuEPO) is a glycoprotein manufactured by recombinant DNA technology that has the same biological effects as endogenous erythropoietin.[13] 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 protein similar to rHuEPO. It differs from rHuEPO by having two additional N-glycosylation sites which slows its clearance.[14,15,16]

Pharmacokinetics[17,18,19,20,21,22]

Chronic Kidney Disease Patients

Drug	Adults			Children		
	Half-Life (hours)		SC Bioavailability (%)	Half-Life (hours)		SC Bioavailability (%)
	IV	SC		IV	SC	
darbepoetin (Aranesp)	21-25.3	49	37	22.1	42.8	54
rHuEPO (Epogen, Procrit)	4-13	5-24	14-31	--	--	--

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

Contraindications[23,24,25]

Darbepoetin and rHuEPO are contraindicated in patients with uncontrolled hypertension and hypersensitivity to any of the components.

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.

Black box warnings[26,27,28]

The erythropoiesis-stimulating proteins have several black box warnings.

Renal failure patients: The erythropoiesis-stimulating proteins can increase the risk of death and serious cardiovascular events when administered with a target Hb of >12 g/dL. Two clinical trials demonstrated higher death rates and higher incidence of serious cardiovascular events when higher Hb targets were achieved (13.5 versus 11.3 g/dL and 14 versus 10 g/dL). Patients with renal failure should be treated with erythropoiesis-stimulating proteins to achieve and maintain Hb of 10 to 12 g/dL.

Cancer patients: The erythropoiesis-stimulating proteins shorten overall survival and/or time to tumor progression in clinical studies in patients with advanced breast, head and neck, lymphoid, and non-small cell lung malignancies when dosed to a target Hb of >12 g/dL. The risk of shortened survival and tumor progression has not been excluded when erythropoiesis-stimulating proteins are dosed to target Hb of less than 12 g/dL. To minimize these risks, as well as the risk of serious cardiovascular and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusion. Use erythropoiesis-stimulating proteins only for the treatment of anemia due to concomitant myelosuppressive chemotherapy. These agents should be discontinued following the completion of chemotherapy.

Perisurgical patients: rHuEPO has been shown to increase the risk of deep venous thromboses in patients not receiving prophylactic anticoagulation. Consider deep venous thrombosis prophylaxis.

Warnings

Increased risk of cardiovascular and thrombotic events[29,30,31]

In adults with anemia due to CKD, erythropoiesis-stimulating proteins have been associated with an increased risk of cardiovascular events including death when higher levels of Hb were achieved. The serious thrombotic events reported include myocardial infarction, stroke, congestive heart failure, and hemodialysis graft occlusion. The increased risk of cardiovascular events may be associated with higher levels of Hb or with higher rates of rise of Hb (exceeding 1 g/dL over two weeks). Target Hb should not exceed 12 g/dL when used to treat anemia with CKD, zidovudine-treated HIV infection, and anemia associated with cancer chemotherapy.

In the 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.[32,33] 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 in such time the patient required dialysis or underwent kidney transplantation. The study was terminated early. 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 (HR=1.34, 95% CI 1.03, 1.74; p=0.03). The events that occurred were 65 deaths, 101 CHF hospitalizations, 25 MIs, and 23 nonfatal strokes. All-cause mortality did not differ between the groups (p=0.0674). Discontinuation rate in the study was 38 percent and should be taken into consideration when evaluating these results.

A randomized trial enrolling 1,265 hemodialysis patients with ischemic heart disease or CHF evaluated the risks and benefits of normalizing Hb (goal of 42–45 percent hematocrit; equivalent to approximately 14–15 g/dL of Hb) with rHuEPO compared to low Hb goal (goal of 30 percent hematocrit or approximately 10 g/dL of Hb).[34] This study was terminated early. Increased mortality was observed in the patients randomized to the high target group (35 percent

mortality) compared to the low target group [29 percent mortality (HR=1.3; 95% CI 0.9-1.9)]. The reason for the increased mortality in the study is unknown. The incidences of nonfatal MI (3.1 versus 2.3 percent), vascular access thromboses (39 versus 29 percent) and all other thrombotic events (22 versus 18 percent) were higher in the higher target group. This study was supported by the manufacturer of Epogen.

Increased mortality and/or tumor progression

The erythropoiesis-stimulating proteins have been shown to shorten survival in patients with metastatic breast cancer, head and neck malignancies, lymphoid malignancy receiving chemotherapy, and advanced non-small cell lung cancer when administered to a target Hb of >12 g/dL. Erythropoiesis-stimulating proteins have also been shown to increase the risk of death when administered with a target Hb of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. Erythropoiesis-stimulating proteins are not indicated for this population.

Darbepoetin was evaluated in a multicenter, Phase III, double-blind, randomized, placebo-controlled study involving patients (n=989) with cancer who had anemia unrelated to concurrent chemotherapy.[35,36] Patients had a baseline Hb ≤11 g/dL with active cancer and were not receiving chemotherapy or radiation treatment. Patients were randomized to treatment for 16 weeks and then followed for an additional 16 weeks for safety and effectiveness. Darbepoetin did not reduce RBC transfusions compared to placebo (18 versus 24 percent, respectively, p=0.15; HR 0.89; 95% CI 0.65–1.22) in the initial 16-week treatment period. During the 16-week treatment period, more deaths were reported in patients receiving darbepoetin (250/515, 49 percent) compared to patients receiving placebo (216/470 patients, 46 percent; HR=1.25; 95% CI 1.04-1.51). Mortality was not a primary endpoint of the study; survival is still being followed in this study. Darbepoetin is not indicated for the treatment of anemia in cancer patients not receiving chemotherapy.

A study with rHuEPO (target Hb 12 to 14 g/dL) in patients (n=70) with non-small cell lung cancer with disease-related anemia was terminated early after an unplanned safety analysis revealed a significant difference in the median survival in favor of the patients in the placebo arm (63 days rHuEPO versus 129 days placebo; hazard ratio, 1.84; p=0.04).[37] rHuEPO is not indicated for the treatment of anemia in cancer patients not receiving chemotherapy.

Most recently, the FDA has been reviewing data from a breast cancer trial (PREPARE) and a cervical cancer trial (GOG-191).[38] In GOG-191, those patients randomized to receive an erythropoiesis-stimulating protein had a significantly higher rate of potentially life-threatening blood clots. Both the PREPARE and GOG-191 studies had higher rates of death and/or tumor progression in patients who received an erythropoiesis-stimulating protein compared to patients who did not. The FDA is expected to conduct another public advisory committee meeting in 2008 to review these data further.

Deep venous thrombosis (DVT)

An increased incidence of thrombotic events has also been observed in patients with cancer treated with erythropoiesis-stimulating proteins.[39,40] Cancer patients receiving darbepoetin had more reports of pulmonary emboli, thrombophlebitis, and thrombosis occur than compared to placebo controls.[41]

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.[42,43] 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 receiving rHuEPO and seven patients receiving standard of care had other thrombotic events. Darbepoetin is not approved for this indication.

Pure red cell aplasia[44,45,46]

Pure red cell aplasia and severe anemia with and without other cytopenias has 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 CKD patients. Any patient demonstrating a sudden loss of response to darbepoetin or rHuEPO with severe anemia and low reticulocyte count should be evaluated.

Hypertension in chronic renal disease patients[47,48,49]

Patients with uncontrolled hypertension should not begin therapy with darbepoetin or rHuEPO. Blood pressure may rise with darbepoetin or rHuEPO during therapy. Blood pressure monitoring and hypertension control should be considered during therapy with darbepoetin or rHuEPO. Approximately 25 percent of CKD patients on dialysis require the addition or modification of antihypertensive therapy.

Other warnings

Thrombotic events and seizures have been reported in clinical trials involving CKD patients treated with erythropoiesis-stimulating proteins.

Use of erythropoiesis-stimulating proteins 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 well-being.[50]

Drug Interactions[51,52,53]

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

Adverse Effects

CKD patients

Drug	Hypertension (%)	Headache (%)	Myalgia/ Arthralgia (%)	Nausea (%)	Thrombotic Events# (%)	Edema (%)
darbepoetin (Aranesp)[54] n=1,598	23	16	21/11	14	0.22 events per patient year	11
rHuEPO (Epogen, Procrit)[55, 56] n=200	24	16	11	11	0.04-0.5 events per patient year	9
(placebo n=135)	(19)	(12)	(6)	(9)		(10)

Adverse effects data are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses.
#Thrombotic events include pulmonary embolism, thromboembolism, thrombosis, and thrombophlebitis (deep or superficial)

For children with CKD receiving rHuEPO, adverse reactions reported are similar to those reported in studies with adults.[57,58]

Cancer patients receiving chemotherapy

Drug	Fatigue (%)	Fever (%)	Dizziness (%)	Thrombotic Events (%)	Diarrhea (%)	Edema (%)
darbepoetin (Aranesp)[59] n=873	33	19	14	6.2	22	21
placebo n=221	(30)	(16)	(8)	(4.1)	(12)	(10)
rHuEPO (Epogen, Procrit)[60, 61] 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. 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)[62, 63] n=144	25	38	19	18	16	16
placebo n=133	(31)	(29)	(14)	(14)	(18)	(8)

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

Surgery patients

Drug	Pyrexia (%)	Headache (%)	Injection site reaction (%)	Nausea (%)	Constipation (%)	Vomiting (%)
rHuEPO (Epogen, Procrit)[64, 65] 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. Incidences for the placebo group are indicated in parentheses.

Special Populations

Pediatrics[66,67,68]

As reported in package inserts, the pharmacokinetics of rHuEPO are similar in both adults and children. There are limited data available in neonates.[69,70,71,72] Both rHuEPO products are FDA-approved for the treatment of anemia in pediatric CKD patients one month of age and older who require dialysis. Additionally, data exist to support the use rHuEPO in pediatric CKD 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 six months and older receiving chemotherapy.

Limited data have shown that darbepoetin pharmacokinetics are similar in adults and children.[73]

Safety and efficacy of darbepoetin have not been established in pediatric CKD patients less than one year old for the initial treatment of anemia or conversion from another erythropoiesis-stimulating protein.[74] Open-label use of darbepoetin in 33 children with CKD 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.[75] Pediatric patients (age one to 18 years) with CKD receiving or not receiving dialysis were enrolled in an open-label, randomized study.[76] 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. Adverse effects reported were fever, headache, upper respiratory infection, hypertension, hypotension, cough, and injection site pain. Similar findings were reported in a group of 39 pediatric patients ages 11 to 18 years with CKD.[77] 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 (ages one to 18 years) with CKD.[78] 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.

The safety and efficacy of darbepoetin have not been established for pediatric patients with chemotherapy-induced anemia.[79]

The safety and effectiveness of rHuEPO have been evaluated in a double-blind, randomized trial for the treatment of chemotherapy-induced anemia in 111 pediatric patients ages five to 18 years.[80,81,82] Transfusions were reduced significantly in those patients receiving rHuEPO in the first 28 days (51 versus 69 percent; $p<0.05$). 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.

Pregnancy[83,84,85]

Products in this class are Pregnancy Category C.

Geriatrics[86,87,88]

No differences in overall safety or efficacy have been observed between older and younger patients in clinical trials.

For CKD patients on dialysis, no differences in safety or effectiveness for rHuEPO were observed between geriatric and younger patients in a clinical trial.

Dosages

Drug	CKD		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)[89,90]	0.45 mcg/kg IV or SC once weekly	≤12	--	--	2.25 mcg/kg SC once weekly or 500 mcg SC every three weeks*	≤12	--	--
rHuEPO (Epogen, Procrit)[91,92]	Adults: 50-100 units/kg IV or SC three times weekly Pediatric: 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 Pediatric: 600 units/kg IV weekly (max 40,000 units weekly*	10-12	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	>10-≤13

- Some patients have been treated successfully with darbepoetin given SC every two weeks.
- * Discontinue therapy when chemotherapy is complete.

Availability

Drug	Single Dose Vials	Multiple Dose Vials	Prefilled Syringe** and SureClick Autoinjectors
darbepoetin (Aranesp)	• 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)	• 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	--

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

Dosing considerations[93]

Prior to and during rHuEPO therapy, the 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 rHuEPO.

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

Chronic kidney disease

In the patient with CKD, darbepoetin dose should not be changed more frequently than once per month. 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 dose reduction. If the Hb increases by more than 1 g/dL with in a two-week period, darbepoetin dose should be reduced by 25 percent.

For rHuEPO dosing in the patient with CKD, the target Hb should not exceed 12 g/dL.[94,95] If the Hb is increasing and approaching 12 g/dL 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. Dose of rHuEPO should be reduced by 25 percent if Hb levels increase by more than 1 g/dL over a two-week period.

Chemotherapy-related anemia

The FDA has advised prescribers of safety changes regarding Hb rate of rise and target levels when the ESAs are used to treat anemia resulting from concomitant chemotherapy in patients with nonmyeloid malignancies or to reduce the need for transfusions in patients requiring a minimum of two months of chemotherapy.

The FDA recommends that dosing of darbepoetin be interrupted and modified if Hb levels increase at a rate greater than 1 g/dL over a two-week period. Patient-specific Hb target levels may range from 10 to 12 g/dL but should not exceed 12 g/dL in men and women. If the Hb increases by more than 1 g/dL in a two-week time period, or when the Hb exceeds 11 g/dL, darbepoetin dose should be reduced by 40 percent. Darbepoetin dosing should be withheld at Hb levels of 12 g/dL or greater; therapy with darbepoetin therapy should be withheld until the Hb approaches a level where transfusion may be required. Reinitiate darbepoetin at a 40 percent dose reduction of the prior dose.[96,97] Darbepoetin may be increased to 4.5 mcg/kg if there is less than 1 g/dL increase in Hb after six weeks of darbepoetin therapy. Darbepoetin therapy should be discontinued following the completion of chemotherapy course.

For rHuEPO dosing in the patient with chemotherapy-related anemia, the target Hb should not exceed 12 g/dL.[98,99] If the Hb is increasing and approaching 12 g/dL the dose of rHuEPO should be reduced by 25 percent. If the Hb continues to rise, rHuEPO should be withheld until the Hb is less than 11 g/dL. Therapy with rHuEPO should be restarted when the Hb approaches a level when a transfusion may be necessary; restart with a dose 25 percent less than the previous dose. Dose of rHuEPO should be reduced by 25 percent if Hb levels increase

by more than 1 g/dL over a two-week period. rHuEPO should be discontinued following the completion of chemotherapy course.

These safety changes were approved based on the results of investigational studies that showed an increased incidence of adverse outcomes (including increased mortality and thrombotic vascular events) in patients treated with rHuEPO to achieve high target Hb levels (> 12 g/dL) beyond that required for correction of anemia.[100,101,102]

Zidovudine-treated HIV-infected patients

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 darbepoetin for adults[103]

Previous weekly rHuEPO (Epogen/Procrit) dose (units)	Equivalent weekly darbepoetin (Aranesp) dose (mcg)
< 1,500	6.25
1,500 to 2,499	6.25
2,500 to 4,999	12.5
5,000 to 10,999	25
11,000 to 17,999	40
18,000 to 33,999	60
34,000 to 89,999	100
> 90,000	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.

The FDA-approved dosage conversion is not linear; at higher doses, the equivalence ratio can be higher than rHuEPO 500 units: darbepoetin 1 mcg. Alternative methods of determining equivalency include a dose-conversion based on peptic mass (rHuEPO 200 units = darbepoetin 1 mcg).[104]

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.[105,106] The FDA noted that patients not responding to four weekly doses of 60,000 units are unlikely to respond to higher doses of the product.

Clinical Trials

Search Strategy

Studies were identified through searches performed on PubMed, www.ifpma.org/clinicaltrials, 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 of the comparative trials between rHuEPO and darbepoetin have been performed in an open-label manner in a variety of types of anemia.[107,108,109,110,111,112,113,114,115,116,117,118,119,120] Retrospective analyses have also evaluated data from patients receiving darbepoetin and rHuEPO for a variety of anemia indications.[121,122,123, ,124,125,126,127,128]

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 509 hemodialysis patients when administered at a reduced dosing frequency.[129] 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.[130] 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 more than 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).[131] 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.[132] 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 regards 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

Chronic kidney disease

A meta-analysis of randomized controlled clinical trials evaluated erythropoietin with differing targets of Hb in patients with anemia and CKD.[133] The meta-analysis included a total of nine clinical trials with 5,143 enrolled patients. Studies enrolled a minimum of 100 patients and were at least 12 weeks in length. For all-cause mortality (risk ratio 1.17, 95% CI 1.01-1.35; p=0.031) and arteriovenous access thrombosis (1.34, 1.16-1.54; p=0.0001), there was a significantly higher risk in the higher Hb target group compared to the lower Hb target group.

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.[134] 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). 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.

In 2006, the Agency for Healthcare Research and Quality (AHRQ) conducted a comparative effectiveness review of rHuEPO and darbepoetin in chemotherapy-induced anemia by analyzing seven comparative trials (including randomized, open-label and descriptive chart reviews) of rHuEPO versus darbepoetin as well as placebo-controlled trials.[135] The AHRQ concluded that there is no clinically significant difference between rHuEPO and darbepoetin in patients with chemotherapy-induced anemia, in Hb response, transfusion reduction, and thromboembolic events. The review also reported there is a reduced need for RBC transfusions in patients on rHuEPO and darbepoetin compared to patients only receiving transfusions in chemotherapy-induced anemia.

Summary

Darbepoetin (Aranesp) and rHuEPO (Epogen/Procrit) have proven to be comparable with respect to safety and efficacy in reducing the relative risk of RBC transfusions in the treatment of chemotherapy-induced anemia in patients with cancer.[136,137,138] At the recommended doses of each, Hb levels are maintained within the target range in most patients, with a similar occurrence of adverse effects. Several studies have shown that both darbepoetin (Aranesp) and rHuEPO (Epogen/Procrit) are also effective when given at prolonged intervals.

In the patients with CKD on dialysis or pre-dialysis, darbepoetin (Aranesp) and rHuEPO (Epogen/Procrit) are effective in reducing the need for RBC transfusions. Intravenous route is preferred for patients on hemodialysis; pre-dialysis CKD patients may receive intravenous or subcutaneous administration of rHuEPO (Epogen/Procrit). rHuEPO (Epogen/Procrit) is recommended to be given as three times weekly, and darbepoetin (Aranesp) is given once weekly. In some patients, every other week administration of darbepoetin (Aranesp) may be preferable.

Controversy remains over relative dosage equivalence between darbepoetin (Aranesp) and rHuEPO (Epogen/Procrit). Because the relationship is not linear, the dosages used most often to maintain an equivalent Hb level is the most appropriate comparison.[139] In studies where relative doses based on hematopoietic response are specified, the equivalent weekly dosage is consistent with the relative peptide mass of the two agents (rHuEPO 200 units : darbepoetin 1 mcg). In meta-analyses, ratios between 218:1 and 322:1 fall into the 95 percent confidence interval.[140] Retrospective chart analyses, however, 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.[141,142,143]

Due to the relative inefficiency of the IV route of administration, approximately 300 units of IV rHuEPO (Epogen/Procrit) are required to achieve a hematopoietic response equivalent to darbepoetin (Aranesp) 1 mcg IV. For comparison, the use of the generally accepted CMS ratio of 400:1 is prudent, given the data available at present.

For patients with renal failure, the erythropoiesis-stimulating proteins can increase the risk of death and serious cardiovascular events when administered with a target Hb of greater than 12 g/dL. To reduce cardiovascular risk, use the lowest dose of rHuEPO (Epogen/Procrit) and darbepoetin (Aranesp) that will gradually increase the Hb concentrations to a level sufficient to avoid the need for RBC transfusion.

Erythropoiesis-stimulating proteins shortened overall survival and/or time to tumor progression in clinical trials in patients with metastatic breast cancer, head and neck, lymphoid, and non-small cell lung malignancies when administered to a target Hb of >12 g/dL. Erythropoiesis-stimulating proteins should only be administered to patients with anemia who are receiving chemotherapy, and should be discontinued following completion of chemotherapy.

Careful monitoring and appropriate dose adjustments of erythropoiesis-stimulating proteins are required to reduce the risk of cardiovascular and thrombotic events and shortened survival and/or tumor progression.

References

[1] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[2] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[3] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[4] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[5] Graber S, Krantz S. Erythropoietin alfa and the Control of Red Cell Production. Ann Rev Med. 1978; 29:51-66.
[6] Adamson JW. Regulation of red blood cell production. Am J Med. 1996; 101:4S-6S.
[7] Graber S, Krantz S. Erythropoietin alfa and the Control of Red Cell Production. Ann Rev Med. 1978; 29:51-66.
[8] Eschbach J, Adamson J. Anemia of End-Stage Renal Disease (ESRD). Kidney Intl. 1985; 28:1-5.
[9] Eschbach J, Egrie J, Downing M, et al. Correction of the Anemia of End-Stage Renal Disease with Recombinant Human Erythropoietin. NEJM. 1987; 316:73-78.
[10] Rodgers GM, Cella D, Chanan-Khan A, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Cancer and treatment related anemia. V1.2008 Available at: http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf. Accessed on January 29, 2008.
[11] National Kidney Foundation. KDOQI Clinical practice guidelines and clinical practice recommendations for anemia of chronic kidney disease. Am J Kidney Dis. 2006; 47(suppl 3):S1-146. Available at http://www.kidney.org/professionals/KDOQI/guidelines_anemia/index.htm. Accessed January 29, 2008.
[12] Available at: http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=203. Accessed February 4, 2008.
[13] Egrie J, Strickland T, Lane J, et al. Characterization and Biological Effects of Recombinant Human Erythropoietin. Immunobiol. 1986; 72:213-224.
[14] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[15] Egrie J, Browne J. Development and characterization of novel erythropoiesis stimulating protein (NESP). British J Cancer. 2001; 84(Suppl 1):3-10.
[16] Nissenson A. Novel erythropoiesis stimulating protein for managing the anemia of CKD. Am J Kidney Dis. 2001; 38:1390-1397.
[17] Macdougall I, Gray S, Elston O, et al. Pharmacokinetics of novel erythropoiesis stimulating protein compared with rHuEPO in dialysis patients. J Am Soc Nephrol. 1999; 10:2392-2395.
[18] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[19] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[20] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[21] Lerner G, Kale A, Warady B, et al. Pharmacokinetics of darbepoetin alfa in pediatric patients with chronic kidney disease. Pediatr Nephrol. 2002; 17:933-937.
[22] Allon M, Kleinman K, Walczyk M, et al. Pharmacokinetics and pharmacodynamics of darbepoetin alfa and epoetin in patients undergoing dialysis. Clin Pharmacol Ther. 2002; 72:546-555.
[23] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[24] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[25] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[26] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[27] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[28] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[29] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[30] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[31] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[32] Available at: http://download.veritasmedicine.com/PDF/CR004588_CSR.pdf. Accessed February 4, 2008.
[33] Singh AK, Szczech L, Tang KL, et al for the CHOIR Investigators. Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease. N Engl J Med. 2006; 355(20):2085-98.
[34] Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998; 339:584-90.
[35] Available at: http://www.fda.gov/medwatch/safety/2007/Aranesp_DHCP_012707.htm. Accessed February 4, 2008.
[36] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[37] Wright JR, Ung YC, Julian JA, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. J Clin Oncol. 2007; 25(9):1027-32.
[38] Available at: http://www.fda.gov/cder/drug/early_comm/ESA.htm. Accessed February 4, 2008.

[39] Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. J Clin Oncol. 2005; 23(25):5960-72.
[40] Wright JR, Ung YC, Julian JA, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. J Clin Oncol. 2007; 25(9):1027-32.
[41] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[42] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[43] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[44] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[45] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[46] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[47] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[48] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[49] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[50] Available at: http://www.fda.gov/cder/drug/advisory/RHE200711.htm. Accessed February 4, 2008.
[51] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[52] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[53] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[54] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[55] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[56] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[57] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[58] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[59] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[60] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[61] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[62] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[63] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[64] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[65] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[66] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[67] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[68] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[69] Arif B, Ferhan K. Recombinant human erythropoietin therapy in low-birthweight preterm infants: a prospective controlled study. Pediatr Int. 2005; 47(1):67-71.
[70] Reiter PD, Rosenberg AA, Valuck R, et al. Effect of short-term erythropoietin therapy in anemic premature infants. J Perinatol. 2005; 25(2):125-9.
[71] Ohlsson A, Aher SM. Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database Syst Rev. 2006; 3:CD004863.
[72] Aher SM, Ohlsson A. Early versus late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database Syst Rev. 2006; 3:CD004865.
[73] Blumer J, Berg S, Adamson PC, et al. Pharmacokinetic evaluation of darbepoetin alfa for the treatment of pediatric patients with chemotherapy-induced anemia. Pediatr Blood Cancer. 2007; 49(5):687-93.
[74] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[75] Geary DF, Keating LE, Vigneux A, et al. Darbepoetin alfa (Aranesp) in children with chronic renal failure. Kidney Int. 2005; 68(4):1759-65.
[76] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[77] André JL, Deschênes G, Boudailliez B, et al. Darbepoetin, effective treatment of anaemia in paediatric patients with chronic renal failure. Pediatr Nephrol. 2007; 22(5):708-14.
[78] Warady BA, Arar MY, Lerner G, et al. Darbepoetin alfa for the treatment of anemia in pediatric patients with chronic kidney disease. Pediatr Nephrol. 2006; 21(8):1144-52.
[79] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[80] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[81] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[82] Razzouk BI, Hord JD, Hockenberry M, et al. Double-blind, placebo-controlled study of quality of life, hematologic end points, and safety of weekly epoetin alfa in children with cancer receiving myelosuppressive chemotherapy. J Clin Oncol. 2006; 24(22):3583-9.
[83] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[84] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[85] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[86] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[87] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[88] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[89] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[90] National Kidney Foundation. K/DOQI clinical practice guidelines for anemia of chronic kidney disease, 2000. Am J Kidney Dis. 2001; 37(suppl 1):S182-S238.
[91] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[92] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[93] Available at: http://www.fda.gov/cder/drug/advisory/RHE200711.htm. Accessed February 4, 2008.

[94] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[95] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[96] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[97] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[98] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[99] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[100] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[101] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[102] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[103] Aranesp [package insert]. Thousand Oaks, CA; Amgen; November 2007.
[104] Locatelli F, Olivares J, Walker R, et al. Novel erythropoiesis stimulating protein for treatment of anemia in chronic renal insufficiency. Kidney Int. 2001; 60:741-747.
[105] Epogen [package insert]. Thousand Oaks, CA; Amgen; November2007.
[106] Procrit [package insert]. Raritan, NJ; Ortho Biotech; November2007.
[107] Allon M, Kleinman K, Walczyk M, et al. Pharmacokinetics and pharmacodynamics of darbepoetin alfa and epoetin in patients undergoing dialysis. Clin Pharmacol Ther. 2002; 72:546-555.
[108] Vanrenterghem Y, Barany P, Mann JF, et al. Randomized trial of darbepoetin alfa for treatment of renal anemia at a reduced dose frequency compared with rHuEPO in dialysis patients. Kidney Int. 2002; 62:2167-2175.
[109] Brunkhorst R, Bommer J, Braun J, et al. Darbepoetin alfa effectively maintains haemoglobin concentrations at extended dose intervals relative to intravenous or subcutaneous recombinant human erythropoietin in dialysis patients. Nephrol Dial Transplant. 2004; 19:1224-1230.
[110] Glaspy J, Jadeja J, Justice G, et al. Darbepoetin alfa given every 1 or 2 weeks alleviates anemia associated with cancer chemotherapy. Br J Cancer. 2002; 87:268-276.
[111] Glaspy J, Tchekmedyian N. Darbepoetin alfa administered every 2 weeks alleviates anemia in cancer patients receiving chemotherapy. Oncology. 2002; 16(10 Suppl 11):23-29.
[112] Locatelli F, Olivares J, Walker R, et al. Novel erythropoiesis stimulating protein for treatment of anemia in chronic renal insufficiency. Kidney Int. 2001; 60:741-747.
[113] Schwartzberg LS, Yee LK, Senecal FM, et al. A randomized comparison of every-w-2eek darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia in patients with breast, lung, or gynecologic cancer. The Oncologist. 2004; 9:696-707.
[114] Vanrenterghem Y, Baraby P, Mann JF, et al. Randomized trial of darbepoetin alfa for treatment of renal anemia at a reduced dose frequency compared with rHuEPO in dialysis patients. Kidney Int. 2002; 6(6):2167-2175.
[115] Locatelli F, Canaud B, Giacardy F, et al. Treatment of anaemia in dialysis patients with unit dosing of darbepoetin alfa at a reduced dose frequency relative to recombinant human erythropoietin (rHuEPO). Nephrol Dial Transplant. 2003; 18:362-369.
[116] Glaspy J, Vadhan-Raj S, Patel R, et al. Randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy –induced anemia: The 20030125 Study Group Trial. J Clin Oncol. 2006; 24(15):2290-2297.
[117] Waltzman R, Croot C, Justice GR, et al. Randomized comparison of epoetin alfa (40,000 units weekly) and darbepoetin alfa (200 mcg every 2 weeks) in anemic patients with cancer receiving chemotherapy. Oncologist. 2005; 10(8):642-50.
[118] Glaspy J, Vadhan-Raj S, Patel R, et al. Randomized Comparison of Every-2-Week Darbepoetin Alfa and Weekly Epoetin Alfa for the Treatment of Chemotherapy-Induced Anemia: The 20030125 Study Group Trial. J Clin Oncol. 2006; 24(15): 2290-2297.
[119] Senecal FM, Yee L, Gabrail N, Charu V, et al. Treatment of chemotherapy-induced anemia in breast cancer: results of a randomized controlled trial of darbepoetin alfa 200 microg every 2 weeks versus epoetin alfa 40,000 U weekly. Clin Breast Cancer. 2005; 6(5):446-54.
[120] Mann J, Kessler M, Villa G, et al. Darbepoetin alfa once every 2 weeks for treatment of anemia in dialysis patients: a combined analysis of eight multicenter trials. Clin Nephrol. 2007; 67(3):140-8.
[121] Thames WA, Smith SL, Scheifele AC, et al. Evaluation of the US Oncology Network's Recommended Guidelines for Therapeutic Substitution with Darbepoetin 200 mcg every 2 weeks in both naïve patients and patients switched from epoetin alfa. Pharmacotherapy. 2004; 24(3):313-323.
[122] Schwartzberg L, Shiffman R, Tomita D, et al. A multicenter retrospective cohort study of the practice patterns and clinical outcomes of the use of darbepoetin alfa and epoetin alfa for chemotherapy-induced anemia. Clin Ther. 2003; 25(11):2781-2796.
[123] Herrington JD, Davidson SL, Tomita DK, et al. Utilization of darbepoetin alfa and epoetin alfa for chemotherapy-induced anemia. Am J Health-Syst Pharm. 2005; 62:54-62.
[124] Duh MS, Mody SH, McKenzie RS, et al. Dosing patterns and treatment costs of erythropoietic agents in elderly patients with pre-dialysis chronic kidney disease in managed care organizations. Drugs Aging. 2006; 23(12):969-76.
[125] Patton J, Reeves T, Wallace J. Effectiveness of darbepoetin alfa versus epoetin alfa in patients with chemotherapy-induced anemia treated in clinical practice. Oncologist. 2004; (4):451-8.
[126] Papatheofanis FJ, McKenzie RS, Mody SH, et al. Dosing patterns, hematologic outcomes, and costs of erythropoietic agents in predialysis chronic kidney disease patients with anemia. Curr Med Res Opin. 2006; 22(5):837-42.
[127] Linde T, Furuland H, Wikström B. Effect of switching from subcutaneous to intravenous administration of epoetin-alpha in haemodialysis patients: results from a Swedish multicentre survey. Scand J Urol Nephrol. 2005; 39(4):329-33.
[128] Bradbury BD, Wang O, Critchlow CW, et al. Exploring relative mortality and epoetin alfa dose among hemodialysis patients. Am J Kidney Dis. 2008; 51(1):62-70.
[129] Nissenson A, Swan S, Lindberg J, et al. Randomized, controlled trial of darbepoetin alfa for the treatment of anemia in hemodialysis patients. Am J Kidney Dis. 2002; 40:110-118.
[130] Littlewood T, Bajetta E, Nortier J, et al. Effects of rHuEPO on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. J Clin Oncol. 2001; 19:2865-2874.

[131] Witzig TE, Silberstein PT, Loprinzi CL, et al. Phase III, randomized, double-blind study of epoetin alfa compared with placebo in anemic patients receiving chemotherapy. J Clin Oncol. 2005; 23(12):2606-17.
[132] Vansteenkiste J, et al. Darbepoetin Alfa Reduces Anemia and Fatigue in Lung Cancer. Natl Cancer Inst. 2002; 94:1211-1220.
[133] Phrommintikul A, Haas SJ, Elsik M, et al. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. Lancet. 2007; 369(9559):381-8.
[134] Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. J Natl Cancer Inst. 2006; 98(10):708-14.
[135] Seidenfled J, Piper M, Bohlius J, et al. Comparative effectiveness of epoetin and darbepoetin for managing anemia in patients undergoing cancer treatment, Comparative effectiveness review no. 3. (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract no. 290-02-0026.) Rockville, MD: Agency for Healthcare Research and Quality. December 2006. Available at: http://effectivehealthcare.ahrq.gov/repFiles/EPO%20Final.pdf. Accessed on February 4, 2008.
[136] Bohlius J, Wilson J, Seidenfeld J, et al. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst Rev. 2006; 3:CD003407.
[137] Seidenfled J, Piper M, Bohlius J, et al. Comparative effectiveness of epoetin and darbepoetin for managing anemia in patients undergoing cancer treatment, Comparative effectiveness review no. 3. (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract no. 290-02-0026.) Rockville, MD: Agency for Healthcare Research and Quality. December 2006. Available at:. http://effectivehealthcare.ahrq.gov/repFiles/EPO%20Final.pdf Accessed on February 4, 2008.
[138] Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. J Natl Cancer Inst. 2006; 98(10):708-14.
[139] Scott SD. Dose conversion from recombinant human erythropoietin to darbepoetin alfa: recommendations from clinical studies. Pharmacotherapy. 2002; 22:160S-165S.
[140] Barnett AI and Cremieux PY. Dose Conversion from Epoetin alfa to Darbepoetin alfa for Patients with Chronic Kidney Disease Receiving Hemodialysis. Pharmacotherapy. 2003; 23:690-694.
[141] Schwartzberg L, Shiffman R, Tomita D, et al. A multicenter retrospective cohort study of practice patterns and clinical outcomes of the use of darbepoetin alfa and epoetin alfa for chemotherapy-induced anemia. Clin Ther. 2003; 25:2781-2796.
[142] Thames WA, Smith SL, Scheifele AC, et al. Evaluation of the US Oncology Network's recommended dosing guidelines for therapeutic substitution with darbepoetin alfa 200 mcg every 2 weeks in both naïve patients and patients switched from epoetin alfa. Pharmacotherapy. 2004; 24:313-323.
[143] Patton J, Reeves T, Wallace J. Effectiveness of darbepoetin alfa versus epoetin alfa in patients with chemotherapy-induced anemia treated in clinical practice. The Oncologist. 2004; 9:451-458.

