VENTURA COUNTY HEALTH CARE PLAN

Prior Authorization DRUG Guidelines

EPOGEN®; PROCRIT® (Epoetin alfa)

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Epogen is a Colony Stimulating Factor. It induces erythropoiesis by stimulating the division and differentiation of committed erythroid progenitor cells; induces the release of reticulocytes from the bone marrow into the bloodstream, where they mature to erythrocytes. There is a dose response relationship with this effect. This results in an increase in reticulocyte counts followed by a rise in hematocrit and hemoglobin levels. Erythropoietin, an endogenous glycoprotein produced by the kidneys, serves the physiologic function of stimulating erythropoiesis.[1-2] Epoetin alfa, a 165-amino-acid glycoprotein manufactured by recombinant DNA technology, has the same biological effects as endogenous erythropoietin. The Food and Drug Administration (FDA) has approved epoetin alfa for the treatment of anemia in the following patients: 1) those with chronic kidney disease (CKD), including patients who require dialysis and those who do not require dialysis to decrease the need for red blood cell (RBC) transfusions; 2) those with human immunodeficiency virus (HIV) infection who are receiving zidovudine; 3) treatment of anemia in cancer patients on chemotherapy; and 4) treatment of patients who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery to reduce the need for allogeneic RBC transfusions.[1-2] Epoetin alfa has not been shown to improve quality of life, fatigue, or patient well-being. It is not indicated for use in: 1) patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless they are also receiving concomitant myelosuppressive chemotherapy; 2) in patients with cancer given myelosuppressive chemotherapy when the anticipated outcome is cure; 3) in those scheduled for surgery who are willing to donate autologous blood; 4) in those undergoing cardiac or vascular surgery; and 5) as a substitute for RBC transfusions in patients who require immediate correction of anemia.

Pre-Authorization Criteria: Treatment of anemia due to concurrent myelosuppressive chemotherapy in patients with nonmyeloid malignancies who are receiving palliative chemotherapy for a planned minimum of 2 additional months; treatment of anemia due to chronic kidney disease (including patients on dialysis) to decrease the need for RBC transfusion; treatment of anemia associated with HIV therapy when endogenous erythropoietin levels are ≤500 mUnits/mL; reduction of allogeneic RBC transfusions for elective, noncardiac, nonvascular surgery when perioperative hemoglobin is >10 and ≤13 g/dL and there is a high risk for blood loss

Exclusions:

Cancer patients receiving hormonal therapy, therapeutic biologic products, or radiation therapy unless also receiving concurrent myelosuppressive chemotherapy

Cancer patients receiving myelosuppressive chemotherapy when the expected outcome is curative

Surgery patients who are willing to donate autologous blood

Surgery patients undergoing cardiac or vascular surgery

As a substitute for RBC transfusion in patients requiring immediate correction of anemia

Note: VCHCP requires that unlabeled or investigational use of Epogen be prescribed by a nephrologist, hematologist, or an oncologist.

DOSING:

In CKD, controlled trials demonstrate that patients experienced greater risks for death, serious adverse CV reactions, and stroke when given ESAs to target a Hb > 11.0 g/dL. No trial has identified a Hb target level, ESA dose, or dosing strategy that does not increase such risks. Use the lowest epoetin alfa dose sufficient to reduce the need for RBC transfusions. Physicians and patients should weigh the possible benefits of decreasing transfusions against the increased risk of death and or other serious CV adverse events. For patients with CKD on dialysis, initiate epoetin alfa therapy when the Hb is < 10.0 g/dL. If the Hb level approaches or exceeds 11.0 g/dL, reduce or interrupt the epoetin alfa dose. The recommended epoetin alfa starting dose for adults is 50 to 100 units/kg three times weekly intravenously (IV) or subcutaneously (SC). For pediatric patients, a starting dose of 50 units/kg three times weekly IV or SC is recommended. For patients on hemodialysis, the IV route is recommended. For CKD patients not on dialysis, initiate epoetin alfa therapy only when Hb is < 10.0 g/dL and the following considerations apply: 1) the rate of Hb decline indicates the likelihood of requiring a RBC transfusion and, 2) reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal. If Hb exceeds 10.0 g/dL, reduce or interrupt the epoetin alfa dose and use the lowest dose of epoetin alfa needed to reduce the need for RBC transfusions. The recommended starting dose for adults is 50 to 100 units/kg three times weekly IV or SC. For patients on cancer chemotherapy, only prescribers enrolled in the ESA APPRISE Oncology Program may prescribe and/or dispense epoetin alfa. Initiate epoetin alfa in patients receiving cancer chemotherapy only if Hb is < 10.0 g/dL, and if there is a minimum of 2 additional months of planned chemotherapy. Use the lowest epoetin alfa dose necessary to avoid RBC transfusions. The recommended starting dose and schedules for epoetin alfa in adults are 150 units/kg SC three times weekly until completion of a chemotherapy course or 40,000 units SC every week until completion of a chemotherapy course. For pediatric patients (those aged 5 to 18 years), the recommended dose is 600 units/kg IV

weekly until completion of a chemotherapy course. For zidovudine-treated HIV patients, the recommended starting dose in adults is 100 units/kg IV or SC three times weekly. If Hb does not increase after 8 weeks of therapy, increase the epoetin alfa dose by around 50 to 100 units/kg at 4- to 8-week intervals until Hb reaches a level to avoid RBC transfusions or 300 units/kg. Withhold if Hb exceeds 12.0 g/dL and resume therapy at a dose 25% below the previous dose when Hb declines to less than 11.0 g/dL. For surgery patients, the recommended epoetin alfa dose is 300 units/kg per day SC for 14 days total administered daily for 10 days before surgery, on the day of surgery, and for 4 days after surgery. Alternatively, surgery patients may receive 600 units SC in 4 doses given 21, 14, and 7 days before surgery and on the day of surgery.[1-2]

Contraindications and Warnings

Epoetin alfa is contraindicated in patients with uncontrolled hypertension, pure RBC hyperplasia that commences after epoetin alfa treatment or with other erythropoietin protein drugs, and serious allergic reactions to epoetin alfa. Do not use multi-dose vials in neonates, infants, pregnant women and nursing mothers. The epoetin alfa labeling also has a warning regarding increased mortality, serious CV events, thromboembolic events and stroke.[1-2] Patients with CKD had an increased risk of death, serious CV events and stroke when ESAs were given to a target Hb level ≥ 13.0 g/dL in clinical trials compared to lower targets (9.0 to 11.3 g/dL).[1-2] Using ESAs to target a Hb level > 11.0 g/dL increases the risk of serious adverse CV reactions and has not been shown to provide added benefit. Use caution in those with coexistent CV disease and stroke. Those with CKD and an insufficient Hb response to ESA therapy may have a greater risk for CV reactions and mortality compared with other patients. A rate of Hb rise > 1.0 g/dL over 2 weeks may contribute to the risks. In controlled clinical trials involving cancer patients, epoetin alfa and other ESAs increased the risks for death and serious adverse CV reactions. These adverse reactions included myocardial infarction (MI) and stroke. In controlled clinical trials, ESAs increased the risk of death in those undergoing coronary artery bypass graft (CABG) surgery and the risk of DVT in those undergoing orthopedic procedures.

The Normal Hematocrit Study (NHS) was a prospective, randomized, open-label study of 1,265 patients with CKD on dialysis with documented evidence of congestive heart failure (CHF) or ischemic heart disease. It was designed to test the hypothesis that a higher target hematocrit (Hct) would lead to improved outcomes vs. those with a lower Hct target. In this trial, patients were randomized to epoetin alfa treatment targeted to a maintenance Hb of either 14.0 ± 1.0 g/dL or 10 ± 1.0 g/dL.[1,4] The trial was terminated early with adverse safety findings of higher mortality in the higher Hct target group. Higher mortality (35% to 29%) was noted for those randomized to a target Hb of 14.0 g/dL than for those randomized to a target Hb of 10.0 g/dL. For all-cause mortality, the hazard ratio (HR) was 1.27 (95% confidence interval [CI]: 1.04, 1.54; P = 0.018). The incidence of nonfatal MI, vascular access thrombosis, and other thrombotic events was also higher in the group randomized to a target Hb of 14.0 g/dL.

In a clinical trial in 1,432 CKD patients with anemia who were not undergoing dialysis, patients were prospectively randomized in an open-label manner to determine if treatment with epoetin alfa to a target Hb of 13.5 g/dL would improve mortality and CV outcomes compared to treatment to a target Hb of 11.3 g/dL.[1-3] Final results showed that 125 of 715 patients (18%) randomized to the higher target Hb group reached the composite endpoint of death, MI, stroke and hospitalization for CHF, compared with 97 of 717 patients (14%) in the lower target Hb group (P = 0.03).[1-3]

In a randomized, double-blind, placebo-controlled trial involving 4,038 patients, there was an increased risk of stroke when darbepoetin alfa was given to patients with anemia, type 2 diabetes, and CKD who were not receiving dialysis with an estimated glomerular filtration rate of 20 to 60 mL/min. Patients were randomized to darbepoetin treatment targeted to a Hb > 13.0 g/dL or to placebo. Those in the placebo group could receive darbepoetin if Hb levels were < 9.0 g/dL. There were not differences between groups among the primary endpoints of the composite outcomes of death or a CV event and of death or end stage renal disease (ESRD). However, the risk of stroke was increased nearly two-fold in the darbepoetin-treated group vs. the placebo group (HR 1.92; 95% CI: 1.38, 2.68; P < 0.001).[1,5]

The warning in the epoetin alfa label also states that there has been an increased incidence of thrombotic events, some serious and life-threatening, in patients with cancer treated with ESAs.[1-2] In a randomized trial with epoetin alfa, 939 women with metastatic breast cancer who were receiving chemotherapy were assigned to epoetin alfa or placebo for up to one year on a weekly schedule.[1-2,6] Hb levels were designed to be maintained between 12.0 g/dL and 14.0 g/dL (Hct between 36% and 42%). Increased mortality in the first 4 months after randomization was noted among the patients who received epoetin alfa (8.7%) compared with the patients who received placebo (3.4%), which terminated the trial prematurely. Also, in the first 4 months of the study, the incidence of fatal thrombotic vascular events was higher in the group given epoetin alfa (1.1% vs. 0.2%). Based on Kaplan-Meier estimates, the proportion of patients surviving at 12 months after randomization was lower in the epoetin alfa group compared with the placebo group (70% vs. 76%; P = 0.012).[1-2,6]

An increased incidence of DVT was observed in patients receiving epoetin alfa undergoing surgical orthopedic procedures. In a randomized controlled study (referred to as the SPINE study), 680 adult patients not receiving prophylactic anticoagulation and undergoing spinal surgery had a higher rate of DVT (4.7%) when they received four doses of epoetin alfa (7, 14, and 21 days before surgery and the day of surgery) compared with the patients receiving standard of care (2.1%). Also, twelve patients given epoetin alfa compared with seven patients given standard of care had thrombotic vascular events.[1-2,7] Increased mortality was also noted in a randomized placebo-controlled study of epoetin alfa in adults who were undergoing CABG (seven deaths in 126 patients randomized to epoetin vs. no deaths among 56 patients given placebo).[1-2,8] Four of the seven deaths occurred during the period of study drug administration and all four deaths were associated with thrombotic events.[8] ESAs are not approved for reduction of allogeneic RBC transfusions in patients scheduled for cardiac surgery.

The warning in the epoetin alfa label also states that increased mortality and/or increased risk of tumor progression or recurrence have been reported in cancer patients.[1-2] These findings were noted in studies of patients with advanced head and neck cancer receiving radiation therapy, in patients receiving chemotherapy for metastatic breast cancer or lymphoid malignancy, and in patients with non-small cell lung cancer or various malignancies who were not receiving chemotherapy or radiotherapy.

The warning in the epoetin alfa labels also describes decreased overall survival. In the BEST trial, which was previously described, mortality at 4 months was significantly higher in the epoetin alfa arm (8.7% vs. 3.4%). The most common investigator-attributed cause of death within the first 4 months was disease progression. A total of 28 of 41 deaths in the epoetin alfa

arm and 13 of 16 deaths in the placebo arm were thought to be caused by disease progression.[1-2,6] Between the two groups, investigator-assessed time to tumor progression was not different. Survival at 12 months was lower in the epoetin alfa arm (70% vs. 76%; P = 0.012).

In a Phase III, randomized, double-blind trial 344 anemic patients with lymphoid malignancy receiving chemotherapy were given darbepoetin or placebo. After a median follow-up to 29 months, overall mortality rates were significantly higher among patients randomized to darbepoetin alfa as compared with placebo (HR 1.36).[1-2]

In a Phase III, multicenter, double-blind cancer study involving epoetin alfa vs. placebo, patients with advanced non-small cell lung cancer received only palliative radiotherapy or no active therapy and were given epoetin alfa to achieve and maintain Hb levels between 12.0 and 14.0 g/dL. Following an interim analysis of 70 of 300 patients, a significant difference in survival in favor of the patients in the placebo arms of the trial was observed (median survival 63 days vs. 129 days; P = 0.04).[1-2,9]

A Phase III, double-blind, 16-week, randomized cancer trial of darbepoetin vs. placebo was also performed involving 989 anemic patients with active malignant disease.[1-2,10] Patients were not receiving nor planning to receive chemotherapy or radiation therapy. There was no evidence of a statistically significant reduction in the proportion of patients receiving RBC transfusions. The median survival was shorter in the darbepoetin alfa treatment group (8 months) compared with the placebo group (10.8 months).

The epoetin alfa warnings also discuss decreased progression-free survival and overall survival. In a randomized, controlled cancer trial called PREPARE, patients were given darbepoetin or placebo to prevent anemia in 733 women receiving neo-adjuvant breast cancer treatment. An interim analysis was done after a median follow-up of approximately 3 years and the survival rate was lower (86% vs. 90%) and the relapse-free survival rate was lower (72% vs. 78%) in the darbepoetin-treated arm compared to the control arm.[1-2]

A randomized controlled study enrolled 114 of a planned 460 cervical cancer patients receiving chemotherapy and radiotherapy. Patients were given epoetin alfa to maintain Hb between 12.0 and 14.0 g/dL or were randomized to transfusion support as needed. The trial was terminated early due to an increase in thromboembolic events in the epoetin alfa patients compared with control (19% vs. 9%).[1-2,11] Both local recurrence (21% vs. 20%) and distant recurrence (12% vs. 7%) were more frequent in the epoetin alfa-treated group compared to control (59% vs. 62%).[1-2] Overall survival at 3 years was lower in the epoetin-alfa treated group compared with the control.

In another randomized, controlled study patients with head and neck cancer (n = 351) were randomized to receive epoetin beta or placebo to achieve a target Hb of 14.0 to 15.0 g/dL for women and men, respectively. Locoregional progression-free survival was significantly shorter in patients receiving epoetin beta (a median of 406 days for epoetin beta vs. 745 days for placebo [P = 0.0008]). The overall survival was significantly shorter in patients receiving epoetin beta.[1-2,12]

The epoetin alfa product labeling also warns of decreased locoregional control. In a study involving 522 cancer patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy, patients were given darbepoetin alfa with radiotherapy or

radiotherapy alone. An interim analysis of 484 patients showed that locoregional control at 5 years was significantly shorter for patients receiving darbepoetin (P = 0.02). Also, overall survival was shorter in patients receiving darbepoetin (P = 0.08).[1-2]

A meta-analysis reviewed approximately 50 randomized trials regarding the use of ESAs for cancer-related anemia.[13] Some conclusions were that use of ESAs in patients with cancer increased mortality and worsened overall survival. The benefits of the products (e.g., decreased risk of transfusions) should be balanced with the risks that may occur in patients.

The epoetin alfa product labeling also warns about hypertension in CKD patients. Patients with uncontrolled hypertension should not be treated with epoetin alfa and blood pressure should be adequately controlled before therapy initiation.[1-2] Seizures have also occurred in CKD patients in clinical trials. Cases of pure red cell aplasia (PRCA) and severe anemia, with or without cytopenias, associated with neutralizing antibodies to erythropoietin have been reported in patients treated with epoetin alfa. This has predominantly been noted in patients with CKD receiving ESAs by SC administration. PRCA has also been noted in patients receiving ESAs while undergoing treatment for hepatitis C with interferon products and ribavirin.

PATIENT EDUCATION - You will require frequent blood tests to determine appropriate dosage. Do not take other medications, vitamin or iron supplements, or make significant changes in your diet without consulting prescriber. Report signs or symptoms of edema (eg, swollen extremities, difficulty breathing, rapid weight gain), onset of severe headache, acute back pain, chest pain, muscular tremors, or seizure activity.

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Revision Date	Content Revised (Yes/No)	Contributors	Review/Revision Notes
1/24/17	No	Catherine Sanders, MD; Robert Sterling, MD	Annual review
1/1/18	No	Catherine Sanders, MD; Robert Sterling, MD	Archived – excluded from Formulary effective 1/1/18
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