Erythropoiesis Stimulating Proteins Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-approved Indications
darbepoetin (Aranesp®)[1]	Amgen	▪ Treatment of anemia associated with chronic kidney disease (CKD) including patients on dialysis and patients not on dialysis ▪ Treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy and, upon initiation, a minimum of 2 additional months chemotherapy is planned – Darbepoetin is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure or in in whom anemia can be managed by transfusion – Darbepoetin is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy – Darbepoetin is not indicated as a substitute for red blood cell (RBC) transfusion in patients who require immediate correction of anemia – Darbepoetin use has not been demonstrated in controlled clinical trials to improve quality of life, fatigue, or patient well-being
luspatercept-aamt (Reblozyl®)[2]	Celgene	▪ Treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions ▪ Treatment of anemia failing an erythropoiesis stimulating agent and requiring ≥ 2 RBC units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) – Luspatercept-aamt is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia
PEG-EPO (Mircera®)[3]	Roche/Vifor	▪ Treatment of anemia associated with chronic renal failure (CRF) in adult patients on dialysis and adult patients not on dialysis ▪ Treatment of anemia associated with CRF in pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an erythropoiesis stimulating agent (ESA) – PEG-EPO use has not been demonstrated in controlled clinical trials to improve quality of life, fatigue, or patient well-being – PEG-EPO is not indicated for treatment of anemia in patients receiving cancer chemotherapy – PEG-EPO is not indicated as a substitute for red blood cell (RBC) transfusion in patients who require immediate correction of anemia

PEG-EPO = methoxy polyethylene glycol epoetin beta; rHuEPO = recombinant human epoetin alfa; HIV = human immunodeficiency virus

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FDA-Approved Indications (continued)

Drug	Manufacturer	FDA-approved Indications
rHuEPO (Epogen®)[4]	Amgen	▪ Treatment of anemia associated with CRF including patients on dialysis and patients not on dialysis to decrease the need for red blood cell (RBC) transfusion ▪ Treatment of anemia related to therapy with zidovudine (≤ 4,200 mg per week) in HIV-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL ▪ Treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy and, upon initiation, hemoglobin < 10 g/dL and there is a minimum of 2 additional months of planned chemotherapy
rHuEPO (Procrit®)[5]	Amgen (distributed by Janssen)	▪ Indicated to reduce the need for allogenic RBC transfusion among patients with perioperative hemoglobin > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery – rHuEPO is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy – rHuEPO is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure or in in whom anemia can be managed by transfusion – rHuEPO is not indicated as a substitute for red blood cell (RBC) transfusion in patients who require immediate correction of anemia – rHuEPO is not indicated in patients undergoing cardiac or vascular surgery – rHuEPO is not indicated for patients who are willing to donate autologous blood pre-operatively – rHuEPO use has not been demonstrated in controlled clinical trials to improve quality of life, fatigue, or patient well-being

PEG-EPO = methoxy polyethylene glycol epoetin beta; rHuEPO = recombinant human epoetin alfa; HIV = human immunodeficiency virus

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FDA-Approved Indications (continued)

Drug	Manufacturer	FDA-approved Indications
rHuEPO-epbx* (Retacrit®)[6]	Pfizer (Hospira)	▪ Treatment of anemia associated with CKD including patients on dialysis and patients not on dialysis to decrease the need for red blood cell (RBC) transfusion ▪ Treatment of anemia due to zidovudine administered at ≤ 4,200 mg per week in HIV-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL ▪ Treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy and, upon initiation, there is a minimum of 2 additional months of planned chemotherapy ▪ Reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery – Epoetin alfa-epbx is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy – Epoetin alfa-epbx is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure or in in whom anemia can be managed by transfusion – Epoetin alfa-epbx is not indicated as a substitute for RBC transfusion in patients who require immediate correction of anemia – Epoetin alfa-epbx is not indicated in patients undergoing cardiac or vascular surgery – Epoetin alfa-epbx is not indicated for patients who are willing to donate autologous blood pre-operatively – Epoetin alfa-epbx use has not been demonstrated in controlled clinical trials to improve quality of life, fatigue, or patient well-being

PEG-EPO = methoxy polyethylene glycol epoetin beta; rHuEPO = recombinant human epoetin alfa; HIV = human immunodeficiency virus

* Epoetin alfa-epbx (Retacrit) is considered biosimilar to rHuEPO (Epogen/Procrit) for its indications. Biosimilar, a term used for biologic products, means that approval is based on data demonstrating that it is highly similar to another FDA-approved biological product (a reference product) and there are no clinically meaningful differences between the 2 products.

OVERVIEW

Anemia is a frequent complication, affecting over 3 million Americans, associated with a number of serious diseases, such as chronic kidney disease (CKD), diabetes, heart disease, and cancer, as well as chronic inflammatory conditions like rheumatoid arthritis or inflammatory bowel disease. These conditions can cause anemia by interfering with the production of oxygen-carrying red blood cells (RBCs).[7] Sometimes, as in the case of cancer chemotherapy, anemia can be caused by the treatment itself. Erythropoietin is a glycoprotein produced in the kidneys that stimulates RBC production from bone marrow. Erythropoietin acts on the erythroid progenitor cells in the bone marrow to cause late differentiation and maturity of the RBCs.[8,9,10] Endogenous production of erythropoietin by the kidney is normally regulated by the level of tissue oxygenation. Hypoxia and anemia generally increase the production of erythropoietin, which in turn stimulates erythropoiesis. In normal subjects, plasma erythropoietin levels range from 0.01 to 0.03 units/mL and may increase 100- to 1,000-fold during hypoxia or anemia.[11] In contrast, patients with CKD have impaired production of erythropoietin, which is the primary cause of their anemia.[12,13] Anemia in cancer patients may be related to the disease itself or the effect of concomitantly administered chemotherapeutic agents.

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The v4.2021 National Comprehensive Cancer Network (NCCN) guidelines state that erythropoiesis stimulating agents (ESAs) are associated with an increased risk of thrombosis, decreased survival, and shortened time to tumor.[14] Physicians are advised to use the lowest ESA dose possible to maintain hemoglobin (Hb) levels sufficient to avoid blood transfusions, to prescribe according to Food and Drug Administration (FDA) guidelines, and to obtain patient consent. ESAs should not be administered outside of the treatment period, which is defined as anemia following the initiation of chemotherapy and continues up to 6 weeks following the end of treatment. There is not enough evidence to support the use of ESAs for the treatment of anemia related to myelosuppressive chemotherapy with curative intent, patients receiving non-myelosuppressive therapy, or patients with cancer not receiving therapy.

The American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) joint clinical practice guidelines for the use of ESAs in patients with cancer updated their recommendations in 2019,.[15,16] The guidelines continue to emphasize that before initiating therapy for anemia in a patient with cancer, consideration should be given to the risks of thromboembolism, the possibility of death, and minimizing ESA use, particularly in patients with malignancy being treated with curative intent. ESAs may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose hemoglobin level is < 10 g/dL. Another option for these patients is a red blood cell transfusion, depending on the severity of the anemia or other clinical circumstances. Hemoglobin may be increased to the lowest concentration needed to avoid or reduce the need for red blood cell transfusions, which may vary by patient and condition. Starting and modifying doses should follow the FDA dosing guidelines outlined in the product information of each ESA. ESAs should be discontinued in patients who do not respond (< 1 to 2 g/dL increase in Hb or no decrease in transfusion requirements) within 6 to 8 weeks. Patients who do not respond to ESA treatment should be re-evaluated for underlying tumor progression, iron deficiency, or other etiologies for anemia. Epoetin beta and alfa, darbepoetin, and biosimilar epoetin alfa are expected to be equivalent with respect to effectiveness and safety.

The ASCO and ASH Update Committee maintains that all ESAs are equivalent with respect to effectiveness and safety. The international Kidney Disease: Improving Global Outcomes (KDIGO) group 2012 guidelines state that each ESA is effective in achieving and maintaining target Hb levels.[17] KDIGO recommends that ESAs not be used to maintain Hb concentration > 11.5 g/dl in adults with CKD. In all adult patients, KDDIGO recommends that ESAs not be used to increase Hb levels to > 13 g/dL.

Responsiveness to rHuEPO therapy in human immunodeficiency virus (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.[18,19]

In 2011, the FDA published a safety communication regarding a more conservative dosing approach to ESAs in patients with CKD due to increased risks of cardiovascular (CV) events. The FDA warned of an increased risk of death, CV events, and strokes in CKD patients when their HB levels were greater than 11 g/dL. However, no clinical trials have been performed which have identified a HB target level or ESA dose that would not increase these risks.[20]

Methoxy polyethylene glycol epoetin beta (PEG-EPO, Mircera) is approved for the treatment of anemia due to CKD in adult patients that are both receiving and not receiving dialysis. It is not indicated for the correction of anemia in cancer patients.[21]

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Epoetin alfa-epbx (Retacrit), or rHuEPO-epbx, is the first FDA-approved biosimilar to epoetin-alfa (Epogen, Procrit). It is approved for the treatment of anemia due to CKD in patients on dialysis and not on dialysis, use of zidovudine in patients with HIV infection, and the effects of concomitant myelosuppressive chemotherapy. It is also approved for the reduction of allogeneic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery.[22]

Beta thalassemia, a rare inherited blood disorder marked by the reduction of functional hemoglobin levels, has an incidence of approximately 1 in 100,000 individuals in the general population.[23] There are 3 subtypes of beta thalassemia, which are characterized by the severity of symptoms and classified as minor, intermedia, and major. Individuals with beta thalassemia major require regular blood transfusions, as often as once every 2 to 4 weeks, and are dependent on medical care for survival.[24] Treatment for beta thalassemia is highly dependent on type of thalassemia, progression and severity of disease, and the presence or absence of certain symptoms. Treatment options may include regular blood transfusions, chelation therapy, folic acid treatment, removal of the spleen and/or gallbladder, and bone marrow transplantation. Luspatercept-aamt (Reblozyl) is the first FDA-approved erythroid maturation agent, which reduces patient transfusion burden by regulating late-stage RBC maturation.[25] It is approved for the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell transfusions.

PHARMACOLOGY

Recombinant human epoetin alfa (rHuEPO) is a glycoprotein manufactured by recombinant DNA technology that has the same biological effects as endogenous erythropoietin.[26] 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 2 additional N-glycosylation sites which slow its clearance.[27,28,29]

PEG-EPO (Mircera) is a synthetic, continuous erythropoietin receptor activator.[30] It has a slowed clearance, similar to that of darbepoetin, due to the addition of the conjugated PEG polymer.[31]

Luspatercept-aamt (Reblozyl) is a recombinant fusion protein that works as an erythroid maturation agent by differentiating late-stage erythroid precursors.[32]

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PHARMACOKINETICS[33,34,35,36,37,38]

Chronic Renal Failure Patients

Drug	Adults			Children		
	Half-Life (hours)		SC Bioavailability (%)	Half-Life (hours)		SC Bioavailability (%)
	IV	SC		IV	SC	
darbepoetin (Aranesp)	21	46-70	37	--	--	54
PEG-EPO (Mircera)	134	139	62	--	--	--
rHuEPO (Epogen, Procrit)	4-13	--	--	4-13	--	--
rHuEPO-epbx (Retacrit)	4-13	--	--	4-13	--	--

In patients with chemotherapy-induced anemia, the half-life of subcutaneous darbepoetin is 74 hours. The pharmacokinetic profile of PEG-EPO shows that hemodialysis, hepatic impairment, and subcutaneous injection site had no effect on serum concentration. For rHuEPO and its biosimilar, the pharmacokinetics in children and adolescents is similar to adults. Pharmacokinetic profiles for rHuEPO and its biosimilar (Retacrit) are not available for HIV-positive patients.

The mean half-life of subcutaneous luspatercept-aamt is approximately 11 days. The median time to maximum concentration was observed at approximately 7 days post-dose in both healthy adults and patients with beta thalassemia. The pharmacokinetic profile of luspatercept-aamt illustrates that hepatic impairment, mild to moderate renal impairment, subcutaneous injection site, and RBC transfusion burden do not affect concentration levels.

CONTRAINDICATIONS/WARNINGS[39,40,41,42,43]

Contraindications

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

Luspatercept-aamt (Reblozyl) has no contraindications.

Boxed Warnings

The ESAs have several boxed warnings.

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

Patients with CKD experienced greater risks for death, serious adverse CV reactions, and stroke when administered ESAs to target hemoglobin level of greater than 11 g/dL. No trial has identified a

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hemoglobin target level, darbepoetin, PEG-EPO, or rHuEPO dose, or dosing strategy that does not increase these risks. Use the lowest darbepoetin, PEG-EPO, rHuEPO, or rHuEPO-epbx dose sufficient to reduce the need for RBC transfusions.

In cancer patients, ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers. To decrease these risks, as well as the risk of serious cardio- and thrombovascular events, the lowest dose needed to avoid RBC transfusion should be used in patients receiving darbepoetin, rHuEPO, or rHuEPO-epbx. PEG-EPO is not indicated for use in cancer patients. Darbepoetin, rHuEPO, or rHuEPO-epbx should only be used for treatment of anemia due to concomitant myelosuppressive chemotherapy and are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure or in whom anemia can be managed by transfusion. Darbepoetin or rHuEPO should be discontinued following the completion of a chemotherapy course.

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

Luspatercept-aamt has no boxed warnings.

Warnings

Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism

Patients with previous risk factors for thrombosis may be at higher risk for thrombosis with the use of ESAs. Patients should be evaluated for risk factors, such as history of thromboembolism, hypercoagulability, hypertension, heritable mutation, elevated pre-chemotherapy platelet counts, steroid use, prolonged immobilization, recent surgery, multiple myeloma treatments, and use of hormonal agents. The absolute risk of thrombotic events was 7.5% in patients using rHuEPO and darbepoetin and 4.9% in control patients.[44] In clinical trials with patients with CKD comparing higher Hb targets (13 to 14 g/dL) to lower targets (9 to 11.3 g/dL), ESAs increased the risk of death, myocardial infarction, stroke, congestive heart failure, thrombosis of hemodialysis vascular access, and other thromboembolic events in the groups with higher Hb targets.[45,46] Using ESAs to treat to a Hb level over 11 g/dL increases the risk of adverse events and has not been shown to provide additional benefit. Use caution with ESAs in patients with coexistent CVD and stroke. Patients with CKD and an insufficient Hb response to ESAs may be at a greater risk for CV adverse effects and mortality than other patients. A rate of Hb rise greater than 1 g/dL over a 2-week period may contribute to these risks.

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

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

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Patients with beta thalassemia have an increased risk for thrombosis and thromboembolism. Patients should be monitored for signs and symptoms of thromboembolic events and promptly treated as necessary. Practitioners should consider thromboprophylaxis in patients with beta thalassemia who are at increased risk and are being treated with luspatercept-aamt.

Increased Mortality and/or Tumor Progression in Patients with Cancer

ESAs resulted in decreased locoregional control/progression-free survival and/or overall survival in patients with metastatic breast cancer receiving chemotherapy, patients with head and neck malignancies receiving radiation therapy, patients with lymphoid malignancy receiving chemotherapy, and advanced non-small cell lung cancer or various malignancies not receiving chemotherapy or radiotherapy. A study with darbepoetin alfa (Aranesp) in patients with anemia receiving chemotherapy for advanced non-small cell lung cancer demonstrated noninferiority to placebo in overall survival and progression-free survival (ruling out a 15% increase), but thrombovascular events occurred more frequently with darbepoetin alfa than with placebo. ESAs, excluding PEG-EPO, 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.

Luspatercept-aamt is only approved for adults with beta thalassemia who require regular red blood cell transfusions and does not carry a warning for increased mortality and/or tumor progression in patients with cancer.

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. 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%) had a higher incidence of DVT than the standard of care group (2.1%). Additionally, 12 patients (3.5%) receiving rHuEPO and 7 patients (2.1%) receiving standard of care had other thrombotic events. Darbepoetin, PEG-EPO, and luspatercept-aamt are 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 (7 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 4 deaths were associated with thrombotic events. ESAs are not approved for reduction in allogeneic RBC transfusions in patients scheduled for cardiac surgery.

Hypertension

Patients with uncontrolled hypertension should not begin therapy with darbepoetin, PEG-EPO, rHuEPO, or rHuEPO-epbx. Approximately 40% of patients with chronic renal failure (CRF) receiving darbepoetin, 25% of patients on dialysis receiving rHuEPO, and 27% of dialysis and non-dialysis CRF patients 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, PEG-EPO, 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, PEG-EPO, rHuEPO, or rHuEPO-epbx should be reduced or withheld.

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Over 10% of patients with normal blood pressure developed hypertension while being treated with luspatercept-aamt. Blood pressure should be monitored prior to each administration of luspatercept-aamt. Patients with new-onset hypertension or exacerbations of pre-existing hypertension should be managed using anti-hypertensive agents.

Seizures

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

Pure Red Cell Aplasia

Pure red cell aplasia (PRCA) and severe anemia, with and without other cytopenias, have been reported with darbepoetin, PEG-EPO, and rHuEPO. The presence of neutralizing antibodies has been observed. Most cases have been associated with ESAs given subcutaneously in patients with CRF, but PRCA has also been reported in patients receiving darbepoetin and rHuEPO and undergoing treatment for hepatitis C infection with interferon and ribavirin. Although the condition is considered rare, PRCA has been linked to the development of anti-erythropoietin antibodies in patients who received recombinant ESAs. Any patient demonstrating a sudden loss of response to darbepoetin, PEG-EPO, or rHuEPO with severe anemia and low reticulocyte count should be evaluated for the etiology of loss of effect. If anti-erythropoietin antibody-associated anemia is suspected, all recombinant DNA-produced erythropoietic agents (darbepoetin, rHuEPO, rHuEPO-epbx, PEG-EPO,) should be withheld. ESAs should be stopped in patients with antibody-mediated anemia; patients should not be immediately switched to another ESA since antibodies may cross-react.[47,48]

Serious Allergic Reactions

Serious allergic reactions, including anaphylaxis, angioedema, bronchospasm, skin rash, urticaria, and Stevens-Johnson syndrome/toxic epidermal necrolysis have been reported with darbepoetin, PEG-EPO, and rHuEPO. Any patient showing signs of serious allergic reactions should immediately and permanently discontinue treatment and receive appropriate therapy.

Other Warnings

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

Risk Evaluation and Mitigation Strategies (REMS)[49]

Previously, the FDA required that darbepoetin and rHuEPO be prescribed and used under a risk evaluation and mitigation strategy (REMS) program when used for patients with cancer. However, the REMS requirements for these agents were discontinued in April 2017.

DRUG INTERACTIONS[50,51,52,53,54,55]

No formal drug interaction studies have been performed with the ESAs.

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ADVERSE EFFECTS[56,57,58,59,60,61]

CRF Patients

Drug	Hypertension (%)	Arthralgia (%)	Medical Device Malfunction (%)	Vascular Access Complication (%)	Edema (%)
darbepoetin (Aranesp) n=766	31	nr	Nr	8	17
PEG-EPO (Mircera) n=1,789	13	nr	Nr	5	nr
rHuEPO (Epogen, Procrit) n=148 on dialysis (placebo n=96)	27.7 (12.5)	16.2 (3.1)	8.1 (4.2)	8.1 (4.2)	nr
rHuEPO (Epogen, Procrit) n=131 not on dialysis (placebo n=79)	13.7 (10.1)	12.2 (7.6)	Nr	nr	nr
rHuEPO-epbx (Retacrit) n=148 on dialysis (placebo n=96)	27.7 (12.5)	16.2 (3.1)	8.1 (4.2)	8.1 (4.2)	nr
rHuEPO-epbx (Retacrit) n=131 not on dialysis (placebo n=79)	13.7 (10.1)	12.2 (7.6)	Nr	nr	nr

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

For children with CRF receiving rHuEPO, adverse effects reported are similar to those reported in studies with adults. Studies have not evaluated the effects of darbepoetin or PEG-EPO when administered to pediatric patients as the initial treatment for the anemia associated with CRF.

Cancer Patients Receiving Chemotherapy

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

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

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Zidovudine-treated HIV-infected Patients

Drug	Injection Site Irritation (%)	Pyrexia (%)	Urticaria (%)	Cough (%)	Rash (%)
rHuEPO (Epogen, Procrit) n=144; placebo n=153	7 (4)	42 (34)	3 (1)	26 (14)	19 (7)
rHuEPO-epbx (Retacrit) n=144; placebo n=153					

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

Surgery Patients

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

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.

Beta Thalassemia Patients

Drug	Bone pain (%)	Arthralgia (%)	Diarrhea (%)	Fatigue (%)	Abdominal pain (%)	Cough (%)	Diarrhea (%)
luspatercept-aamt (Reblozyl) n=223; placebo n=109	20 (8)	19 (12)	12 (10)	14 (13)	14 (12)	21 (14)	12 (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.

MDS-RS and MDS/MPN-RS-T associated Anemia Patients

Drug	Musculo-skeletal pain (%)	Dizziness (%)	Fatigue (%)	Nausea (%)	Hyper-sensitivity reactions (%)	Diarrhea (%)
luspatercept-aamt (Reblozyl) n=153; placebo n=76	20 (14)	18 (7)	41 (22)	16 (11)	10 (7)	16 (9)

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.

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SPECIAL POPULATIONS[62,63,64,65,66,67]

Pediatrics

There are limited data for ESAs available in neonates.[68,69,70,71] Multidose vials of rHuEPO are formulated with benzyl alcohol; therefore, do not administer rHuEPO from multidose vials, or from single-dose vials admixed with bacteriostatic saline containing benzyl alcohol, to neonates or infants. When therapy with rHuEPO is needed in neonates and infants, use a benzyl alcohol-free formulation.

Pharmacokinetic profiles of rHuEPO are similar in both adults and children. Both rHuEPO products and its biosimilar are FDA-approved for the treatment of anemia in pediatric CRF patients 1 month of age to 16 years who require dialysis and for children with cancer ages 5 to 18 years for the treatment of anemia due to concurrent myelosuppressive chemotherapy. Additionally, data exist to support the use of rHuEPO and its biosimilar in patients 8 months to 17 years old with zidovudine-treated HIV infection.

Safety and efficacy of darbepoetin has not been established in the initial treatment of pediatric patients with CKD or in the transition from another erythropoietin to darbepoetin in pediatric CKD patients less than 1 year of age. PEG-EPO (Mircera) is indicated for pediatric patients ages 5 to 17 years on hemodialysis who are converting from another erythropoiesis stimulating agent (ESA) after their hemoglobin level was stabilized with an ESA. Safety and efficacy of darbepoetin or PEG-EPO have not been established for pediatric patients with chemotherapy-induced anemia.

A study of the conversion from rHuEPO to darbepoetin among pediatric CRF patients over 1 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 or PEG-EPO in pediatric CRF patients less than 1 year of age, have not been established. 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% (range: 32% to 70%), which was higher than that obtained in adult CRF patients on dialysis.

The safety and efficacy of luspatercept-aamt (Reblozyl) in pediatric patients has not been established and is not recommended.

Pregnancy

Previously, rHuEPO and darbepoetin were assigned Pregnancy Category C. However, their labeling was updated in compliance with the Pregnancy and Lactation Labeling Rule (PLLR) and includes descriptive text. Data are too limited with rHuEPO-epbx, rHuEPO and darbepoetin in pregnant women to inform of a drug-associated risk. Use of rHuEPO from multidose vials is contraindicated in pregnant women; single-dose vials should be used to avoid the administration of benzyl alcohol. Other products in this class are Pregnancy Category C, with the exception of luspatercept-aamt (Reblozyl), which may cause embryo-fetal harm when administered to pregnant women. Effective contraception should be used during treatment and for at least 3 months after the last dose is administered.

Geriatrics

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-epbx and rHuEPO were observed between geriatric and younger patients in

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clinical trials. Insufficient numbers of patients aged 65 years 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.

Insufficient numbers of CKD patients aged 65 years or older were enrolled in clinical studies of PEG-EPO to determine whether they respond differently from younger subjects. Insufficient numbers of beta thalassemia patients aged 65 or older were enrolled in clinical studies of Luspatercept-aamt to determine whether they responded differently from younger subjects.

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DOSAGES[72,73,74,75,76,77]

Drug	CRF		Zidovudine-treated HIV-infected Patients	Chemotherapy-associated Anemia in Cancer Patients	Beta Thalassemia or MDS-RS or MDS/MPN-RS-T associated anemia	Surgery
	Starting Dose		Starting Dose	Starting Dose	Starting Dose	Starting Dose
darbepoetin (Aranesp)	Dialysis: Adults: 0.45 mcg/kg IV or SC once weekly or 0.75 mcg/kg every 2 weeks Pediatrics: 0.45 mcg/kg IV or SC once weekly	Not on dialysis: Adults: 0.45 mcg/kg IV or SC every 4 weeks Pediatrics: 0.45 mcg/kg IV or SC once weekly or 0.75 mcg/kg every 2 weeks	--	2.25 mcg/kg SC once weekly or 500 mcg SC every 3 weeks* Target Hb: sufficient to avoid RBC transfusion s	--	--
PEG-EPO (Mircera)	All Adults: 0.6 mcg/kg IV or SC once every 2 weeks Pediatrics: IV administration once every 4 weeks at the dose based on the total weekly ESA dose at time of conversion		--	--	--	--
luspatercept-aamt (Reblozyl)	--		--	--	Adults: 1 mg/kg SC once every 3 weeks	--

*Discontinue when chemotherapy completed.

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Dosages (continued)

Drug	CRF		Zidovudine-treated HIV-infected Patients	Chemotherapy-associated Anemia in Cancer Patients	Beta Thalassemia or MDS-RS or MDS/MPN-RS-T associated anemia	Surgery
	Starting Dose		Starting Dose	Starting Dose	Starting Dose	Starting Dose
rHuEPO (Epogen, Procrit)	Dialysis: Adults: 50-100 units/kg IV or SC 3 times weekly Pediatrics: 50 units/kg IV or SC 3 times weekly	Not on dialysis Adults: 50-100 units/kg IV or SC 3 times weekly	Adults: 100 units/kg IV or SC 3 times weekly	Adults: 150 units/kg SC 3 times weekly or 40,000 units SC once weekly* Pediatrics: 600 units/kg IV weekly (max 60,000 units weekly)* Target Hb: sufficient to avoid RBC transfusion	--	Adults: 300 units/kg SC daily for 10 days prior to surgery, day of surgery, and 4 days after surgery OR 600 units/kg once weekly starting 3 weeks prior to, and on day of surgery
rHuEPO-epbx (Retacrit)	Adults: 50-100 units/kg IV or SC 3 times weekly Pediatrics: 50 units/kg 3 times weekly		Adults: 100 units/kg IV or SC 3 times weekly	Adults: 150 units/kg SC 3 times weekly or 40,000 units SC once weekly* Pediatrics: 600 units/kg IV weekly (max 60,000 units weekly)* Target Hb: sufficient to avoid RBC transfusion	--	Adults: 300 units/kg SC daily for 10 days prior to surgery, day of surgery, and 4 days after surgery OR 600 units/kg once weekly starting 3 weeks prior to, and on day of surgery

*Discontinue when chemotherapy completed.

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Availability

Drug	Single-Dose Vials	Multiple Dose Vials	Prefilled Syringe and SureClick Autoinjectors
darbepoetin (Aranesp)	25, 40, 60, 100, 200, 300 mcg/mL in 1 mL vials	--	10 mcg/0.4 mL, 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
luspatercept-aamt (Reblozyl)	25, 75 mg vial	--	--
PEG-EPO (Mircera)	--	--	30 mcg/0.3 mL, 50 mcg/0.3 mL, 75 mcg/0.3 mL, 100 mcg/0.3 mL, 150 mcg/0.3 mL, 200 mcg/0.3 mL
rHuEPO* (Epogen, Procrit)	2,000, 3,000, 4,000, 10,000 units/mL in 1 mL vials (Epogen, Procrit) 40,000 units/mL in 1 mL vials (Procrit only)	10,000 units/mL in 2 mL vial† (Epogen, Procrit) 20,000 units/mL in 2 mL vial† (Epogen, Procrit)	--
rHuEPO-epbx (Retacrit)	2,000, 3,000, 4,000, 10,000, 40,000 units/mL in 1 mL vials	20,000 units/mL in 1 mL vial† 20,000 units/mL in 2 mL vial†	--

* All formulations of rHuEPO contain albumin

† Contains preservative

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Dosing Considerations

Prior to and during ESA therapy, patients' iron stores, including transferrin saturation and serum ferritin, should be evaluated. Transferrin saturation should be at least 20%, 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

The dose of ESA should be individualized to maintain Hb levels sufficient to reduce the need for RBC transfusion. Do not increase the dose of ESA more than once per 4 weeks; however, reductions in ESAs may occur more frequently.

For patients with CKD on dialysis, darbepoetin, PEG-EPO, rHuEPO, or rHuEPO-epbx therapy may be initiated when Hb is less than 10 g/dL. When the Hb is increasing and approaching 11 g/dL, the dose of the ESA should be reduced by 25%. If the Hb continues to increase, the ESA should be withheld until the Hb begins to decrease. Reinitiate the ESA at 25% below the previous dose. If the Hb increases by more than 1 g/dL within a 2-week period, the ESA dose should be reduced by 25% or more.

If the increase in hemoglobin is less than 1 g/dL over 4 weeks and iron stores are adequate, the dose of darbepoetin, PEG-EPO, or rHuEPO may be increased by approximately 25% of the previous dose. Further increases may be made at 4-week intervals until the specified Hb is obtained. Increases in dose should not be made more frequently than once a month.

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

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

PEG-EPO should be administered IV once every 4 weeks to pediatric patients (ages 5-17 years) whose Hb level has already been stabilized by another ESA. The dose is based on the total weekly dose of the prior ESA at the time of conversion. For patients converting from epoetin alfa to PEG-EPO, the dose is 4 x previous weekly epoetin alfa dose (units) divided by 125. For darbepoetin alfa, the dose is 4 x previously weekly darbepoetin alfa dose (mcg) divided by 0.55.

Chemotherapy-related Anemia

Therapy with darbepoetin, rHuEPO, or rHuEPO-epbx should only be initiated if the Hb is less than 10 g/dL and if there is a minimum of 2 additional months of planned chemotherapy. The dose of darbepoetin, rHuEPO, or rHuEPO-epbx should be titrated for each patient to achieve and maintain the lowest Hb level sufficient to avoid the need for RBC transfusion.

For either weekly or every 3 week dosing schedules of darbepoetin, the dose should be adjusted for each patient to maintain the lowest Hb level sufficient to avoid RBC transfusion. If the rate of Hb

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increase is more than 1 g/dL per 2-week period or when the Hb reaches a level needed to avoid transfusion, the dose should be reduced by 40% 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% below the previous dose.

For patients receiving weekly administration, if there is less than a 1 g/dL increase in Hb after 6 weeks of therapy and Hb remains less than 10 g/dL, the dose of darbepoetin should be increased up to 4.5 mcg/kg. Discontinue darbepoetin if, after 8 weeks of therapy, there is no response as measured by Hb levels or if transfusions are still required. Discontinue darbepoetin following the completion of a chemotherapy course.

Reduce rHuEPO or rHuEPO-epbx dose by 25% when Hb reaches a level needed to avoid RBC transfusion or increases more than 1 g/dL in any 2-week period. rHuEPO and its biosimilar should be withheld when Hb exceeds a level needed to avoid RBC transfusion. rHuEPO and rHuEPO-epbx should be restarted at 25% below the previous dose when the Hb approaches a level where RBC transfusions may be required. rHuEPO and rHuEPO-epbx should be discontinued following the completion of chemotherapy course. After the initial 4 weeks of rHuEPO or rHuEPO-epbx, if the Hb increases by less than 1 g/dL and remains < 10 g/dL, increase rHuEPO dose to 300 units/kg 3 times per week in adults or 60,000 units weekly in adults or 900 units/kg (maximum of 60,000 units) weekly in children. If, after 8 weeks of rHuEPO or rHuEPO-epbx therapy, there is no response as measured by Hb levels, or if RBC transfusions are still required, discontinue the agent.

Zidovudine-treated HIV-infected Patients

Prior to beginning rHuEPO or rHuEPO-epbx, 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% when treatment is resumed.

If a satisfactory response is not seen within 8 weeks of therapy, rHuEPO or rHuEPO-epbx dose can be increased by 50 to 100 units/kg 3 times weekly. Response should be evaluated every 4 to 8 weeks, and the dose adjusted accordingly by 50 to 100 units/kg increments 3 times weekly. If a patient has not responded to rHuEPO or rHuEPO-epbx 300 units/kg 3 times weekly for 8 weeks, discontinue the agent.

Beta Thalassemia Patients

Luspatercept-aamt should be reconstituted according to product labeling instructions and administered subcutaneously by a healthcare professional. Hemoglobin levels should be assessed and reviewed prior to each administration. The dose should be titrated based on response at the initiation of therapy. If a patient does not have a reduction in RBC transfusion burden after at least 2 consecutive doses (6 weeks), the dose should be increased to 1.25 mg/kg every 3 weeks. If there is no reduction in RBC transfusion burden after 3 consecutive doses (9 weeks) at the maximum dose of 1.25 mg/kg, treatment should be discontinued. Treatment should also be discontinued if unacceptable toxicity occurs at any stage. Dose modifications according to predose hemoglobin levels ≥ 11.5 g/dL in the absence of transfusions, rapid hemoglobin increases, or toxicities are also provided in the luspatercept-aamt product labeling.

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Myelodysplastic Syndromes with Ring Sideroblasts (MDSRS) or Myelodysplastic/ Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis (MDS/MPN-RS-T) Associated Anemia Patients

Prior to each luspatercept-aamt dose, patient's hemoglobin and transfusion record should be reviewed. If insufficient response at the initiation of treatment, the dose should be titrated accordingly. If the patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the starting dose, the dose should be increased to 1.33 mg/kg every 3 weeks. If the patient is still not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1.33 mg/kg dose, the dose should be increased to 1.75 mg/kg. Treatment should be discontinued if there is no reduction in RBC transfusion burden after at least 3 consecutive doses at 1.75 mg.kg. Dose modifications for predose hemoglobin levels ≥ 11.5 g/dL in the absence of transfusions, rapid hemoglobin increases, and toxicities are also provided in the luspatercept-aamt product labeling.

Dose Conversions

FDA-labeled dose conversion of rHuEPO to darbepoetin for patients with CKD on dialysis

Previous weekly rHuEPO (Epogen/Procrit) dose (units)	Equivalent weekly darbepoetin (Aranesp) dose in adults (mcg)	Equivalent weekly darbepoetin (Aranesp) dose in pediatric patients (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 2 to 3 times per week and once every 2 weeks for those who received rHuEPO once weekly; the same route of administration should be maintained. For patients with CKD not on dialysis, the above table does not accurately reflect the once monthly administration of darbepoetin.

Clinical study results suggest that greater relative potency differences are seen between rHuEPO and darbepoetin alfa when the dosing intervals are longer and when rHuEPO dose requirements are higher. Although 200 units of rHuEPO contains the same peptide mass as 1 mcg of darbepoetin alfa, a fixed ratio of 200:1 does not necessarily predict an appropriate dose conversion between the 2 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.[78] Retrospective chart analyses have shown that the 2 most commonly used doses, rHuEPO (Epogen/Procrit) 40,000 units weekly and darbepoetin (Aranesp) 200 mcg every 2 weeks, result in similar hematologic outcomes with the higher Hb targets.[79,80,81]

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FDA-labeled dose conversion of rHuEPO or darbepoetin to PEG-EPO for patients with CKD

Previous weekly rHuEPO (Epogen/Procrit) dose (units/week)	Previous weekly darbepoetin (Aranesp) dose (mcg/week)	Equivalent PEG-EPO (Mircera) dose in adults (mcg)	
		Monthly PEG-EPO (Mircera) dose in adults (mcg)	Once every 2 week PEG-EPO (Mircera) dose in adults (mcg/every 2 weeks)
< 8,000	< 40	120	60
8,000 to 16,000	40 to 80	200	100
> 16,000	> 80	360	180

PEG-EPO can be administered once monthly or once every 2 weeks for CKD patients with stabilized hemoglobin due to treatment with rHuEPO or darbepoetin; the same route of administration should be maintained. The dose of PEG-EPO is based on the total weekly dose of rHuEPO or darbepoetin. When converting patients with CKD from rHuEPO or darbepoetin to PEG-EPO, dosing should be based on the guidance for conversion provided in the approved package insert for PEG-EPO (Mircera) and doses should be titrated individually according to each patient's hemoglobin response.

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% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Several comparative trials between rHuEPO and darbepoetin have been performed in an open-label manner in a variety of types of anemia.[82,83,84,85,86,87,88,89,90,91,92,93,94,95,96] Retrospective analyses have also evaluated data from patients receiving darbepoetin and rHuEPO for a variety of anemia indications.[97,98,99,100,101,102,103,104]

Use of erythropoiesis-stimulating agents in anemic patients with HIV that have been treated with zidovudine have not been demonstrated in controlled clinical trials to improve quality of life, fatigue, or patient well-being.[105,106,107]

Pfizer, the manufacturer of epoetin alfa-epbx (Retacrit), conducted multiple *in vitro* analytical and non-clinical (e.g., pharmacokinetic) studies comparing their biosimilar product to either epoetin alfa product (Epogen/Procrit). These studies demonstrated that their product was highly similar to epoetin alfa (Epogen/Procrit). A composite of data was used by the FDA to determine that epoetin alfa-epbx is *biosimilar* to epoetin alfa (Epogen/Procrit); thus, it was approved for all eligible indications.

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Chronic Renal Failure

darbepoetin (Aranesp) – pediatrics

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% of children receiving darbepoetin less than once weekly.[108] Pediatric patients (age 1 to 17 years) with CRF receiving or not receiving dialysis were enrolled in an open-label, randomized study.[109] 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% between weeks 8 and 12, and 91% 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.[110] Mean darbepoetin dose in the observational, prospective study was 0.63 mcg/kg/week to achieve target Hb of 11 to 13 g/dL.

One-hundred and sixteen pediatric patients (aged 1 to 18 years) with CKD stages 3 through 5D, Hb < 10 g/dL, and no prior ESA experience were randomized by age and dialysis status to receive darbepoetin alfa SC once weekly or every 2 weeks.[111] The agent was titrated to achieve Hb levels of 10 to 12 g/dL over a period of 25 weeks. Health-related outcomes reported by patient and patents (measured by the Pediatric Quality of Life Inventory [PedsQL]) were also measured. Patients in both treatment groups had the mean Hb concentration increase to ≥ 11 g/dL over the first 3 months of treatment and were able to remain within the 10 to 12 g/dL Hb target range. Adverse events were similar between treatment groups and PedsQL scores showed modest improvements.

darbepoetin (Aranesp) versus rHuEPO (Epogen/Procrit) – pediatrics

A randomized, open-label, 28-week trial compared the efficacy and safety of darbepoetin and rHuEPO in 124 children (age 1 to 18 years) with CKD.[112] 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% confidence interval [CI], -0.45 to 1.07). Safety was comparable between the groups.

darbepoetin (Aranesp) once weekly versus rHuEPO (Epogen/Procrit) 3 times 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.[113] Patients receiving rHuEPO therapy were randomized to continue rHuEPO administered IV 3 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.

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PEG-EPO (Mircera) once every 4 weeks versus darbepoetin (Aranesp) once weekly or once every 2 weeks

A randomized, open-label, multicenter, parallel-group study was conducted to compare the safety and efficacy of PEG-EPO compared to darbepoetin for the correction of anemia in 307 non-dialysis, CKD patients.[114] The patients consisted of ESA-naïve adults (≥ 18 years) with CKD Stage 3 or 4, an estimated glomerular filtration rate of 15 to 59 mL/min/1.73 m^2, a baseline Hb concentration < 10.5 g/dL and adequate iron status defined as serum ferritin ≥ 100 µg/L or transferrin saturation (TSAT) ≥ 20% or < 10% hypochromic red blood cells (RBCs), and were randomized (1:1) to receive 1.2 mcg/kg of PEG-EPO SC once every 4 weeks, darbepoetin 0.4 mcg/kg SC once weekly, or darbepoetin 0.75 mcg/kg SC once every 2 weeks for a 20-week correction period and an 8-week evaluation period. Hb response rate and change in average Hb concentration between baseline and evaluation were the 2 primary endpoints evaluated. The Hb response rate for PEG-EPO was 94.1% and darbepoetin was 93.5% (once weekly) and 95% (once every 2 weeks) showing the results to be comparable. PEG-EPO was shown to be non-inferior to both dosing frequencies of darbepoetin, with similar mean Hb changes from baseline of 1.62 g/dL and 1.66 g/dL, respectively, but did show a steady rise in Hb, with fewer patients (25.8%) above the target range during the first 8 weeks compared with darbepoetin (47.7%). Adverse event rates were comparable between the treatment groups.

PEG-EPO (Mircera) once every 2 weeks versus rHuEPO (Epogen/Procrit) 3 times weekly

A randomized, open-label, multicenter, parallel-group study was conducted to compare the efficacy of PEG-EPO to rHuEPO for Hb level correction in 181 ESA-naïve, CKD dialysis patients.[115] The patients were randomized (3:1) to receive PEG-EPO administered IV once every 2 weeks compared to rHuEPO administered IV 3 times per week for a 24-week correction period. The Hb response rate for PEG-EPO was 93.3% and rHuEPO was 91.3% with mean change in Hb level from baseline to end of correction period of 12.28 g/dL for PEG-EPO and 12.19 g/dL with rHuEPO showing the results to be comparable. Both treatments were found to be generally well tolerated.

Chemotherapy-induced Anemia

darbepoetin (Aranesp) versus placebo

In a multicenter, double-blind, placebo-controlled trial, 320 patients with lung cancer and anemia were randomly assigned to receive darbepoetin 2.25 mcg/kg or placebo once weekly.[116] By 12 weeks, patients receiving darbepoetin required about half as many blood transfusions (27 versus 52%, 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%, p<0.001). Treated patients also had more improvement in fatigue scores (56 versus 44%, p=0.019) than patients receiving placebo. With regard to quality of life (QoL), 56% of the patients in the darbepoetin group and 44% in the placebo group had an improvement in the FACT-fatigue cancer chemotherapy score (p=0.052). Adverse events were similar in each group.

rHuEPO (Epogen/Procrit) versus placebo

In a randomized, double-blind, placebo-controlled clinical trial, the effects of rHuEPO on transfusion requirements, hematopoietic parameters, QoL, and safety in anemic cancer patients receiving non-platinum chemotherapy were assessed.[117] 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

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randomized to rHuEPO 150 to 300 units/kg or placebo 3 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%, 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 perform 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).[118] Increases of ≥ 2 g/dL in Hb were observed in 31.7% and 72.7% 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% 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).

rHuEPO (Epogen/Procrit) versus placebo – pediatrics

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 5 to 18 years.[119] After week 4, patients in the rHuEPO group were significantly more likely than those in the placebo group to remain transfusion-free (38.7% versus 22.5%; p=0.01). There was no improvement in health-related quality of life with no evidence of effectiveness for fatigue, energy, or strength between the group receiving rHuEPO or placebo. Adverse events were similar between the 2 groups.

rHuEPO (Epogen/Procrit) once weekly or every 3 weeks versus darbepoetin (Aranesp) once every 3 weeks

In an open-label, multicenter, prospective trial, 239 patients with cancer chemotherapy-associated anemia (CAA) and Hb < 10.5 g/dL were randomized to receive rHuEPO 40,000 units SC once weekly, extended schedule rHuEPO (either 80,000 units every 3 weeks or 120,000 units every 3 weeks), or darbepoetin 500 mcg every 3 weeks for 15 weeks.[120] The primary endpoint evaluated was the proportion of patients achieving Hb ≥ 11.5 g/dL or increment of Hb > 2 g/dL from baseline without transfusion. Secondary endpoints were transfusion requirements, adverse events, and patient-reported outcomes. It was determined that there were no significant differences in patients requiring RBC transfusions, adverse events, patient-reported outcomes, or between treatment arms in the proportion of patients achieving Hb response (68.9% for weekly rHuEPO, 61.7% for rHuEPO 80,000 units every 3 weeks, 65.5% for rHuEPO 120,000 units every 3 weeks, and 66.7% for the darbepoetin arm; p>0.41 for all comparisons). The median Hb increment from baseline was found to be higher in the weekly rHuEPO arm and the darbepoetin arm compared to the 2 extended schedule rHuEPO arms. Also, the Hb response was achieved more quickly in the weekly rHuEPO arm. The 2 FDA-approved dosing schedules tested (weekly rHuEPO and darbepoetin every 3 weeks) were reasonable options for CAA.

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Beta Thalassemia

luspatercept-aamt (Reblozyl) once every 3 weeks versus placebo

A randomized, double-blind, placebo-controlled study was conducted in 338 adult patients with beta thalassemia who required regular red blood cell transfusions (6 to 20 RBC units per 24 weeks with no transfusion-free period ≥ 35 days during that time).[121] Patients were randomized 2:1 to receive luspatercept-aamt 1 mg/kg or placebo subcutaneously every 3 weeks for at least 48 weeks. All patients were able to continue receiving best supportive care (RBC transfusions, iron-chelating agents, and other support as needed). The efficacy of luspatercept-aamt was based upon the proportion of patients achieving RBC transfusion burden reduction (≥ 33% decrease from baseline) with a reduction of ≥ 2 units from week 13 to week 24. Nearly 20% of patients were able to reduce their number of transfusion units by ≥ 33%, compared with 3.6% of patients receiving placebo (p<0.0001). Ten percent of patients reduced their number of transfusion units by at least half, compared with 0.9% of patients receiving placebo (p=0.0017).

Myelodysplastic Syndromes with Ring Sideroblasts (MDSRS) or Myelodysplastic/ Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis (MDS/MPN-RS-T) Associated Anemia

luspatercept-aamt (Reblozyl) once every 3 weeks versus placebo

A randomized, double-blind, placebo-controlled study was conducted in 229 patients with patients with an International Prognosis Scoring System – Revised (IPSS-R) classification risk category of either very low, low, or intermediate-risk myelodysplastic syndromes who have ring sideroblasts and require red blood cell transfusions (2 or more RBC units over 8 weeks).[122] Patients were randomized 2:1 to receive luspatercept-aamt 1 mg/kg or placebo subcutaneously every 3 weeks. The dose could be increased after completion of the first 2 cycles if the patient had ≥ 1 RBC transfusion in the prior 6 weeks. Two dose level increases were allowed (to 1.33 mg/kg and to 1.75 mg/kg), if needed. Dose modifications were provided for adverse reactions and changes in hemoglobin levels. All patients received supportive care, including RBC transfusions, when necessary. The primary efficacy assessment was conducted after completion of 24 weeks. The efficacy of luspatercept-aamt in adult patients with MDS-RS and MDS-RS-T was established based upon the proportion of patients who were red blood cell transfusion independent (RBC-TI), defined as the absence of any RBC transfusion during any consecutive 8-week period occurring entirely in the 24 week period. Treatment with luspatercept resulted in a statistically significantly greater proportion of patients achieving RBC-TI ≥ 8 weeks (37.9%) compared to placebo (13.2%) (p<0.0001).

META-ANALYSES

Multiple meta-analyses have been conducted on these agents. However, meta-analyses evaluating head-to-head trials with clinical outcomes are limited.

A Cochrane review 56 studies (n=15,596) of ESAs for the treatment of CKD found that each agent was superior to placebo in prevention of blood transfusions, but there was insufficient evidence to suggest that one agent is superior to another.[123] While one meta-analysis suggests dose efficiency with darbepoetin compared to rHuEPO, another Cochrane review of ESAs in dialysis patients found that darbepoetin is non-inferior to rHuEPO in achieving hemoglobin targets.[124,125]

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A meta-analysis of 9 trials (n=2,024) comparing rHuEPO and darbepoetin in patients with CKD found no difference between agents in all-cause mortality (darbepoetin versus rHuEPO: odds ratio [OR], 1.33; 95% CI, 0.88 to 2.01).[126] In addition, a meta-analysis of 17 studies of ESAs in CKD patients (with or without dialysis) found that higher hemoglobin target resulted in no statistically or clinically significant differences in quality of life, as measured using the Short-Form Health Survey (SF-36) (95% CI crossed 0 for all domains) or the Kidney Dialysis Questionnaire (KDQ) (95% CI crossed 0 for all domains in both measurements of quality of life [SF-36 or KDQ]).[127] No clinically significant differences were found during subgroup analyses as well. A benefit on mortality (or difference between agents) or quality of life was not found in earlier meta-analyses as well.[128,129]

Results in cancer patients using ESAs have been similar. Multiple meta-analyses have found a benefit in transfusion reduction, but no benefit in mortality or disease progression.[130,131] One Cochrane review of 53 studies (n=4,993) on the use of ESAs in patients using chemotherapy agents found worsened overall survival (hazard ratio [HR], 1.06; 95% CI, 1 to 1.12) and increased mortality (HR, 1.17; 95% CI, 1.06 to 1.3) in patients using ESAs.[132] Other meta-analyses in cancer patients have found similar results.[133,134,135]

SUMMARY

Based on available evidence, darbepoetin (Aranesp) and rHuEPO (Epogen/Procrit) appear to have comparable safety and efficacy in reducing the need for red blood cell transfusions in the treatment of chemotherapy-induced anemia in patients with cancer. In patients with chronic renal failure on dialysis or pre-dialysis, darbepoetin (Aranesp), PEG-EPO (Mircera), and rHuEPO (Epogen/Procrit) are effective in achieving and maintaining Hb levels sufficient to avoid RBC transfusions. Epoetin alfa-epbx (Retacrit), or rHuEPO-epbx, is an FDA-approved biosimilar to rHuEPO (Epogen/Procrit); however, epoetin alfa-epbx (Retacrit) is not considered interchangeable with rHuEPO (Epogen/Procrit). Darbepoetin (Aranesp), PEG-EPO (Mircera), and rHuEPO (Epogen/Procrit) have similar occurrences of adverse effects when used according to their labeling. Luspatercept-aamt (Reblozyl) is indicated for the treatment of adult patients with beta thalassemia who require regular red blood cell transfusions and for the treatment of anemia in adults with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis after failure of an ESA and who require 2 or more RBC units over 8 weeks.

Product information for all agents in the class, with the exception of luspatercept-aamt, contain boxed warnings regarding risk for increased mortality, serious cardiovascular and thromboembolic events, and increased risk of tumor progression or recurrence.

To reduce risk, use the lowest dose of the erythropoiesis stimulating agent that will gradually increase the hemoglobin concentrations to a level sufficient to avoid the need for red blood cell transfusion. Additionally, therapy with rHuEPO (Epogen/Procrit), epoetin alfa-epbx (Retacrit), PEG-EPO (Mircera), and darbepoetin (Aranesp) for chronic kidney disease should not exceed target hemoglobin of greater than 11 g/dL.

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