Therapeutic Class Overview
Erythropoiesis Stimulating Agents

INTRODUCTION

- Iron deficiency anemia is the most common form of anemia. Anemia is also associated with a variety of conditions including cancer, chronic kidney disease (CKD), rheumatoid arthritis, human immunodeficiency virus (HIV), chronic heart failure, and chronic obstructive pulmonary disease (*Schrier and Camaschella 2018, Schrier 2018*).
- Management of anemia of chronic disease is often more complex, and administration of erythropoiesis-stimulating agents (ESAs) or red blood cell (RBC) transfusions may be necessary for patients with severe, symptomatic anemia (eg, hemoglobin [Hb] <10 g/dL) (*Schrier and Camaschella 2018*).
- Although allogeneic RBC transfusions provide rapid correction of Hb stores, they are also accompanied by significant risks, which include transmission of communicable diseases, allergic and immune transfusion reactions, volume overload, hyperkalemia, and iron overload (*Carson and Kleinman 2019*).
- Erythropoietin is a naturally occurring glycoprotein hormone that stimulates the production and maturation of erythrocytes in the bone marrow. Erythrocytes, or RBCs, are responsible for transporting oxygen from the lungs to the peripheral tissues. Erythropoietin is primarily produced and released into the bloodstream by the kidneys. Renal production of erythropoietin is stimulated when the renal oxygen sensor is triggered by hypoxia or low tissue oxygen (*Hörl 2013*).
- The ESAs were first introduced in the early 1980's to provide a treatment option for anemia in patients with CKD, and later, in patients with malignancies who were unable to maintain their Hb within the acceptable ranges (*Schrier et al 2018*).
- Although ESAs may decrease the need for RBC transfusions, multiple meta-analyses of randomized controlled trials (RCTs) have demonstrated an increase in mortality, cardiovascular events, and cancer progression without significant improvements in morbidity or quality of life (QoL) for patients receiving therapy (*Collister et al 2016, Grant et al 2013, Palmer et al 2014a, Tonia et al 2012*).
- The ESAs approved by the Food and Drug Administration (FDA) in the United States include Epogen (epoetin alfa), Procrit (epoetin alfa), Aranesp (darbepoetin alfa), Retacrit (epoetin alfa-epbx), and Mircera (methoxy polyethylene glycol-epoetin beta). Retacrit is the first and only FDA-approved ESA biosimilar in the United States.
- Epoetin alfa and darbepoetin alfa products carry boxed warnings regarding shortened survival and increased risk of tumor progression or recurrence in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers. Furthermore, the warnings emphasize to use ESAs only for the treatment of anemia due to concomitant myelosuppressive chemotherapy and to discontinue ESAs following completion of a chemotherapy course. ESAs should not be initiated in cancer patients receiving myelosuppressive therapy when the anticipated outcome is cure.
- Medispan Therapeutic Class: Erythropoietins

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Biosimilar Availability
Aranesp (darbepoetin alfa)	Amgen	09/17/2001	-
Epogen, Procrit (epoetin alfa)	Amgen	06/01/1989	+
Retacrit (epoetin alfa-epbx)*	Hospira/Pfizer	05/15/2018	-
Mircera (methoxy polyethylene glycol-epoetin beta)	Galenica	11/14/2007	-

*Retacrit is an ESA biosimilar to Epogen/Procrit.

(*DRUGS@FDA 2019, Purple Book: lists of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Aranesp (darbepoetin alfa)†	Epogen, Procrit, Retacrit (epoetin alfa; epoetin alfa-epbx)‡	Mircera (methoxy polyethylene-epoetin beta)§
Treatment of anemia associated with chronic kidney disease, including patients on dialysis and patients not on dialysis	✔ †	✔ *	✔
Treatment of anemia associated with chronic kidney disease in pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their Hb level was stabilized with an ESA			✔
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	✔	✔	
Treatment of anemia due to zidovudine administered at ≤ 4200 mg/week in human immunodeficiency virus (HIV)-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL		✔	
Reduce the need for allogeneic red blood cell transfusions among patients with perioperative Hb > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery		✔	

*To decrease the need for transfusions in these patients.

† The safety and effectiveness of Aranesp was studied in pediatric patients 1 month to 16 years old who have CKD and are receiving or not receiving dialysis; safety and efficacy of Aranesp in pediatric patients with cancer have not been established.

‡ Indicated in pediatric patients 1 month to 16 years of age for treatment of anemia in CKD requiring dialysis, and in patients 5 to 18 years of age for treatment of anemia due to concomitant myelosuppressive chemotherapy. Limited data are available on the use of epoetin in children with HIV receiving zidovudine.

§Mircera is indicated for the treatment of anemia due to CKD in patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their Hb level was stabilized with an ESA

- **Limitations of use:**
  - All ESAs have not been shown to improve QoL, fatigue, or patient well-being.
  - ESAs are not indicated as a substitute for RBC transfusions in patients who require immediate correction of anemia.
- Aranesp, Epogen, Procrit, and Retacrit are not indicated for use:
  - In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
  - In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
  - In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion.
- Epogen, Procrit, and Retacrit are not indicated for use:
  - In patients scheduled for surgery who are willing to donate autologous blood.
  - In patients undergoing cardiac or vascular surgery.
- Mircera is not indicated for use:

- In the treatment of anemia due to cancer chemotherapy.

(*Prescribing information: Aranesp 2019, Epogen 2018, Mircera 2018, Procrit 2018, Retacrit 2019*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Only a few clinical studies have compared the efficacy and safety of epoetin alfa to darbepoetin alfa for the treatment of anemia due to CKD or myelosuppressive chemotherapy. None of these agents have been shown to improve QoL, fatigue, or patient well-being. Since initial FDA-approval, the ESAs have been shown to increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence. Earlier studies utilized ESA to maintain higher Hb targets than the targets recommended currently. Numerous observational, non-interventional, retrospective, and single-center studies have evaluated these agents in the correction of anemia due to CKD or myelosuppressive chemotherapy. However, these studies are not included in this review.
- Retacrit (epoetin alfa-epbx) was approved as a biosimilar to Epogen/Procrit (epoetin alfa) in May 2018 (*FDA News Release 2018*). The approval of Retacrit was based on a review of evidence including extensive structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamic data, clinical immunogenicity data, and other clinical safety and effectiveness data demonstrating its biosimilarity. Retacrit was approved as a biosimilar, not as an interchangeable product.

Anemia in CKD

- ESAs provided an attractive solution to decreasing the number of allogeneic blood transfusions; however, multiple meta-analyses of RCTs have demonstrated an increase in mortality, cardiovascular events, and cancer progression without improvement in morbidity or QoL for patients receiving therapy (*Collister et al 2016, Grant et al 2013, Palmer et al 2014a*).
- According to a Cochrane review, use of ESAs in predialysis patients corrected anemia and avoided blood transfusions compared to placebo or no treatment (*Cody et al 2016*). A total of 19 studies (N = 993) evaluated ESAs, with the majority of the studies being published prior to 2000. ESAs improved Hb (mean difference [MD] 1.90 g/dL, 95% CI, -2.34 to -1.47) and decreased the number of patients with blood transfusions (risk ratio [RR] 0.32, 95% confidence interval [CI], 0.12 to 0.83). No differences with the measure of kidney disease progression were observed. Endpoints of QoL and change in exercise capacity were not measured in a manner which was suitable for analysis.
- The harms of high Hb targets compared to lower Hb targets were evaluated. The Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease (CHOIR) trial was a notable trial that found that patients with CKD with a higher target Hb had higher risk for the composite outcome of death, nonfatal myocardial infarction, stroke, and hospitalization for congestive heart failure (CHF) than patients with a lower Hb target (17.5 vs 13.5%; hazard ratio [HR], 1.34; 95% CI, 1.03 to 1.74; p = 0.03) (*Singh et al 2006*). Analysis of study data in the intent-to-treat (ITT) population and including all events from randomization until study termination or 30 days after the last dose showed a higher incidence of events in the high-Hb group (HR, 1.3; 95% CI, 1.01 to 1.62; p = 0.04). Even though the trial was halted early, evidence suggested that higher Hb levels led to an increased rate of adverse events. The prescribing information and warnings for all drugs of this class were updated to reflect these findings. Findings were similar to the Normal Hematocrit Study performed in patients with CKD on dialysis with CHF or ischemic heart disease (*Besarab et al 1998*).
- A systematic review evaluated 9 trials comparing epoetin alfa and darbepoetin alfa for all-cause mortality in patients with anemia in adults with CKD including those on dialysis (N = 2024). Duration of the trials was 20 to 52 weeks. No significant difference in mortality between epoetin and darbepoetin was detected (odds ratio [OR] 1.33; 95% CI, 0.88 to 2.01) (*Wilhelm-Leen et al 2015*).
- Numerous trials have evaluated extended dosing intervals of epoetin for patients with CKD. In general, larger doses given less frequently demonstrated similar outcomes with epoetin alfa and darbepoetin (*Benz et al 2007, Patel et al 2012, Pergola et al 2009, Pergola et al 2010, Provenzano et al 2004, Provenzano et al 2005, Spinowitz et al 2008a, Warady et al 2018*). A systematic review confirmed that various dosing frequencies of darbepoetin and epoetin result in similar mean final Hb values in patients receiving hemodialysis (*Hahn et al 2014*). Many of these dosing regimen studies

were completed in small patient populations and open-label design. The FDA-approved dosing regimen for epoetin alfa is 3 times weekly for patients with CKD.

- Patients with CKD on dialysis should receive intravenous (IV) darbepoetin and epoetin alfa. Cases of pure red cell aplasia and severe anemia have been reported more frequently with the subcutaneous (SC) administration of ESAs in patients with CKD. Comparisons of the method of administration (IV vs SC) have been completed with epoetin and darbepoetin. In an open-label, German study, switching patients on dialysis from SC darbepoetin to IV administration led to stable mean Hb levels and mean weekly darbepoetin doses (*Bommer et al 2008*). Another open-label study showed that switching patients on dialysis from SC epoetin to IV darbepoetin resulted in stable mean Hb levels at stable darbepoetin doses after 3 months (*Chazot et al 2009*). Mircera is indicated for IV or SC administration.
- In a double-blind, multicenter, placebo-controlled, randomized clinical trial, the safety of darbepoetin in patients with type 2 diabetes mellitus, CKD, and anemia were evaluated (*Pfeffer et al 2009*). The patients had a baseline Hb level of ≤11 g/dL. The primary endpoint of the TREAT study was the composite of death or a non-fatal cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke or hospitalization for myocardial ischemia) and death or end-stage renal disease. The primary cardiovascular composite outcome of death or nonfatal cardiovascular event occurred in 632 patients (31.4%) of the darbepoetin group and 602 patients (29.7%) treated with placebo (HR for darbepoetin vs placebo, 1.05; 95% CI, 0.94 to 1.17; p = 0.41). For the individual endpoints contributing to the composite, there were no statistically significant differences between the groups for any parameter except for fatal and non-fatal stroke which occurred more frequently with darbepoetin (5% vs 2.6%; HR, 1.92; 95% CI, 1.38 to 2.68; p < 0.001). For the composite endpoint of death or end-stage renal disease, no significant difference was detected (darbepoetin 32.4% vs 30.5% placebo; HR, 1.06; 95% CI, 0.95 to 1.19; p = 0.29). The study was performed from 2004 to 2007, when the standard of care target Hb level was 13 g/dL. Additional notification was sent to investigators and participants of the adverse outcomes with higher Hb targets; however, the study protocol was not modified. A third party vendor assayed Hb levels and reported the dosage adjustment necessary for patients receiving darbepoetin. At baseline, the darbepoetin group had a lower proportion of patients with a history of CHF (31.5 vs 35.2%; unadjusted p = 0.01). In summary, darbepoetin in patients with anemia, diabetes and chronic renal disease did not increase the risk of the composite outcome of death or cardiovascular outcome and death or end-stage renal disease. It was noted that stroke, fatal or non-fatal, occurred more frequently in patients who received darbepoetin compared to placebo.
- A systematic review evaluated darbepoetin and the other ESAs in 21 studies in patients with CKD for the effect on blood transfusion (*Palmer et al 2014b*). Darbepoetin reduced the need for blood transfusions compared to placebo or no treatment; however, in 3 studies comparing darbepoetin to epoetin, darbepoetin had uncertain effects on RBC transfusions and all-cause mortality compared to epoetin. Darbepoetin and methoxy polyethylene glycol-epoetin beta were similar for risk of RBC transfusions.
- A Cochrane review compared the efficacy and safety of the ESAs (Mircera, epoetin alfa, epoetin beta, darbepoetin alfa, and biosimilar ESAs) in adults with CKD. A total of 56 studies (N = 15,596) were included in the analysis. In network analyses, there was moderate to low confidence that the ESAs prevented blood transfusions compared to placebo. The authors concluded that there was insufficient evidence to suggest superiority of any ESA formulation based on available safety and efficacy data (*Palmer et al 2014a*).
- A systematic review evaluated 17 studies (N = 10,049) with ESAs for effects on health-related quality of life (HRQoL) in CKD patients (*Collister et al 2016*). Higher Hb target levels (range: 10.2 to 13.6 g/dL) resulted in no statistically significant improvements in Short-Form 36 (SF-36) domains or for the Kidney Disease Questionnaire (KDQ) compared to patients on placebo or lower Hb target levels (range: 7.4 to 12 g/dL). For the KDQ, patients with higher Hb targets had an improvement of 0.5 (95% CI, -2.2 to 1.2) points in the physical symptom domain, 0.5 point improvement in the fatigue domain (95% CI, -1.6 to 0.5), and 0.2 point improvement in the depression domain (95% CI, -1.1 to 0.8). A clinically meaningful benefit is considered a minimum of 0.5 point improvement on the KDQ. The systematic review is consistent with the prescribing information and previously published reports.
- Very few randomized controlled studies comparing darbepoetin and epoetin alfa have been published. Two non-inferiority studies comparing epoetin alfa to darbepoetin alfa in the treatment of anemia of CKD demonstrated no difference in efficacy between the 2 agents. In a study of adult patients with CKD by *Nissenson et al*, the mean changes in Hb levels from baseline to the evaluation period were similar between the darbepoetin alfa (0.16 to 0.09 g/dL) and epoetin alfa (0 to 0.06 g/dL) groups (difference, 0.16 g/dL; 95% CI, -0.06 to 0.38; p value not reported). In a second study by *Vanrenterghem et al* (N = 522) of patients with CKD on dialysis, the mean change in Hb was 0.05 g/dL in the

darbepoetin alfa group compared to 0 g/dL in the epoetin alfa treatment (difference, 0.05 g/dL; 95% CI, -0.14 to 0.24; p values not reported). No statistically significant differences in the mean change in Hb levels from baseline, the primary endpoint were reported. In addition, in both studies there were no differences in safety profiles, and no antibodies detected to either treatment (*Nissenson et al 2002, Vanrenterghem et al 2002*). An open-label trial comparing darbepoetin SC 0.45 mcg/kg once weekly and epoetin SC 50 units/kg twice weekly found similar efficacy in achieving a Hb response and similar safety profile in 166 patients with CKD not on dialysis (*Locatelli et al 2001*).

- The safety and efficacy of Mircera were established in Phase 3, multicenter, open-label, active-controlled trials that randomized patients with CKD with anemia to treatment with either Mircera or a comparator ESA.
- Four of the clinical trials assessed Mircera in the maintenance of Hb levels among patients currently treated with other ESAs for anemia of CKD (*Canaud et al 2008, Levin et al 2007, Spinowitz et al 2008b, Sulowicz et al 2007*). Patients were randomized to receive Mircera administered either once every 2 weeks or once every 4 weeks, or to continue their current ESA schedule and dose. Throughout the trials, treatment with Mircera consistently maintained Hb concentrations within the targeted range (10 to 13.5 g/dL) and demonstrated non-inferiority compared to other ESAs.
- In addition, an extension trial was conducted that demonstrated the long-term safety and efficacy of Mircera administered every 4 weeks in maintaining stable Hb levels in patients with CKD not on dialysis following correction with Mircera administered every 2 weeks (*Kessler et al 2010*).
- Other direct-comparative trials have been conducted to evaluate the safety and efficacy of Mircera to other ESAs. In the trials, mean Hb concentrations remained constant within the recommended target range in all treatment groups and further confirmed the efficacy and safety of once monthly Mircera for correction and maintenance of Hb (*Al-Ali et al 2015, Carrera et al 2010, Roger et al 2011*).
  - The PATRONUS study evaluated Mircera IV every 4 weeks to IV darbepoetin alfa every 4 weeks in patients on hemodialysis (N = 490) (*Carrera et al 2010*). For the primary endpoint, Hb response rate (average Hb ≥ 10.5 g/dL with a decrease from baseline of ≤ 1 g/dL) was significantly higher in patients on Mircera (64.1%) in comparison to those given IV darbepoetin alfa (40.4%) ($p < 0.0001$).
- A systematic review compared the efficacy and tolerability of Mircera with darbepoetin alfa for the treatment of anemia in non-dialysis dependent patients (N = 1155) with CKD (*Alsalimy et al 2014*), Based on the analysis, changes in Hb level from baseline demonstrated that Mircera was clinically non-inferior to darbepoetin alfa.
- Two studies evaluated Mircera in the correction of Hb levels in anemic patients with CKD who were not treated with an ESA at baseline.
  - In the ARCTOS study, patients (N = 324) not currently receiving dialysis were randomized to Mircera administered every 2 weeks or darbepoetin alfa administered once a week for 28 weeks. Hb response rate, defined as an increase ≥1 g/dL vs baseline and a concentration ≥11 g/dL, was achieved in 97.5% of patients treated with Mircera and 96.3% of patients treated with darbepoetin alfa (*Macdougall et al 2008*).
  - In the second study, patients who were receiving either peritoneal dialysis or hemodialysis were randomized to Mircera IV every 2 weeks or epoetin alfa or beta IV administered 3 times weekly for 24 weeks. Hb response rate was achieved in 93.3% of patients treated with Mircera and 91.3% of patients treated with epoetin (*Klinger et al 2007*). Peak Hb levels were 12.28 g/dL for Mircera and 12.19 g/dL for epoetin.
- A Cochrane systematic review and meta-analysis evaluated the effect of treatment with continuous erythropoiesis receptor activator (Mircera) on health outcomes from 27 RCTs in 5410 adults with anemia and CKD, vs a different ESA (darbepoetin alfa or epoetin alfa or beta) or placebo (*Saglimbene et al 2017*).
  - The analysis demonstrated that overall, there was low certainty evidence that Mircera had little or no effects on patient-centered outcomes, including little or no effects on mortality (RR 1.07, 95% CI 0.73 to 1.57; RR 1.11, 95% CI 0.75 to 1.65), major adverse cardiovascular events (RR 5.09, 95% CI 0.25 to 105.23; RR 5.56, 95% CI 0.99 to 31.30), need for blood transfusion (RR 1.02, 95% CI 0.72 to 1.46; RR 0.94, 95% CI 0.55 to 1.61), or additional iron therapy (RR 1.03, 95% CI 0.91 to 1.15; RR 0.99, 95% CI 0.95 to 1.03) vs epoetin alfa/beta or darbepoetin alfa respectively.
  - There was insufficient evidence to compare the effect of Mircera to placebo on clinical outcomes.
  - No studies reported comparative treatment effects of different ESAs on HRQoL.
- A systematic review and meta-analysis of 30 randomized controlled trials in adults with CKD did not find statistically significant differences for efficacy and safety between ESA biosimilars and their originators. When comparing epoetin alfa and darbepoetin alfa, darbepoetin alfa had more favorable results for blood transfusions (RR 2.18, 95% CI 1.31 to 3.62) (*Amato et al 2018*).

Anemia associated with chemotherapy

- In patients with anemia due to chemotherapy, ESAs should be avoided when the anticipated outcome of chemotherapy is cure. The use of ESAs for anemia from myelosuppressive chemotherapy should be at the lowest dose to avoid RBC transfusions and should be discontinued upon the completion of chemotherapy.
- The Agency for Healthcare Research and Quality (AHRQ) performed an updated meta-analysis of 59 randomized controlled studies, 5 of which directly compared epoetin alfa to darbepoetin alfa in patients diagnosed with malignant disease that were anemic or at risk for anemia from chemotherapy and/or radiotherapy or the underlying malignant disease. Of the endpoints evaluated, AHRQ found that the evidence did not show any clinically significant differences between epoetin alfa and darbepoetin alfa with regard to transfusion risk (pooled relative risk [RR], 1.14; 95% CI, 0.82 to 1.59; I^2=43%; 5 trials; N = 2005), on-study mortality (pooled HR, 0.9; 95% CI, 0.67 to 1.2; I^2 = 72%; 2 trials; N = 1567) and thromboembolic events (pooled RR, 0.86; 95% CI, 0.61 to 1.21; I^2 = 0%; 3 trials; N = 1873). ESA therapy was associated with higher thromboembolic event rates (pooled RR, 1.51; 95% CI, 1.3 to 1.74; I^2 = 0%; 37 trials; N = 12,570) and rates of on-study mortality (pooled HR, 1.17; 95% CI, 1.04 to 1.31; I^2 = 0%; 37 trials; N = 11,266) compared to controls. Of the other endpoints evaluated, it was determined that the evidence was not sufficient for conclusions on effects of either epoetin alfa or darbepoetin alfa compared to control on HRQoL, tumor response and progression, overall survival or adverse outcomes (*Grant et al 2013*).
- In another systematic review, ESAs were associated with a hematological response (defined as ≥2 g/dL increase in Hb or ≥6% increase in hematocrit) compared to control (risk ratio, 3.39; 95% CI, 3.1 to 3.71; 31 trials; N = 6413). However, there was significant heterogeneity between trials (I^2 = 53%). It was noted that all trials indicated a beneficial effect of ESAs on hematological response (*Tonia et al 2012*). Other meta-analyses have reported similar findings (*Bohlius et al 2009*).
- In a patient-level meta-analysis, the effectiveness of darbepoetin in improving Hb levels and blood transfusions was evaluated in patients with chemotherapy-induced anemia with an initial Hb of ≤10 g/dL (*Pirker et al 2016*). Patient level data were obtained from 4, Phase 3, randomized, double-blind, placebo-controlled trials of darbepoetin of 12 to 18 weeks in duration; for this analysis, data were extracted for patients with baseline Hb ≤10 g/dL (n = 261 for darbepoetin; n = 273 for placebo). This represented only 33% of the enrolled population. A second analysis evaluated darbepoetin only and identified 15 studies (n = 3768) without front loading and 6 studies with front loading (n = 901). For the endpoint of Hb increase of ≥1 g/dL or ≥2 g/dL vs placebo, darbepoetin improved Hb levels (HR 2.07, 95% CI, 1.62 to 2.63) and (HR 2.91, 95% CI, 2.09 to 4.06), respectively. Mean time to ≥1 g/dL increase in Hb was 43 days (95% CI, 37 to 50 days) for darbepoetin and not evaluable for placebo. Median time to a ≥2 g/dL increase was 78 days (95% CI, 71–not evaluable days) for darbepoetin and not evaluable for placebo. Transfusions were more commonly required between the start of week 5 and end of week 12 in patients who received placebo than in patients who received darbepoetin. Note that only Amgen sponsored studies were included in this analysis, and Amgen supported the meta-analysis.
- In an open-label, multicenter, randomized noninferiority trial, the impact on epoetin 40,000 units weekly on tumor outcomes was compared with the best supportive care for the treatment of anemia in 2098 patients receiving chemotherapy for metastatic breast cancer (*Leyland-Jones et al 2016*). The median progression-free survival (PFS) (based on investigator-determined disease progression) was 7.4 months in both groups (HR 1.089, 95% CI, 0.988 to 1.200) with the upper bound exceeding the prespecified noninferiority margin of 1.15. There was a reduction in the number of RBC transfusions in the epoetin-treated patients vs best supportive care (5.8 vs 11.4%; p < 0.001), while the rate of thrombotic vascular events was higher (2.8 vs 1.4%, respectively; p = 0.038). Overall, the noninferiority of treatment with epoetin was not established, and RBC transfusion was shown to be the best approach to manage anemia in patients with metastatic breast cancer receiving chemotherapy.
- Extended dosing intervals have been investigated. These extended dosing intervals of epoetin such as once every 3 weeks are not FDA-approved (*Glaspy et al 2009*).

Anemia associated with zidovudine in patients with HIV

- Early trials with epoetin in HIV were performed when zidovudine was one of only a few antiretrovirals available for treatment of HIV. Since the late 1980's and 1990's, numerous antiretroviral treatment options have become available and resulted in limited use of zidovudine. A meta-analysis of 4, small, double-blind, randomized trials evaluated the efficacy and safety of epoetin compared to placebo in improving hematocrit values in patients with HIV or Acquired Immunodeficiency Syndrome (AIDS) (*Henry et al 1992*). In the 12-week trials, epoetin significantly increased hematocrit

from baseline compared to placebo in patients with an endogenous erythropoietin level of ≤500 IU/L (mean change, 4.6 vs 0.5, respectively; p = 0.0002; mean difference, 3.9; 95% CI, 1.8 to 6).

- A meta-analysis of 6 randomized, clinical trials with 537 subjects evaluated the risk of death associated with epoetin or placebo in patients with HIV or AIDS and anemia (*Martí-Carvajal et al 2011*). None of the studies included evaluated death as a primary outcome. The risk of death was not statistically significant for epoetin versus placebo or when comparing epoetin once weekly vs 3 times weekly. Studies had significant attrition bias.

Reduced need for transfusions associated with surgery

- Clinical trials have evaluated the use of epoetin in reducing the need for blood transfusions in adults undergoing elective surgeries (*de Andrade et al 1996, Faris et al 1996, Goldberg et al 1996, Zhao et al 2016*). Epoetin is associated with an increased risk of deep venous thrombosis; therefore, appropriate preventative measures should be utilized.
- In a double-blind, multicenter, placebo-controlled trial, the efficacy and safety of epoetin 300 units/kg and 100 units/kg were compared to placebo in 316 adult patients scheduled for elective orthopedic surgery. The primary outcome was the rate of transfusion which was significantly lower in patients receiving epoetin 300 units/kg with a pretreatment Hb of >10 to ≤13 g/dL (epoetin 300 units/kg,16%; epoetin 100 units/kg, 23%; placebo, 45%; p = 0.024) (*de Andrade et al 1996*).
- Epoetin has been shown to reduce the need for blood transfusions in 200 patients undergoing elective orthopedic surgeries compared to placebo (*Faris et al 1996*). Epoetin 100 units/kg/day (17%) and epoetin 300 units/kg/day (25%) led to a reduction in the percentage of patients who required a blood transfusion following a major elective orthopedic surgery compared to control (54%; p ≤ 0.001 for both epoetin groups vs placebo). There was no significant difference between the 2 epoetin groups (p value not reported). The mean number of units transfused for each patient was significantly lower in the epoetin groups compared to the placebo group (epoetin 100 units/kg/day, 0.37±0.96; epoetin 300 units/kg/day, 0.58±1.15; placebo, 1.42±1.67; p < 0.01 for both epoetin groups compared to placebo). There was no significant difference between the epoetin groups (p > 0.05).
- A meta-analysis evaluated 7 studies (N = 2439) to evaluate efficacy and safety of treatment with erythropoietin compared with controls (placebo or no intervention) in patients undergoing total hip or knee arthroplasty (*Voorn et al 2016*). Erythropoietin was shown to reduce exposure to RBC transfusion in both hip (RR 0.45, 95% CI, 0.33 to 0.61) and knee (RR 0.38, 95% CI 0.27 to 0.53) arthroplasty, without differences between indications (p = 0.44), and the mean number of transfused RBC units was decreased in erythropoietin-treated patients (mean difference -0.57, 95% CI -0.86 to -0.29) for both indications. There were no differences detected in thromboembolic and vascular adverse events (RR 1.14, 95% CI 0.71 to 1.84), nor other adverse events (RR 1.01, 95% CI 0.94 to 1.01) between erythropoietin compared with controls.
- A systematic review and meta-analysis evaluated 15 RCTs (N = 2155) to evaluate the hematopoiesis-promoting effect and potential complications, preoperative use of erythropoietin in patients scheduled for total hip or knee arthroplasty (*Zhao et al 2016*). Preoperative use of erythropoietin was associated with lower exposure to allogeneic blood transfusion (OR = 0.41) and higher hemoglobin concentration after surgery (standardized mean difference 0.86; p < 0.001). Complications were not generally reported, but there was no significant difference between the group with and without erythropoietin based on given data.

CLINICAL GUIDELINES

CKD

- The Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dL in adults with CKD. In all adult patients, ESAs should not be used to increase Hb concentrations above 13 g/dL (*KDIGO 2012*). Current practice guidelines for anemia of CKD do not specify a preferred agent. The guidelines recommend that 'copy' versions of ESAs should only be those which have been designated true biosimilars (*KDIGO 2012*).
- Based on the recommendations from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NHF – KDOQI) Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in CKD, the Hb level at which ESA therapy should be initiated as well as the Hb target during therapy should be based on the individual patient, potential benefits (including improvement in QoL and avoidance of transfusion) and potential harms of therapy (including the risk of life-threatening adverse events). Generally speaking, the guidelines recommend that patients with CKD, both dialysis and nondialysis, receiving ESA therapy have a Hb target range of 11 to 12 g/dL, and the Hb levels should not exceed 13 g/dL. This recommendation is based on clinical studies demonstrating that patients with a Hb ≥13 g/dL do not

have improvements in survival, hospitalization or left ventricular hypertrophy and may in fact be more prone to excessive adverse cardiovascular events compared to individuals with lower Hb targets (*KDOQI 2006, KDOQI 2007*).
  - In June 2011, the FDA released more conservative recommendations for using the ESAs in patients with anemia of CKD resulting from data showing that using ESAs to target a Hb level of >11 g/dL increased the risk of cardiovascular events, without providing any additional benefit to patients (*FDA Drug Safety Communication 2011*). For patients with anemia of CKD who are not on dialysis, ESA treatment can be considered when the Hb level is <10 g/dL, and the dose should be reduced or interrupted when Hb exceeds 10 g/dL. For patients with anemia of CKD currently on dialysis, ESA treatment should be initiated when the Hb level is <10 g/dL and the dose should be reduced or interrupted when Hb approaches or exceeds 11 g/dL.
  - The KDOQI US Commentary on the 2012 KDIGO guidelines state KDOQI continues to endorse the FDA-recommended upper cutoff of 11 g/dL (*Kliger et al 2013*).
- The European Renal Best Practice guidelines state Hb target range in patients with CKD should be 11 to 12 g/dL, ESAs should not be used to maintain Hb above 11.5 g/dL, and Hb should not exceed 13 g/dL (*Locatelli et al 2009, Locatelli et al 2010, Locatelli et al 2013*). Continuous erythropoiesis receptor activator (Mircera), a modified recombinant human erythropoietin, has a considerably longer half-life than other ESAs and should be dosed once every 2 weeks for anemic correction and once every 4 weeks for maintenance of Hb levels. The safety and tolerability of continuous erythropoiesis receptor activator are similar to that of other ESAs. Biosimilars of epoetin alfa can only be administered intravenously and should not be used in exchange of the original ESA or other ESAs without physician's approval. A lower Hb target range of 10 to 12 g/dL is reasonable in nondialysis patients with type 2 diabetes. In initiating and maintaining ESA therapy, the potential benefits of reducing blood transfusions and anemia-related symptoms should be balanced against the risks of harm in individual patients (eg, stroke, vascular access loss, or hypertension). ESAs should be used with great caution, if at all, in CKD patients with active malignancy, in particular when cure is the anticipated outcome, or with a history of stroke or malignancy. The lowest possible ESA dose should be used to reach the Hb target.

Chemotherapy Associated Anemia

- Based on the recommendations from the clinical guidelines, ESAs should be considered equivalent with respect to effectiveness and safety for the management of chemotherapy-induced anemia in patients with cancer (*Rizzo et al 2010*).

Perioperative Use of ESA

- Literature supports the use of ESAs with or without iron, as ESAs are effective in reducing the number of patients requiring allogeneic blood transfusions and reducing the volume of allogenic blood transfused (*American Society of Anesthesiologists Task Force 2015*) (Category A1-B evidence – supported by a sufficient number of randomized clinical trials to conduct a meta-analysis and supported by membership opinion).
  - Insufficient evidence exists to evaluate the efficacy of ESA with iron compared to ESA without iron.
  - ESAs with or without iron may be given, when possible, to reduce the need for allogeneic blood transfusions in selected patient populations such as renal insufficiency, anemia of chronic disease, or cases of refusal of transfusion.

SAFETY SUMMARY

- Contraindications:
  - Epoetin alfa from multiple-dose vials contains benzyl alcohol and is contraindicated for use in neonates, infants, pregnant women, and lactating women.
    - Benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients.
    - When therapy is needed in neonates and infants, or pregnant or nursing mothers, use single-dose vials.
  - ESAs should not be used in patients with uncontrolled hypertension.
  - ESAs are contraindicated if pure red blood cell aplasia (PRCA) begins after treatment with erythropoietin agents.
- Boxed Warnings:
  - ESAs increase the risk of death, myocardial infarction (MI), stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence.
  - In controlled trials, patients with CKD experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to a target Hb level of > 11 g/dL. No trial has identified a Hb target level, ESA dose, or dosing strategy that does not increase these risks. Use the lowest dose of ESA sufficient to reduce the need for RBC transfusions.

- In patients with cancer, ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in patients with breast, non-small cell lung, head and neck, lymphoid and cervical cancers. The warnings emphasize to only administer darbepoetin, epoetin, or epoetin alfa-epbx for the treatment of anemia due to concomitant myelosuppressive chemotherapy and to discontinue ESAs following completion of a chemotherapy course. ESAs should not be initiated in cancer patients receiving myelosuppressive therapy when the anticipated outcome is cure.
- Mircera is not indicated and is not recommended for the treatment of anemia due to cancer chemotherapy. A dose-ranging study of Mircera was terminated early because of more deaths among patients receiving Mircera than another ESA.
- Perisurgery: Deep venous thrombosis prophylaxis is recommended when epoetin alfa is used preoperatively.

- Key Warnings/Precautions:
  - ESAs increase the risk of seizures in patients with CKD.
  - Epoetin alfa contains albumin, a derivative of human blood. There is an extremely remote risk for transmission of viral diseases.
  - Severe cutaneous reactions, including erythema multiforme and Stevens-Johnson Syndrome/toxic epidermal necrolysis, have been reported in patients treated with ESAs.
  - There is a risk of serious adverse reactions due to benzyl alcohol preservative in multiple-dose vials of epoetin alfa. Do not mix epoetin alfa with bacteriostatic saline (which also contains benzyl alcohol) when administering to neonates, infants, pregnant women, and lactating women.
    - Serious and fatal reactions including “gasping syndrome” may occur in neonates and infants treated with benzyl alcohol-preserved drugs. The “gasping syndrome” is characterized by central nervous system depression, metabolic acidosis, and gasping respirations.
    - There is a potential for similar risks to fetuses and infants exposed to benzyl alcohol in utero or in breast-fed milk, respectively.
    - The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known
  - There is a risk of PRCA with darbepoetin alfa, epoetin alfa, epoetin alfa-epbx, and methoxy polyethylene glycol-epoetin beta therapy.
  - ESAs may decrease progression-free survival and overall survival in patients with breast cancer, lymphoid malignancy, cervical cancer, advanced head and neck cancer, non-small cell lung cancer or other malignancies.
- Risk Evaluation and Mitigation Strategy (REMS):
  - On April 13, 2017, the FDA removed the REMS from Aranesp, Epogen, and Procrit (*FDA REMS program 2019, Information for Epogen/Procrit 2017*). The decision was based on a survey showing that prescribers were already educated on the potential contribution of these products to the decreased survival or increased risk of tumor progression or recurrence when used for anemia due to myelosuppressive chemotherapy. Moreover, most data showed that ESAs were prescribed for FDA-approved indications. Due to removal of the REMS, health care providers and hospitals are no longer required to enroll and become certified to prescribe and dispense these agents.
- Adverse events
  - The most commonly reported adverse events with ESAs include hypertension, arthralgia, muscle spasm, and fever.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aranesp (darbepoetin alfa)	Single-dose vials, single-dose prefilled syringe	IV or SC injection	Anemia associated with CKD for patients on dialysis when Hb < 10 g/dL: Initial, once weekly or once every 2 weeks; maintenance, dose should be individualized to maintain Hb levels that do not exceed 11 g/dL Anemia associated with CKD for patients not on dialysis when Hb is < 10 g/dL, and the rate of decline indicates a blood transfusion is likely	• Safety and efficacy of Aranesp in adults and pediatric patients were similar for the initial treatment of anemia in patients with CKD or in transition from another

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			and reducing RBC transfusion-related risks is a goal: Initial, once every 4 weeks; maintenance, dose should be individualized to maintain Hb levels that do not exceed 10 g/dL. Pediatrics with CKD: Initiate when Hb is < 10 g/dL. Anemia associated with concomitant chemotherapy in patients with non-myeloid malignancies when Hb < 10 g/dL and 2 or more additional months of chemotherapy are planned: Initial, once weekly or once every 3 weeks until completion of a chemotherapy course; maintenance, dose should be individualized to maintain desired response.	erythropoietin.
Epogen, Procrit, Retacrit (epoetin alfa; epoetin alfa-epbx)	Multiple-dose vials (preserved solution)*, single-dose vials (preservative-free solution)	IV or SC injection	Anemia associated with CKD, including patients on dialysis and patients not on dialysis: Initial, 3 times weekly; maintenance, dose should be individualized to maintain Hb levels that do not exceed 11 g/dL (dialysis) or 10 g/dL (non-dialysis). For pediatric patients, 3 times weekly (dialysis). Anemia associated with concomitant chemotherapy in patients with non-myeloid malignancies when Hb < 10 g/dL and 2 or more additional months of chemotherapy are planned: Initial, 3 times weekly or once weekly until completion of a chemotherapy course; maintenance, dose should be individualized to maintain the lowest Hb level sufficient to avoid red blood cell transfusion. Pediatric patients (5 to 18 years of age): weekly until completion of chemotherapy course. Anemia associated with therapy of zidovudine in HIV-infected patients with endogenous serum erythropoietin levels < 500 mUnits/mL: Initial, 3 times weekly for 8 weeks; maintenance, dose should be individualized to maintain desired response. Withhold epoetin if Hb >12 g/dL. Treatment of anemic patients (Hb > 10 to < 13 g/dL) at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions: daily dose for 10 days	• Benzyl alcohol, found in multiple-dose preserved formulations, has been reported to be associated with an increased incidence of neurological and other complications, which are sometimes fatal, in premature infants. Benzyl alcohol has also been associated with serious adverse events and death, particularly in pediatric patients. • Single-dose preservative-free vials should be used in neonates and infants, as well as pregnant and nursing women.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			before surgery, on the day of surgery and for 4 days after surgery; alternative dosing schedule is once weekly, at 21, 14 and 7 days before surgery, with a fourth dose on the day of surgery.	
Mircera (methoxy poly-ethylene glycol-epoetin beta)	Prefilled syringes	IV or SC injection	Anemia associated with CKD, including adult patients on dialysis and patients not on dialysis: Initial, once every 2 weeks; dose should be individualized to maintain Hb levels that do not exceed 11 g/dL (dialysis) or 10 g/dL (non-dialysis). Once the Hb has been stabilized, may be administered once monthly. Treatment of anemia associated with CKD in pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their Hb level was stabilized with an ESA: once every 4 weeks at a dose based on the total weekly ESA dose at the time of conversion	• Should be injected in the abdomen, arm or thigh with SC administration. • Pregnancy Category C†

*Retacrit is only available as single-dose vials.
†Pregnancy Category C = risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

See the current prescribing information for full details.

- The iron status in all patients should be evaluated in all patients before and during treatment, and iron repletion maintained. Other causes of anemia should be corrected or excluded before initiating ESA.
- IV administration of ESAs is recommended for patients receiving hemodialysis.
- For all ESAs, the dosing should be individualized and the lowest dose sufficient to reduce the need for RBC transfusions should be used.

CONCLUSION

- The FDA-approved erythropoiesis-stimulating agents (ESAs) in the United States are Aranesp (darbepoetin alfa), Epogen (epoetin alfa), Procrit (epoetin alfa), Retacrit (epoetin alfa-epbx), and Mircera (methoxy polyethylene-glycol epoetin beta). Retacrit (epoetin alfa-epbx) was approved as a biosimilar to Epogen/Procrit (epoetin alfa) in May 2018 (*FDA News Release 2018*). All agents are indicated for the treatment of anemia associated with CKD.
  - Aranesp, Epogen, Procrit, and Retacrit are also indicated for the treatment of anemia due to the effect of concomitantly administered chemotherapy in patients with non-myeloid malignancies.
  - Epogen, Procrit, and Retacrit are also indicated for treatment of anemia related to therapy with zidovudine in HIV-infected patients as well as the treatment of anemic patients who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery.
- Clinical trials and meta-analyses comparing the efficacy of epoetin alfa and darbepoetin alfa for the treatment of anemia associated with CKD as well as anemia due to concomitant chemotherapy have demonstrated no differences between the agents (*Bohlius et al 2009, Collister et al 2016, Grant et al 2013, Nissenson et al 2002, Palmer et al 2014a, Palmer et al 2014b, Vanrenterghem et al 2002, Tonia et al 2012, Wilhelm-Leen et al 2015*).

- A systematic review and meta-analysis did not find statistically significant differences for efficacy and safety between ESA biosimilars and their originators. When comparing epoetin alfa and darbepoetin alfa, darbepoetin alfa had more favorable results for blood transfusions (*Amato et al 2018*).

- Numerous RCTs provide supportive evidence demonstrating the effectiveness of Mircera for the correction and maintenance of Hb in patients with anemia of CKD. Throughout the trials, treatment with Mircera corrected and maintained Hb concentrations within the targeted Hb range and demonstrated non-inferiority compared to other ESAs (*Al-Ali et al 2015, Carrera et al 2010, Canaud et al 2008, Levin et al 2007, Spinowitz et al 2008b, Sulowicz et al 2007, Roger et al 2011*). A meta-analysis demonstrated a low certainty of evidence that Mircera had little or no effects on patient-centered outcomes, including little or no effects on mortality, major adverse cardiovascular events, or need for blood transfusion vs epoetin alfa/beta or darbepoetin alfa (*Saglimbene et al 2017*).
- The ESAs are commonly used for the treatment of anemia associated with CKD to reduce the need for transfusions. The KDIGO guidelines suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dL in adults with CKD. In adult patients, ESAs should not be used to increase Hb concentrations above 13 g/dL (*KDIGO 2012*). Current practice guidelines for anemia of CKD do not specify a preferred agent. The KDOQI guidelines state that each of the agents is effective at achieving and maintaining target Hb levels, and endorse the FDA-recommended upper cutoff of 11 g/dL (*KDIGO 2012, KDOQI 2006, KDOQI 2007, Kliger et al 2013*).
  - Based on the recommendations from the clinical guidelines, ESAs should be considered equivalent with respect to effectiveness and safety for the management of chemotherapy-induced anemia in patients with cancer (*Rizzo et al 2010*).
- All ESAs carry a boxed warning of increased mortality, serious cardiovascular and thromboembolic events, stroke and increased risk of tumor progression.
  - Multiple-dose vials of Epogen (epoetin alfa) and Procrit (epoetin alfa) contain benzoyl alcohol.
- Aranesp (darbepoetin alfa) is administered weekly or every 2 weeks, Epogen (epoetin alfa), Procrit (epoetin alfa), and Retacrit (epoetin alfa-epbx) are administered 1 to 3 times weekly and Mircera (methoxy polyethylene-glycol epoetin beta) is administered every 2 to 4 weeks.

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