HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EPOGEN safely and effectively. See full prescribing information for EPOGEN.

Epogen® (epoetin alfa) Injection, for intravenous or subcutaneous use
Initial U.S. Approval: 1989

WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE
See full prescribing information for complete boxed warning.

Chronic Kidney Disease:
- **In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL (5.1).**
- **No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.**
- **Use the lowest Epogen dose sufficient to reduce the need for red blood cell (RBC) transfusions (5.1).**

Cancer:
- **ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers (5.2).**
- **Use the lowest dose to avoid RBC transfusions (2.4).**
- **Use ESAs only for anemia from myelosuppressive chemotherapy (1.3).**
- **ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure (1.5).**
- **Discontinue following the completion of a chemotherapy course (2.4).**

Perisurgery:
- **Due to increased risk of deep venous thrombosis (DVT), DVT prophylaxis is recommended (5.1).**

----------RECENT MAJOR CHANGES----------
- Indications and Usage, Limitations of Use (1.5) 4/2017
- Warnings and Precautions, Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients With Cancer (5.2) 4/2017

----------INDICATIONS AND USAGE----------
Epogen is an erythropoiesis-stimulating agent (ESA) indicated for:
- Treatment of anemia due to
  - Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis (1.1).
  - Zidovudine in HIV-infected patients (1.2).
  - The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy (1.3).
- Reduction of allogeneic RBC transfusions in patients undergoing elective, noncardiac, nonvascular surgery (1.4).

Limitations of Use
Epogen has not been shown to improve quality of life, fatigue, or patient well-being (1.5).
Epogen is not indicated for use:
- In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy (1.5).
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure (1.5).
- In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion (1.5).
- In patients scheduled for surgery who are willing to donate autologous blood (1.5).
- In patients undergoing cardiac or vascular surgery (1.5).
- As a substitute for RBC transfusions in patients who require immediate correction of anemia (1.5).

----------DOSAGE AND ADMINISTRATION----------
- CKD Patients: Initial dose: 50 to 100 Units/kg 3 times weekly (adults) and 50 Units/kg 3 times weekly (children on dialysis). Individualize maintenance dose. Intravenous route recommended for patients on hemodialysis (2.2).
- Zidovudine-treated HIV-infected Patients: 100 Units/kg 3 times weekly (2.3).
- Cancer Patients on Chemotherapy: 40,000 Units weekly or 150 Units/kg 3 times weekly (adults); 600 Units/kg intravenously weekly (children ≥ 5 years) (2.4).
- Surgery Patients: 300 Units/kg per day daily for 15 days or 600 Units/kg weekly (2.5).

----------DOSAGE FORMS AND STRENGTHS----------
- Single-dose vial: 2000, 3000, 4000, and 10,000 Units/1 mL (3)
- Multiple-dose vial containing benzyl alcohol: 20,000 Units/2 mL and 20,000 Units/1 mL (3)

----------CONTRAINDICATIONS----------
- Uncontrolled hypertension (5.3)
- Pure red cell aplasia (PRCA) that begins after treatment with Epogen or other erythropoietin protein drugs (5.6)
- Serious allergic reactions to Epogen (5.7)
- Use of the multiple-dose vials in neonates, infants, pregnant women, and nursing mothers (8.1, 8.3, 8.4)

----------WARNINGS AND PRECAUTIONS----------
- Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism: Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit (5.1 and 14.1). Use caution in patients with coexistent cardiovascular disease and stroke (5.1).
- Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients With Cancer (5.2).
- Hypertension: Control hypertension prior to initiating and during treatment with Epogen (5.3).
- Seizures: Epogen increases the risk for seizures in patients with CKD (5.4). Increase monitoring of these patients for changes in seizure frequency or premonitory symptoms (5.4).
- PRCA: If severe anemia and low reticulocyte count develop during Epogen treatment, withhold Epogen and evaluate for PRCA (5.6).

----------ADVERSE REACTIONS----------
- Patients with CKD: Adverse reactions in ≥ 5% of Epogen-treated patients in clinical studies were hypertension, arthralgia, muscle spasm, pyrexia, dizziness, medical device malfunction, vascular occlusion, and upper respiratory tract infection (6.1).
- Zidovudine-treated HIV-infected Patients: Adverse reactions in ≥ 5% of Epogen-treated patients in clinical studies were pyrexia, cough, rash, and injection site irritation (6.1).
- Cancer Patients on Chemotherapy: Adverse reactions in ≥ 5% of Epogen-treated patients in clinical studies were nausea, vomiting, myalgia, arthralgia, stomatitis, cough, weight decrease, leukopenia, bone pain, rash, hyperglycemia, insomnia, headache, depression, dysphagia, hypokalemia, and thrombosis (6.1).
- Surgery Patients: Adverse reactions in ≥ 5% of Epogen-treated patients in clinical studies were nausea, vomiting, pruritus, headache, injection site pain, chills, deep vein thrombosis, cough, and hypertension (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy, nursing mothers, neonates, and infants: Use single-dose vials only and do not mix with benzyl alcohol. Based on animal data, Epogen may cause fetal harm. Pregnancy Surveillance Program is available (8.1, 8.3, and 8.4).
- Pediatric Use: Safety and effectiveness have not been established in CKD patients undergoing dialysis who are less than 1 month old, pediatric patients with cancer less than 5 years old, pediatric patients with CKD not on dialysis, and pediatric patients with HIV infection (8.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

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Chronic Kidney Disease:

- **In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL *[see Warnings and Precautions (5.1)]*.**
- **No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.**
- **Use the lowest Epogen dose sufficient to reduce the need for red blood cell (RBC) transfusions *[see Warnings and Precautions (5.1)]*.**

Cancer:

- **ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers *[see Warnings and Precautions (5.2)]*.**
- **To decrease these risks, as well as the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid RBC transfusions *[see Dosage and Administration (2.4)]*.**
- **Use ESAs only for anemia from myelosuppressive chemotherapy *[see Indications and Usage (1.3)]*.**
- **ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure *[see Indications and Usage (1.5)]*.**
- **Discontinue following the completion of a chemotherapy course *[see Dosage and Administration (2.4)]*.**

Perisurgery:

- **Due to increased risk of Deep Venous Thrombosis (DVT), DVT prophylaxis is recommended *[see Dosage and Administration (2.5), Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

1.1 Anemia Due to Chronic Kidney Disease

Epogen is indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion.

1.2 Anemia Due to Zidovudine in HIV-infected Patients

Epogen is indicated for the treatment of anemia due to zidovudine administered at ≤ 4200 mg/week in HIV-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL.

1.3 Anemia Due to Chemotherapy in Patients With Cancer

Epogen is indicated for the 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 two additional months of planned chemotherapy.

1.4 Reduction of Allogeneic Red Blood Cell Transfusions in Patients Undergoing Elective, Noncardiac, Nonvascular Surgery

Epogen is indicated to 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. Epogen is not indicated for patients who are willing to donate autologous blood pre-operatively.

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1.5 Limitations of Use

Epogen has not been shown to improve quality of life, fatigue, or patient well-being.

Epogen is 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.
- In patients scheduled for surgery who are willing to donate autologous blood.
- In patients undergoing cardiac or vascular surgery.
- As a substitute for RBC transfusions in patients who require immediate correction of anemia.

2 DOSAGE AND ADMINISTRATION

2.1 Evaluation of Iron Stores and Nutritional Factors

Evaluate the iron status in all patients before and during treatment and maintain iron repletion. Correct or exclude other causes of anemia (e.g., vitamin deficiency, metabolic or chronic inflammatory conditions, bleeding, etc.) before initiating Epogen *[see Warnings and Precautions (5.10)]*.

2.2 Patients with Chronic Kidney Disease

In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL. No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks. Individualize dosing and use the lowest dose of Epogen sufficient to reduce the need for RBC transfusions *[see Warnings and Precautions (5.1)]*. Physicians and patients should weigh the possible benefits of decreasing transfusions against the increased risks of death and other serious cardiovascular adverse events *[see Boxed Warning and Clinical Studies (14)]*.

<u>For all patients with CKD:</u>

When initiating or adjusting therapy, monitor hemoglobin levels at least weekly until stable, then monitor at least monthly. When adjusting therapy consider hemoglobin rate of rise, rate of decline, ESA responsiveness and hemoglobin variability. A single hemoglobin excursion may not require a dosing change.

- Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently. Avoid frequent dose adjustments.
- If the hemoglobin rises rapidly (e.g., more than 1 g/dL in any 2-week period), reduce the dose of Epogen by 25% or more as needed to reduce rapid responses.
- For patients who do not respond adequately, if the hemoglobin has not increased by more than 1 g/dL after 4 weeks of therapy, increase the dose by 25%.
- For patients who do not respond adequately over a 12-week escalation period, increasing the Epogen dose further is unlikely to improve response and may increase risks. Use the lowest dose that will maintain a hemoglobin level sufficient to reduce the need for RBC transfusions. Evaluate other causes of anemia. Discontinue Epogen if responsiveness does not improve.

<u>For patients with CKD on dialysis:</u>

- Initiate Epogen treatment when the hemoglobin level is less than 10 g/dL.

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- If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of Epogen.
- The recommended starting dose for adult patients is 50 to 100 Units/kg 3 times weekly intravenously or subcutaneously. For pediatric patients, a starting dose of 50 Units/kg 3 times weekly intravenously or subcutaneously is recommended. The intravenous route is recommended for patients on hemodialysis.

For patients with CKD not on dialysis:

- Consider initiating Epogen treatment only when the hemoglobin level is less than 10 g/dL and the following considerations apply:
  - The rate of hemoglobin decline indicates the likelihood of requiring a RBC transfusion and,
  - Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal
- If the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of Epogen, and use the lowest dose of Epogen sufficient to reduce the need for RBC transfusions.
- The recommended starting dose for adult patients is 50 to 100 Units/kg 3 times weekly intravenously or subcutaneously.

When treating patients who have chronic kidney disease and cancer, physicians should refer to *Warnings and Precautions (5.1 and 5.2).*

Refer patients who self-administer Epogen to the Instructions for Use *[see Patient Counseling Information (17)]*.

2.3 Zidovudine-treated HIV-infected Patients

Starting Dose

The recommended starting dose in adults is 100 Units/kg as an intravenous or subcutaneous injection 3 times per week.

Dose Adjustment

- If hemoglobin does not increase after 8 weeks of therapy, increase Epogen dose by approximately 50 to 100 Units/kg at 4- to 8-week intervals until hemoglobin reaches a level needed to avoid RBC transfusions or 300 Units/kg.
- Withhold Epogen if hemoglobin exceeds 12 g/dL. Resume therapy at a dose 25% below the previous dose when hemoglobin declines to less than 11 g/dL.

Discontinue Epogen if an increase in hemoglobin is not achieved at a dose of 300 Units/kg for 8 weeks.

2.4 Patients on Cancer Chemotherapy

Initiate Epogen in patients on cancer chemotherapy only if the hemoglobin is less than 10 g/dL, and if there is a minimum of two additional months of planned chemotherapy.

Use the lowest dose of Epogen necessary to avoid RBC transfusions.

Recommended Starting Dose

Adults:

- 150 Units/kg subcutaneously 3 times per week until completion of a chemotherapy course or
- 40,000 Units subcutaneously weekly until completion of a chemotherapy course.

Pediatric Patients (5 to 18 years):

- 600 Units/kg intravenously weekly until completion of a chemotherapy course.

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Dose Reduction

Reduce dose by 25% if:

- Hemoglobin increases greater than 1 g/dL in any 2-week period or
- Hemoglobin reaches a level needed to avoid RBC transfusion.

Withhold dose if hemoglobin exceeds a level needed to avoid RBC transfusion. Reinitiate at a dose 25% below the previous dose when hemoglobin approaches a level where RBC transfusions may be required.

Dose Increase

After the initial 4 weeks of Epogen therapy, if hemoglobin increases by less than 1 g/dL and remains below 10 g/dL, increase dose to:

- 300 Units/kg three times per week in adults or
- 60,000 Units weekly in adults
- 900 Units/kg (maximum 60,000 Units) weekly in children

After 8 weeks of therapy, if there is no response as measured by hemoglobin levels or if RBC transfusions are still required, discontinue Epogen.

2.5 Surgery Patients

The recommended Epogen regimens are:

- 300 Units/kg per day subcutaneously for 15 days total: administered daily for 10 days before surgery, on the day of surgery, and for 4 days after surgery.
- 600 Units/kg subcutaneously in 4 doses administered 21, 14, and 7 days before surgery and on the day of surgery.

Deep venous thrombosis prophylaxis is recommended during Epogen therapy *[see Warnings and Precautions (5.1)]*.

2.6 Preparation and Administration

- Do not shake. Do not use Epogen that has been shaken or frozen.
- Protect vials from light.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.
- Discard unused portions of Epogen in preservative-free vials. Do not re-enter preservative-free vials.
- Store unused portions of Epogen in multiple-dose vials at 36°F to 46°F (2°C to 8°C). Discard 21 days after initial entry.
- Do not dilute. Do not mix with other drug solutions except for admixing as described below:
    - Preservative-free Epogen from single-dose vials may be admixed in a syringe with bacteriostatic 0.9% sodium chloride injection, USP, with benzyl alcohol 0.9% (bacteriostatic saline) in a 1:1 ratio using aseptic technique at the time of administration. Risks are associated with benzyl alcohol in neonates, infants, pregnant women, and nursing mothers *[see Use in Specific Populations (8.1, 8.3, 8.4)]*.

3 DOSAGE FORMS AND STRENGTHS

Single-dose vials: 2000, 3000, 4000, and 10,000 Units Epogen /1 mL

Multiple-dose vials (contains benzyl alcohol): 20,000 Units Epogen /2 mL and 20,000 Units Epogen /1 mL

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4 CONTRAINDICATIONS

Epogen is contraindicated in patients with:

- Uncontrolled hypertension *[see Warnings and Precautions (5.3)]*
- Pure red cell aplasia (PRCA) that begins after treatment with Epogen or other erythropoietin protein drugs *[see Warnings and Precautions (5.6)]*
- Serious allergic reactions to Epogen *[see Warnings and Precautions (5.7)]*

Epogen from multiple-dose vials contains benzyl alcohol and is contraindicated in:

- Neonates, infants, pregnant women, and nursing mothers. Benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients. When therapy with Epogen is needed in neonates and infants, use single-dose vials; do not admix with bacteriostatic saline containing benzyl alcohol *[see Use in Specific Populations (8.1, 8.3, 8.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism

- In controlled clinical trials of patients with CKD comparing higher hemoglobin targets (13 - 14 g/dL) to lower targets (9 - 11.3 g/dL), Epogen and other ESAs increased the risk of death, myocardial infarction, stroke, congestive heart failure, thrombosis of hemodialysis vascular access, and other thromboembolic events in the higher target groups.
- Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit *[see Clinical Studies (14.1)]*. Use caution in patients with coexistent cardiovascular disease and stroke *[see Dosage and Administration (2.2)]*. Patients with CKD and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular reactions and mortality than other patients. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may contribute to these risks.
- In controlled clinical trials of patients with cancer, Epogen and other ESAs increased the risks for death and serious adverse cardiovascular reactions. These adverse reactions included myocardial infarction and stroke.
- In controlled 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.

The design and overall results of the 3 large trials comparing higher and lower hemoglobin targets are shown in Table 1.

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Table 1: Randomized Controlled Trials Showing Adverse Cardiovascular Outcomes in Patients With CKD

	Normal Hematocrit Study (NHS) (N = 1265)	**CHOIR (N = 1432)**	**TREAT (N = 4038)**
Time Period of Trial	1993 to 1996	2003 to 2006	2004 to 2009
Population	CKD patients on hemodialysis with coexisting CHF or CAD, hematocrit 30 ± 3% on epoetin alfa	CKD patients not on dialysis with hemoglobin < 11 g/dL not previously administered epoetin alfa	CKD patients not on dialysis with type II diabetes, hemoglobin ≤ 11 g/dL
Hemoglobin Target; Higher vs. Lower (g/dL)	14.0 vs. 10.0	13.5 vs. 11.3	13.0 vs. ≥ 9.0
Median (Q1, Q3) Achieved Hemoglobin level (g/dL)	12.6 (11.6, 13.3) vs. 10.3 (10.0, 10.7)	13.0 (12.2, 13.4) vs. 11.4 (11.1, 11.6)	12.5 (12.0, 12.8) vs. 10.6 (9.9, 11.3)
Primary Endpoint	All-cause mortality or non-fatal MI	All-cause mortality, MI, hospitalization for CHF, or stroke	All-cause mortality, MI, myocardial ischemia, heart failure, and stroke
Hazard Ratio or Relative Risk (95% CI)	1.28 (1.06 - 1.56)	1.34 (1.03 - 1.74)	1.05 (0.94 - 1.17)
Adverse Outcome for Higher Target Group	All-cause mortality	All-cause mortality	Stroke
Hazard Ratio or Relative Risk (95% CI)	1.27 (1.04 - 1.54)	1.48 (0.97 - 2.27)	1.92 (1.38 - 2.68)

Patients with Chronic Kidney Disease

Normal Hematocrit Study (NHS): A prospective, randomized, open-label study of 1265 patients with chronic kidney disease on dialysis with documented evidence of congestive heart failure or ischemic heart disease was designed to test the hypothesis that a higher target hematocrit (Hct) would result in improved outcomes compared with a lower target Hct. In this study, patients were randomized to epoetin alfa treatment targeted to a maintenance hemoglobin of either 14 ± 1 g/dL or 10 ± 1 g/dL. The trial was terminated early with adverse safety findings of higher mortality in the high hematocrit target group. Higher mortality (35% vs. 29%) was observed for the patients randomized to a target hemoglobin of 14 g/dL than for the patients randomized to a target hemoglobin of 10 g/dL. For all-cause mortality, the HR=1.27; 95% CI (1.04, 1.54); p=0.018. The incidence of nonfatal myocardial infarction, vascular access thrombosis, and other thrombotic events was also higher in the group randomized to a target hemoglobin of 14 g/dL.

CHOIR: A randomized, prospective trial, 1432 patients with anemia due to CKD who were not undergoing dialysis and who had not previously received epoetin alfa therapy were randomized to epoetin alfa treatment targeting a maintenance hemoglobin concentration of either 13.5 g/dL or 11.3 g/dL. The trial was terminated early with adverse safety findings. A major cardiovascular event (death, myocardial infarction, stroke, or hospitalization for congestive heart failure) occurred in 125 of the 715 patients (18%) in the higher hemoglobin group compared to 97 of the 717 patients (14%) in the lower hemoglobin group [hazard ratio (HR) 1.34, 95% CI: 1.03, 1.74; p = 0.03].

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TREAT: A randomized, double-blind, placebo-controlled, prospective trial of 4038 patients with: CKD not on dialysis (eGFR of 20 – 60 mL/min), anemia (hemoglobin levels ≤ 11 g/dL), and type 2 diabetes mellitus, patients were randomized to receive either darbepoetin alfa treatment or a matching placebo. Placebo group patients also received darbepoetin alfa when their hemoglobin levels were below 9 g/dL. The trial objectives were to demonstrate the benefit of darbepoetin alfa treatment of the anemia to a target hemoglobin level of 13 g/dL, when compared to a "placebo" group, by reducing the occurrence of either of two primary endpoints: (1) a composite cardiovascular endpoint of all-cause mortality or a specified cardiovascular event (myocardial ischemia, CHF, MI, and CVA) or (2) a composite renal endpoint of all-cause mortality or progression to end stage renal disease. The overall risks for each of the two primary endpoints (the cardiovascular composite and the renal composite) were not reduced with darbepoetin alfa treatment (see Table 1), but the risk of stroke was increased nearly two-fold in the darbepoetin alfa -treated group versus the placebo group: annualized stroke rate 2.1% vs. 1.1%, respectively, HR 1.92; 95% CI: 1.38, 2.68; $p < 0.001$. The relative risk of stroke was particularly high in patients with a prior stroke: annualized stroke rate 5.2% in the darbepoetin alfa- treated group and 1.9% in the placebo group, HR 3.07; 95% CI: 1.44, 6.54. Also, among darbepoetin alfa -treated subjects with a past history of cancer, there were more deaths due to all causes and more deaths adjudicated as due to cancer, in comparison with the control group.

Patients with Cancer

An increased incidence of thromboembolic reactions, some serious and life-threatening, occurred in patients with cancer treated with ESAs.

In a randomized, placebo-controlled study (Study 2 in Table 2 *[see Warnings and Precautions (5.2)]*) of 939 women with metastatic breast cancer receiving chemotherapy, patients received either weekly epoetin alfa or placebo for up to a year. This study was designed to show that survival was superior when epoetin alfa was administered to prevent anemia (maintain hemoglobin levels between 12 and 14 g/dL or hematocrit between 36% and 42%). This study was terminated prematurely when interim results demonstrated a higher mortality at 4 months (8.7% vs. 3.4%) and a higher rate of fatal thrombotic reactions (1.1% vs. 0.2%) in the first 4 months of the study among patients treated with epoetin alfa. Based on Kaplan-Meier estimates, at the time of study termination, the 12-month survival was lower in the epoetin alfa group than in the placebo group (70% vs. 76%; HR 1.37, 95% CI: 1.07, 1.75; $p = 0.012$).

Patients Having Surgery

An increased incidence of deep venous thrombosis (DVT) in patients receiving epoetin alfa undergoing surgical orthopedic procedures was demonstrated *[see Adverse Reactions (6.1)]*. In a randomized, controlled study, 680 adult patients, not receiving prophylactic anticoagulation and undergoing spinal surgery, were randomized to 4 doses of 600 Units/kg epoetin alfa (7, 14, and 21 days before surgery, and the day of surgery) and standard of care (SOC) treatment (n = 340) or to SOC treatment alone (n = 340). A higher incidence of DVTs, determined by either color flow duplex imaging or by clinical symptoms, was observed in the epoetin alfa group (16 [4.7%] patients) compared with the SOC group (7 [2.1%] patients). In addition to the 23 patients with DVTs included in the primary analysis, 19 [2.8%] patients (n = 680) experienced 1 other thrombovascular event (TVE) each (12 [3.5%] in the epoetin alfa group and 7 [2.1%] in the SOC group). Deep venous thrombosis prophylaxis is strongly recommended when ESAs are used for the reduction of allogeneic RBC transfusions in surgical patients *[see Dosage and Administration (2.5)]*.

Increased mortality was observed in a randomized, placebo-controlled study of Epogen in adult patients who were undergoing CABG surgery (7 deaths in 126 patients randomized to Epogen 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.

5.2 Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients With Cancer

ESAs resulted in decreased locoregional control/progression-free survival (PFS) and/or overall survival (OS) (see Table 2).

Adverse effects on PFS and/or OS were observed in studies of patients receiving chemotherapy for breast cancer (Studies 1, 2, and 4), lymphoid malignancy (Study 3), and cervical cancer (Study 5); in patients with advanced head

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and neck cancer receiving radiation therapy (Studies 6 and 7); and in patients with non-small cell lung cancer or various malignancies who were not receiving chemotherapy or radiotherapy (Studies 8 and 9).

Table 2. Randomized, Controlled Studies With Decreased Survival and/or Decreased Locoregional Control

Study/Tumor/(n)	Hemoglobin Target	Achieved Hemoglobin (Median; Q1, Q3*)	Primary Efficacy Outcome	Adverse Outcome for ESA-containing Arm
Chemotherapy				
Study 1 Metastatic breast cancer (n = 2098)	≤12 g/dL†	11.6 g/dL; 10.7, 12.1 g/dL	Progression-free survival (PFS)	Decreased progression-free and overall survival
Study 2 Metastatic breast cancer (n = 939)	12-14 g/dL	12.9 g/dL; 12.2, 13.3 g/dL	12-month overall survival	Decreased 12-month survival
Study 3 Lymphoid malignancy (n = 344)	13-15 g/dL (M) 13-14 g/dL (F)	11 g/dL; 9.8, 12.1 g/dL	Proportion of patients achieving a hemoglobin response	Decreased overall survival
Study 4 Early breast cancer (n = 733)	12.5-13 g/dL	13.1 g/dL; 12.5, 13.7 g/dL	Relapse-free and overall survival	Decreased 3-year relapse-free and overall survival
Study 5 Cervical cancer (n = 114)	12-14 g/dL	12.7 g/dL; 12.1, 13.3 g/dL	Progression-free and overall survival and locoregional control	Decreased 3-year progression-free and overall survival and locoregional control
Radiotherapy Alone				
Study 6 Head and neck cancer (n = 351)	≥ 15 g/dL (M) ≥ 14 g/dL (F)	Not available	Locoregional progression-free survival	Decreased 5-year locoregional progression-free and overall survival
Study 7 Head and neck cancer (n = 522)	14-15.5 g/dL	Not available	Locoregional disease control	Decreased locoregional disease control
No Chemotherapy or Radiotherapy				
Study 8 Non-small cell lung cancer (n = 70)	12-14 g/dL	Not available	Quality of life	Decreased overall survival
Study 9 Non-myeloid malignancy (n = 989)	12-13 g/dL	10.6 g/dL; 9.4, 11.8 g/dL	RBC transfusions	Decreased overall survival

*Q1= 25th percentile;
Q3= 75th percentile
†This study did not include a defined hemoglobin target. Doses were titrated to achieve and maintain the lowest hemoglobin level sufficient to avoid transfusion and not to exceed 12 g/dL.

Decreased Overall Survival

Study 2 was described in the previous section *[see Warnings and Precautions (5.1)]*. Mortality at 4 months (8.7% vs. 3.4%) was significantly higher in the epoetin alfa arm. The most common investigator-attributed cause of death within the first 4 months was disease progression; 28 of 41 deaths in the epoetin alfa arm and 13 of 16 deaths

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in the placebo arm were attributed to disease progression. Investigator-assessed time to tumor progression was not different between the 2 groups. Survival at 12 months was significantly lower in the epoetin alfa arm (70% vs. 76%; HR 1.37, 95% CI: 1.07, 1.75; p = 0.012).

Study 3 was a randomized, double-blind study (darbepoetin alfa vs. placebo) conducted in 344 anemic patients with lymphoid malignancy receiving chemotherapy. With a median follow-up of 29 months, overall mortality rates were significantly higher among patients randomized to darbepoetin alfa as compared to placebo (HR 1.36, 95% CI: 1.02, 1.82).

Study 8 was a multicenter, randomized, double-blind study (epoetin alfa vs. placebo) in which patients with advanced non-small cell lung cancer receiving only palliative radiotherapy or no active therapy were treated with epoetin alfa to achieve and maintain hemoglobin levels between 12 and 14 g/dL. Following an interim analysis of 70 patients (planned accrual 300 patients), a significant difference in survival in favor of the patients in the placebo arm of the study was observed (median survival 63 vs. 129 days; HR 1.84; p = 0.04).

Study 9 was a randomized, double-blind study (darbepoetin alfa vs. placebo) in 989 anemic patients with active malignant disease, neither receiving nor planning to receive chemotherapy or radiation therapy. There was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions. The median survival was shorter in the darbepoetin alfa treatment group than in the placebo group (8 months vs. 10.8 months; HR 1.30, 95% CI: 1.07, 1.57).

Decreased Progression-free Survival and Overall Survival

Study 1 was a randomized, open-label, multicenter study in 2,098 anemic women with metastatic breast cancer, who received first line or second line chemotherapy. This was a non inferiority study designed to rule out a 15% risk increase in tumor progression or death of epoetin alfa plus standard of care (SOC) as compared with SOC alone. The median progression free survival (PFS) per investigator assessment of disease progression was 7.4 months in each arm (HR 1.09, 95% CI: 0.99, 1.20), indicating the study objective was not met. At the time of clinical data cutoff, 1337 deaths were reported. Median overall survival in the epoetin alfa plus SOC group was 17.2 months compared with 17.4 months in the SOC alone group (HR 1.06, 95% CI: 0.95, 1.18). There were more deaths from disease progression in the epoetin alfa plus SOC arm (59% vs. 56%) and more thrombotic vascular events in the epoetin alfa plus SOC arm (3% vs. 1%).

Study 4 was a randomized, open-label, controlled, factorial design study in which darbepoetin alfa was administered to prevent anemia in 733 women receiving neo-adjuvant breast cancer treatment. A final analysis was performed after a median follow-up of approximately 3 years. The 3-year survival rate was lower (86% vs. 90%; HR 1.42, 95% CI: 0.93, 2.18) and the 3-year relapse-free survival rate was lower (72% vs. 78%; HR 1.33, 95% CI: 0.99, 1.79) in the darbepoetin alfa-treated arm compared to the control arm.

Study 5 was a randomized, open-label, controlled study that enrolled 114 of a planned 460 cervical cancer patients receiving chemotherapy and radiotherapy. Patients were randomized to receive epoetin alfa to maintain hemoglobin between 12 and 14 g/dL or to RBC transfusion support as needed. The study was terminated prematurely due to an increase in thromboembolic adverse reactions in epoetin alfa-treated patients compared to control (19% vs. 9%). Both local recurrence (21% vs. 20%) and distant recurrence (12% vs. 7%) were more frequent in epoetin alfa-treated patients compared to control. Progression-free survival at 3 years was lower in the epoetin alfa-treated group compared to control (59% vs. 62%; HR 1.06, 95% CI: 0.58, 1.91). Overall survival at 3 years was lower in the epoetin alfa-treated group compared to control (61% vs. 71%; HR 1.28, 95% CI: 0.68, 2.42).

Study 6 was a randomized, placebo-controlled study in 351 head and neck cancer patients where epoetin beta or placebo was administered to achieve target hemoglobins ≥ 14 and ≥ 15 g/dL for women and men, respectively. Locoregional progression-free survival was significantly shorter in patients receiving epoetin beta (HR 1.62, 95% CI: 1.22, 2.14; p = 0.0008) with medians of 406 days and 745 days in the epoetin beta and placebo arms, respectively. Overall survival was significantly shorter in patients receiving epoetin beta (HR 1.39, 95% CI: 1.05, 1.84; p = 0.02).

Decreased Locoregional Control

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Study 7 was a randomized, open-label, controlled study conducted in 522 patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy alone (no chemotherapy) who were randomized to receive darbepoetin alfa to maintain hemoglobin levels of 14 to15.5 g/dL or no darbepoetin alfa. An interim analysis performed on 484 patients demonstrated that locoregional control at 5 years was significantly shorter in patients receiving darbepoetin alfa (RR 1.44, 95% CI: 1.06, 1.96; p = 0.02). Overall survival was shorter in patients receiving darbepoetin alfa (RR 1.28, 95% CI: 0.98, 1.68; p = 0.08).

5.3 Hypertension

Epogen is contraindicated in patients with uncontrolled hypertension. Following initiation and titration of Epogen, approximately 25% of patients on dialysis required initiation of or increases in antihypertensive therapy; hypertensive encephalopathy and seizures have been reported in patients with CKD receiving Epogen.

Appropriately control hypertension prior to initiation of and during treatment with Epogen. Reduce or withhold Epogen if blood pressure becomes difficult to control. Advise patients of the importance of compliance with antihypertensive therapy and dietary restrictions *[see Patient Counseling Information (17)]*.

5.4 Seizures

Epogen increases the risk of seizures in patients with CKD. During the first several months following initiation of Epogen, monitor patients closely for premonitory neurologic symptoms. Advise patients to contact their healthcare practitioner for new-onset seizures, premonitory symptoms or change in seizure frequency.

5.5 Lack or Loss of Hemoglobin Response to Epogen

For lack or loss of hemoglobin response to Epogen, initiate a search for causative factors (e.g., iron deficiency, infection, inflammation, bleeding). If typical causes of lack or loss of hemoglobin response are excluded, evaluate for PRCA *[see Warnings and Precautions (5.6)]*. In the absence of PRCA, follow dosing recommendations for management of patients with an insufficient hemoglobin response to Epogen therapy *[see Dosage and Administration (2.2)]*.

5.6 Pure Red Cell Aplasia

Cases of PRCA and of severe anemia, with or without other cytopenias that arise following the development of neutralizing antibodies to erythropoietin have been reported in patients treated with Epogen. This has been reported predominantly in patients with CKD receiving ESAs by subcutaneous administration. PRCA has also been reported in patients receiving ESAs for anemia related to hepatitis C treatment (an indication for which Epogen is not approved).

If severe anemia and low reticulocyte count develop during treatment with Epogen, withhold Epogen and evaluate patients for neutralizing antibodies to erythropoietin. Contact Amgen (1-800-77-AMGEN) to perform assays for binding and neutralizing antibodies. Permanently discontinue Epogen in patients who develop PRCA following treatment with Epogen or other erythropoietin protein drugs. Do not switch patients to other ESAs.

5.7 Serious Allergic Reactions

Serious allergic reactions, including anaphylactic reactions, angioedema, bronchospasm, skin rash, and urticaria may occur with Epogen. Immediately and permanently discontinue Epogen and administer appropriate therapy if a serious allergic or anaphylactic reaction occurs.

5.8 Albumin (Human)

Epogen contains albumin, a derivative of human blood *[see Description (11)]*. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A

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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.

5.9 Dialysis Management

Patients may require adjustments in their dialysis prescriptions after initiation of Epogen. Patients receiving Epogen may require increased anticoagulation with heparin to prevent clotting of the extracorporeal circuit during hemodialysis.

5.10 Laboratory Monitoring

Evaluate transferrin saturation and serum ferritin prior to and during Epogen treatment. Administer supplemental iron therapy when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20% *[see Dosage and Administration (2.1)]*. The majority of patients with CKD will require supplemental iron during the course of ESA therapy. Following initiation of therapy and after each dose adjustment, monitor hemoglobin weekly until the hemoglobin level is stable and sufficient to minimize the need for RBC transfusion.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism *[see Warnings and Precautions (5.1)]*
- Increased mortality and/or increased risk of tumor progression or recurrence in Patients With Cancer *[see Warnings and Precautions (5.2)]*
- Hypertension *[see Warnings and Precautions (5.3)]*
- Seizures *[see Warnings and Precautions (5.4)]*
- PRCA *[see Warnings and Precautions (5.6)]*
- Serious allergic reactions *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.

<u>Patients with Chronic Kidney Disease</u>

Adult Patients

Three double-blind, placebo-controlled studies, including 244 patients with CKD on dialysis, were used to identify the adverse reactions to Epogen. In these studies, the mean age of patients was 48 years (range: 20 to 80 years). One hundred and thirty-three (55%) patients were men. The racial distribution was as follows: 177 (73%) patients were white, 48 (20%) patients were black, 4 (2%) patients were Asian, 12 (5%) patients were other, and racial information was missing for 3 (1%) patients.

Two double-blind, placebo-controlled studies, including 210 patients with CKD not on dialysis, were used to identify the adverse reactions to Epogen. In these studies, the mean age of patients was 57 years (range: 24 to 79 years). One hundred and twenty-one (58%) patients were men. The racial distribution was as follows: 164 (78%) patients were white, 38 (18%) patients were black, 3 (1%) patients were Asian, 3 (1%) patients were other, and racial information was missing for 2 (1%) patients.

The adverse reactions with a reported incidence of ≥ 5% in Epogen-treated patients and that occurred at a ≥ 1% higher frequency than in placebo-treated patients are shown in the table below:

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Table 3. Adverse Reactions in Patients With CKD on Dialysis

Adverse Reaction	Epogen-treated Patients (n = 148)	Placebo-treated Patients (n = 96)
Hypertension	27.7%	12.5%
Arthralgia	16.2%	3.1%
Muscle spasm	7.4%	6.3%
Pyrexia	10.1%	8.3%
Dizziness	9.5%	8.3%
Medical Device Malfunction (artificial kidney clotting during dialysis)	8.1%	4.2%
Vascular Occlusion (vascular access thrombosis)	8.1%	2.1%
Upper respiratory tract infection	6.8%	5.2%

An additional serious adverse reaction that occurred in less than 5% of epoetin alfa-treated dialysis patients and greater than placebo was thrombosis (2.7% Epogen and 1% placebo) *[see Warnings and Precautions (5.1)]*.

The adverse reactions with a reported incidence of ≥ 5% in Epogen-treated patients and that occurred at a ≥ 1% higher frequency than in placebo-treated patients are shown in the table below:

Table 4. Adverse Reactions in Patients With CKD Not on Dialysis

Adverse Reactions	Epogen-treated Patients (n = 131)	Placebo-treated Patients (n = 79)
Hypertension	13.7%	10.1%
Arthralgia	12.2%	7.6%

Additional serious adverse reactions that occurred in less than 5% of epoetin alfa-treated patients not on dialysis and greater than placebo were erythema (0.8% Epogen and 0% placebo) and myocardial infarction (0.8% Epogen and 0% placebo) *[see Warnings and Precautions (5.1)]*.

Pediatric Patients

In pediatric patients with CKD on dialysis, the pattern of adverse reactions was similar to that found in adults.

Zidovudine-treated HIV-infected Patients

A total of 297 zidovudine-treated HIV-infected patients were studied in 4 placebo-controlled studies. A total of 144 (48%) patients were randomly assigned to receive Epogen and 153 (52%) patients were randomly assigned to receive placebo. Epogen was administered at doses between 100 and 200 Units/kg 3 times weekly subcutaneously for up to 12 weeks.

For the combined Epogen treatment groups, a total of 141 (98%) men and 3 (2%) women between the ages of 24 and 64 years were enrolled. The racial distribution of the combined Epogen treatment groups was as follows: 129 (90%) white, 8 (6%) black, 1 (1%) Asian, and 6 (4%) other.

In double-blind, placebo-controlled studies of 3 months duration involving approximately 300 zidovudine-treated HIV-infected patients, adverse reactions with an incidence of ≥ 1% in patients treated with Epogen were:

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Table 5. Adverse Reactions in Zidovudine-treated HIV-infected Patients

Adverse Reaction	Epogen (n = 144)	Placebo (n = 153)
Pyrexia	42%	34%
Cough	26%	14%
Rash	19%	7%
Injection site irritation	7%	4%
Urticaria	3%	1%
Respiratory tract congestion	1%	Not reported
Pulmonary embolism	1%	Not reported

Cancer Patients on Chemotherapy

The data below were obtained in Study C1, a 16-week, double-blind, placebo-controlled study that enrolled 344 patients with anemia secondary to chemotherapy. There were 333 patients who were evaluable for safety; 168 of 174 patients (97%) randomized to Epogen received at least 1 dose of study drug, and 165 of 170 patients (97%) randomized to placebo received at least 1 placebo dose. For the once weekly Epogen-treatment group, a total of 76 men (45%) and 92 women (55%) between the ages of 20 and 88 years were treated. The racial distribution of the Epogen-treatment group was 158 white (94%) and 10 black (6%). Epogen was administered once weekly for an average of 13 weeks at a dose of 20,000 to 60,000 IU subcutaneously (mean weekly dose was 49,000 IU).

The adverse reactions with a reported incidence of $\geq$ 5% in Epogen-treated patients that occurred at a higher frequency than in placebo-treated patients are shown in the table below:

Table 6. Adverse Reactions in Cancer Patients

Adverse Reaction	Epogen (n = 168)	Placebo (n = 165)
Nausea	35%	30%
Vomiting	20%	16%
Myalgia	10%	5%
Arthralgia	10%	6%
Stomatitis	10%	8%
Cough	9%	7%
Weight decrease	9%	5%
Leukopenia	8%	7%
Bone pain	7%	4%
Rash	7%	5%
Hyperglycemia	6%	4%
Insomnia	6%	2%
Headache	5%	4%
Depression	5%	4%
Dysphagia	5%	2%
Hypokalemia	5%	3%
Thrombosis	5%	3%

Surgery Patients

Four hundred sixty-one patients undergoing major orthopedic surgery were studied in a placebo-controlled study (S1) and a comparative dosing study (2 dosing regimens, S2). A total of 358 patients were randomly assigned to receive Epogen and 103 (22%) patients were randomly assigned to receive placebo. Epogen was administered daily at a dose of 100 to 300 IU/kg subcutaneously for 15 days or at 600 IU/kg once weekly for 4 weeks.

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For the combined Epogen treatment groups, a total of 90 (25%) and 268 (75%) women between the ages of 29 and 89 years were enrolled. The racial distribution of the combined Epogen treatment groups was as follows: 288 (80%) white, 64 (18%) black, 1 (< 1%) Asian, and 5 (1%) other.

The adverse reactions with a reported incidence of ≥ 1% in Epogen-treated patients that occurred at a higher frequency than in placebo-treated patients are shown in the table below:

Table 7. Adverse Reactions in Surgery Patients

Adverse Reaction	Study S1			Study S2	
	Epogen 300 U/kg (n = 112)[a]	**Epogen 100 U/kg (n = 101)[a]**	**Placebo (n = 103)[a]**	**Epogen 600 U/kg x 4 weeks (n = 73)[b]**	**Epogen 300 U/kg x 15 days (n = 72)[b]**
Nausea	47%	43%	45%	45%	56%
Vomiting	21%	12%	14%	19%	28%
Pruritus	16%	16%	14%	12%	21%
Headache	13%	11%	9%	10%	18%
Injection site pain	13%	9%	8%	12%	11%
Chills	7%	4%	1%	1%	0%
Deep vein thrombosis	6%	3%	3%	0%[c]	0%[c]
Cough	5%	4%	0%	4%	4%
Hypertension	5%	3%	5%	5%	6%
Rash	2%	2%	1%	3%	3%
Edema	1%	2%	2%	1%	3%

[a]Study included patients undergoing orthopedic surgery treated with Epogen or placebo for 15 days.
[b]Study included patients undergoing orthopedic surgery treated with Epogen 600 U/kg weekly for 4 weeks or 300 U/kg daily for 15 days.
[c]DVTs were determined by clinical symptoms.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Epogen.
Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Seizures *[see Warnings and Precautions (5.4)]*
- PRCA *[see Warnings and Precautions (5.6)]*
- Serious allergic reactions *[see Warnings and Precautions (5.7)]*
- Injection site reactions, including irritation and pain
- Porphyria

6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Neutralizing antibodies to epoetin alfa that cross-react with endogenous erythropoietin and other ESAs can result in PRCA or severe anemia (with or without other cytopenias) *[see Warnings and Precautions (5.6)]*.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Epogen with the incidence of antibodies to other products may be misleading.

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7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with Epogen.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

The multiple-dose vials are formulated with benzyl alcohol. Do not administer Epogen from multiple-dose vials, or Epogen from single-dose vials admixed with bacteriostatic saline containing benzyl alcohol, to pregnant women. When therapy with Epogen is needed during pregnancy, use a benzyl alcohol-free formulation *[see Dosage and Administration (2) and Contraindications (4)]*.

Pregnancy Category C (single-dose vials only)

There are no adequate and well-controlled studies of Epogen use during pregnancy. There are limited data on Epogen use in pregnant women. In animal reproductive and developmental toxicity studies, adverse fetal effects occurred when pregnant rats received epoetin alfa at doses approximating the clinical recommended starting doses. Single-dose formulations of Epogen should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There are reports of at least 33 pregnant women with anemia alone or anemia associated with severe renal disease and other hematologic disorders who received Epogen. Polyhydramnios and intrauterine growth restriction were reported in women with chronic renal disease, which is associated with an increased risk for these adverse pregnancy outcomes. There was 1 infant born with pectus excavatum and hypospadias following exposure during the first trimester. Due to the limited number of exposed pregnancies and multiple confounding factors (such as underlying maternal conditions, other maternal medications, and gestational timing of exposure), these published case reports and studies do not reliably estimate the frequency or absence of adverse outcomes.

When healthy rats received Epogen at doses of 100 Units/kg/day during mating and through early pregnancy (dosing stopped prior to organogenesis), there were slight increases in the incidences of pre-and post-implantation loss, and a decrease in live fetuses. This animal dose level of 100 Units/kg/day may approximate the clinical recommended starting dose, depending on the treatment indication. When healthy pregnant rats and rabbits received intravenous doses of up to 500 mg/kg/day of Epogen only during organogenesis, no teratogenic effects were observed in the offspring.

When healthy pregnant rats received Epogen at doses of 500 Units/kg/day late in pregnancy (after the period of organogenesis), offspring had decreased number of caudal vertebrae and growth delays *[see Nonclinical Toxicology (13.3)]*.

Women who become pregnant during Epogen treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-772-6436 (1-800-77-AMGEN) to enroll.

8.3 Nursing Mothers

The multiple-dose vials of Epogen are formulated with benzyl alcohol. Do not administer Epogen from multiple-dose vials, or Epogen from single-dose vials admixed with bacteriostatic saline containing benzyl alcohol, to a nursing woman. When therapy with Epogen is needed in nursing women, use a benzyl alcohol-free formulation *[see Dosage and Administration (2) and Contraindications (4)]*.

It is not known whether Epogen is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Epogen from single-dose vials is administered to a nursing woman.

8.4 Pediatric Use

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The multiple-dose vials are formulated with benzyl alcohol. Do not administer Epogen from multiple-dose vials, or Epogen from single-dose vials admixed with bacteriostatic saline containing benzyl alcohol, to neonates or infants. When therapy with Epogen is needed in neonates and infants, use a benzyl alcohol-free formulation *[see Dosage and Administration (2) and Contraindications (4)]*.

Benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients. The "gasping syndrome," (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages > 99 mg/kg/day in neonates and low-birthweight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birthweight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

Pediatric Patients on Dialysis

Epogen is indicated in pediatric patients, ages 1 month to 16 years of age, for the treatment of anemia associated with CKD requiring dialysis. Safety and effectiveness in pediatric patients less than 1 month old have not been established *[see Clinical Studies (14.1)]*.

The safety data from these studies are similar to those obtained from the studies of Epogen in adult patients with CKD *[see Warnings and Precautions (5) and Adverse Reactions (6.1)]*.

Pediatric Cancer Patients on Chemotherapy

Epogen is indicated in patients 5 to 18 years old for the treatment of anemia due to concomitant myelosuppressive chemotherapy. Safety and effectiveness in pediatric patients less than 5 years of age have not been established *[see Clinical Studies (14.3)]*. The safety data from these studies are similar to those obtained from the studies of Epogen in adult patients with cancer *[see Warnings and Precautions (5) and Adverse Reactions (6.1)]*.

Pediatric Patients With HIV Infection Receiving Zidovudine

Published literature has reported the use of Epogen in 20 zidovudine-treated, anemic, pediatric patients with HIV infection, ages 8 months to 17 years, treated with 50 to 400 Units/kg subcutaneously or intravenously 2 to 3 times per week. Increases in hemoglobin levels and in reticulocyte counts and decreases in or elimination of RBC transfusions were observed.

Pharmacokinetics in Neonates

Limited pharmacokinetic data from a study of 7 preterm, very low birth weight neonates and 10 healthy adults given intravenous erythropoietin suggested that distribution volume was approximately 1.5 to 2 times higher in the preterm neonates than in the healthy adults, and clearance was approximately 3 times higher in the preterm neonates than in the healthy adults.

8.5 Geriatric Use

Of the 4553 patients who received Epogen in the 6 studies for treatment of anemia due to CKD not receiving dialysis, 2726 (60%) were age 65 years and over, while 1418 (31%) were 75 years and over. Of the 757 patients who received Epogen in the 3 studies of CKD patients on dialysis, 361 (47%) were age 65 years and over, while 100 (13%) were 75 years and over. No differences in safety or effectiveness were observed between geriatric and

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younger patients. Dose selection and adjustment for an elderly patient should be individualized to achieve and maintain the target hemoglobin *[see Dosage and Administration (2)]*.

Among 778 patients enrolled in the 3 clinical studies of Epogen for the treatment of anemia due to concomitant chemotherapy, 419 received Epogen and 359 received placebo. Of the 419 who received Epogen, 247 (59%) were age 65 years and over, while 78 (19%) were 75 years and over. No overall differences in safety or effectiveness were observed between geriatric and younger patients. The dose requirements for Epogen in geriatric and younger patients within the 3 studies were similar.

Among 1731 patients enrolled in the 6 clinical studies of Epogen for reduction of allogeneic RBC transfusions in patients undergoing elective surgery, 1085 received Epogen and 646 received placebo or standard of care treatment. Of the 1085 patients who received Epogen, 582 (54%) were age 65 years and over, while 245 (23%) were 75 years and over. No overall differences in safety or effectiveness were observed between geriatric and younger patients. The dose requirements for Epogen in geriatric and younger patients within the 4 studies using the 3 times weekly schedule and 2 studies using the weekly schedule were similar.

Insufficient numbers of patients age 65 years or older were enrolled in clinical studies of Epogen for the treatment of zidovudine in HIV-infected patients to determine whether they respond differently from younger patients.

10 OVERDOSAGE

Epogen overdosage can cause hemoglobin levels above the desired level, which should be managed with discontinuation or reduction of Epogen dosage and/or with phlebotomy, as clinically indicated *[see Pharmacodynamics (12.2)]*. Cases of severe hypertension have been observed following overdose with ESAs *[see Warnings and Precautions (5.3)]*.

11 DESCRIPTION

Epogen (epoetin alfa) is a 165-amino acid erythropoiesis-stimulating glycoprotein manufactured by recombinant DNA technology. It has a molecular weight of approximately 30,400 daltons and is produced by mammalian cells into which the human erythropoietin gene has been introduced. The product contains the identical amino acid sequence of isolated natural erythropoietin.

Epogen is formulated as a sterile, colorless liquid in vials in multiple formulations. Single-dose vials, formulated with an isotonic sodium chloride/sodium citrate-buffered solution, are supplied in multiple strengths. Each 1 mL vial contains 2000, 3000, 4000, or 10,000 Units of epoetin alfa, Albumin (Human) (2.5 mg), citric acid (0.06 mg), sodium chloride (5.9 mg), and sodium citrate (5.8 mg) in Water for Injection, USP (pH 6.9 ± 0.3). Multiple-dose, 2 mL vials contain 10,000 Units epoetin alfa, albumin (human) (2.5 mg), benzyl alcohol (1%), sodium chloride (8.2 mg), citric acid (0.11 mg), and sodium citrate (1.3 mg) per 1 mL Water for Injection, USP (pH 6.1 ± 0.3). Multiple-dose 1 mL vials contain 20,000 Units epoetin alfa, albumin (human) (2.5 mg), benzyl alcohol (1%), sodium chloride (8.2 mg), citric acid (0.11 mg), and sodium citrate (1.3 mg), per 1 mL in Water for Injection, USP (pH 6.1 ± 0.3).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Epogen stimulates erythropoiesis by the same mechanism as endogenous erythropoietin.

12.2 Pharmacodynamics

Epogen increases the reticulocyte count within 10 days of initiation, followed by increases in the RBC count, hemoglobin, and hematocrit, usually within 2 to 6 weeks. The rate of hemoglobin increase varies among patients and is dependent upon the dose of Epogen administered. For correction of anemia in hemodialysis patients, a greater biologic response is not observed at doses exceeding 300 Units/kg 3 times weekly.

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12.3 Pharmacokinetics

In adult and pediatric patients with CKD, the elimination half-life ($t_{1/2}$) of plasma erythropoietin after intravenous administration of Epogen ranged from 4 to 13 hours. After subcutaneous administration, Cmax was achieved within 5 to 24 hours. The $t_{1/2}$ in adult patients with serum creatinine greater than 3 mg/dL was similar between those not on dialysis and those maintained on dialysis. The pharmacokinetic data indicate no apparent difference in Epogen $t_{1/2}$ among adult patients above or below 65 years of age.

A pharmacokinetic study comparing 150 Units/kg subcutaneous 3 times weekly to 40,000 Units subcutaneous weekly dosing regimen was conducted for 4 weeks in healthy subjects (n = 12) and for 6 weeks in anemic cancer patients (n = 32) receiving cyclic chemotherapy. There was no accumulation of serum erythropoietin after the 2 dosing regimens during the study period. The 40,000 Units weekly regimen had a higher C_{max} (3- to 7-fold), longer T_{max} (2- to 3-fold), higher $AUC_{0\text{-}168\,h}$ (2- to 3-fold) of erythropoietin and lower clearance (CL) (50%) than the 150 Units/kg 3 times weekly regimen. In anemic cancer patients, the average $t_{1/2}$ was similar (40 hours with range of 16 to 67 hours) after both dosing regimens. After the 150 Units/kg 3 times weekly dosing, the values of T_{max} and CL were similar (13.3 ± 12.4 vs. 14.2 ± 6.7 hours, and 20.2 ± 15.9 vs. 23.6 ± 9.5 mL/hr/kg) between week 1 when patients were receiving chemotherapy (n = 14) and week 3 when patients were not receiving chemotherapy (n = 4). Differences were observed after the 40,000 Units weekly dosing with longer T_{max} (38 ± 18 hours) and lower CL (9.2 ± 4.7 mL/hr/kg) during week 1 when patients were receiving chemotherapy (n = 18) compared with those (22 ± 4.5 hours, 13.9 ± 7.6 mL/hr/kg, respectively) during week 3 when patients were not receiving chemotherapy (n = 7).

The pharmacokinetic profile of Epogen in children and adolescents appeared similar to that of adults.

The pharmacokinetics of Epogen has not been studied in patients with HIV infection.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

The carcinogenic potential of Epogen has not been evaluated.

Mutagenicity

Epogen was not mutagenic or clastogenic under the conditions tested: Epogen was negative in the *in vitro* bacterial reverse mutation assay (Ames test), in the *in vitro* mammalian cell gene mutation assay (the hypoxanthine-guanine phosphoribosyl transferase [HGPRT] locus), in an *in vitro* chromosomal aberration assay in mammalian cells, and in the *in vivo* mouse micronucleus assay.

Impairment of Fertility

When administered intravenously to male and female rats prior to and during mating, and to females through the beginning of implantation (up to gestational day 7; dosing stopped prior to the beginning of organogenesis), doses of 100 and 500 Units/kg/day of Epogen caused slight increases in pre-implantation loss, post-implantation loss and decreases in the incidence of live fetuses. It is not clear whether these effects reflect a drug effect on the uterine environment or on the conceptus. This animal dose level of 100 Units/kg/day approximates the clinical recommended starting dose, depending on the patient's treatment indication, but may be lower than the clinical dose in patients whose doses have been adjusted.

13.3 Reproductive and Developmental Toxicology

When pregnant rats were administered intravenous Epogen, 500 Units/kg/day, after the period of organogenesis (from day 17 of gestation through day 21 of lactation), their pups exhibited decreased number of caudal vertebrae, decreased body weight gain, and delayed appearance of abdominal hair, eyelid opening, and ossification. This

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animal dose level of 500 Units/kg/day is approximately 5-fold higher than the clinical recommended starting dose, depending on the patient's treatment indication.

When Epogen was administered intravenously during the period of organogenesis to pregnant rats (gestational days 7 to 17) and pregnant rabbits (gestational days 6 to 18), no evidence of teratogenic outcome was observed at the doses tested, up to 500 Units/kg/day. The offspring (F1 generation) of the treated rats were observed postnatally; rats from the F1 generation reached maturity and were mated; no Epogen-related effects were apparent for their offspring (F2 generation fetuses).

14 CLINICAL STUDIES

14.1 Patients With Chronic Kidney Disease

Adult Patients on Dialysis

Patients with chronic kidney disease on dialysis: ESA effects on rates of transfusion

In clinical studies of CKD patients on dialysis, Epogen increased hemoglobin levels and decreased the need for RBC transfusion. Overall, more than 95% of patients were RBC transfusion-independent after receiving Epogen for 3 months. In clinical studies at starting doses of 50 to 150 Units/kg 3 times weekly, adult patients responded with an average rate of hemoglobin rise as presented in Table 8.

Table 8: Average Rate of Hemoglobin Rise in 2 Weeks

Starting Dose (3 Times Weekly Intravenously)	Hemoglobin Increase in 2 Weeks
50 Units/kg	0.5 g/dL
100 Units/kg	0.8 g/dL
150 Units/kg	1.2 g/dL

The safety and efficacy of Epogen were evaluated in 13 clinical studies involving intravenous administration to a total of 1010 anemic patients on dialysis. Overall, more than 90% of the patients treated with Epogen experienced improvement in hemoglobin concentrations. In the 3 largest of these clinical studies, the median maintenance dose necessary to maintain the hemoglobin between 10 to 12 g/dL was approximately 75 Units/kg 3 times weekly. More than 95% of patients were able to avoid RBC transfusions. In the largest US multicenter study, approximately 65% of the patients received doses of 100 Units/kg 3 times weekly or less to maintain their hemoglobin at approximately 11.7 g/dL. Almost 10% of patients received a dose of 25 Units/kg or less, and approximately 10% received a dose of more than 200 Units/kg 3 times weekly to maintain their hemoglobin at this level.

In the Normal Hematocrit Study, the yearly transfusion rate was 51.5% in the lower hemoglobin group (10 g/dL) and 32.4% in the higher hemoglobin group (14 g/dL).

Other ESA trials

In a 26-week, double-blind, placebo-controlled study, 118 patients on dialysis with an average hemoglobin of approximately 7 g/dL were randomized to either Epogen or placebo. By the end of the study, average hemoglobin increased to approximately 11 g/dL in the Epogen-treated patients and remained unchanged in patients receiving placebo. Epogen-treated patients experienced improvements in exercise tolerance and patient-reported physical functioning at month 2 that were maintained throughout the study.

A multicenter, unit-dose study was also conducted in 119 patients receiving peritoneal dialysis who self-administered Epogen subcutaneously. Patients responded to Epogen administered subcutaneously in a manner similar to patients receiving intravenous administration.

Pediatric Patients on Dialysis

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The safety and efficacy of Epogen were studied in a placebo-controlled, randomized study of 113 children with anemia (hemoglobin ≤ 9 g/dL) undergoing peritoneal dialysis or hemodialysis. The initial dose of Epogen was 50 Units/kg intravenously or subcutaneously 3 times weekly. The dose of study drug was titrated to achieve either a hemoglobin of 10 to 12 g/dL or an absolute increase in hemoglobin of 2 g/dL over baseline.

At the end of the initial 12 weeks, a statistically significant rise in mean hemoglobin (3.1 g/dL vs. 0.3 g/dL) was observed only in the Epogen arm. The proportion of children achieving a hemoglobin of 10 g/dL, or an increase in hemoglobin of 2 g/dL over baseline, at any time during the first 12 weeks was higher in the Epogen arm (96% vs. 58%). Within 12 weeks of initiating Epogen therapy, 92.3% of the pediatric patients were RBC transfusion independent as compared to 65.4% who received placebo. Among patients who received 36 weeks of Epogen, hemodialysis patients received a higher median maintenance dose [167 Units/kg/week (n = 28) vs. 76 Units/kg/week (n = 36)] and took longer to achieve a hemoglobin of 10 to 12 g/dL (median time to response 69 days vs. 32 days) than patients undergoing peritoneal dialysis.

Adult Patients With CKD Not Requiring Dialysis

Four clinical studies were conducted in patients with CKD not on dialysis involving 181 patients treated with Epogen. These patients responded to Epogen therapy in a manner similar to that observed in patients on dialysis. Patients with CKD not on dialysis demonstrated a dose-dependent and sustained increase in hemoglobin when Epogen was administered by either an intravenous or subcutaneous route, with similar rates of rise of hemoglobin when Epogen was administered by either route.

Patients with chronic kidney disease not on dialysis: ESA effects on rates of transfusion

In TREAT, a randomized, double-blind trial of 4038 patients with CKD and type 2 diabetes not on dialysis, a post-hoc analysis showed that the proportion of patients receiving RBC transfusions was lower in patients administered an ESA to target a hemoglobin of 13 g/dL compared to the control arm in which an ESA was administered intermittently if hemoglobin concentration decreased to less than 9 g/dL (15% versus 25%, respectively). In CHOIR, a randomized open-label study of 1432 patients with CKD not on dialysis, use of epoetin alfa to target a higher (13.5 g/dL) versus lower (11.3 g/dL) hemoglobin goal did not reduce the use of RBC transfusions. In each trial, no benefits occurred for the cardiovascular or end-stage renal disease outcomes. In each trial, the potential benefit of ESA therapy was offset by worse cardiovascular safety outcomes resulting in an unfavorable benefit-risk profile [*see Warnings and Precautions (5.1)]*.

ESA Effects on rates of death and other serious cardiac adverse events

Three randomized outcome trials (Normal Hematocrit Study [NHS], Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease [CHOIR], and Trial of Darbepoetin Alfa in Type 2 Diabetes and CKD [TREAT]) have been conducted in patients with CKD using Epogen/PROCRIT/Aranesp to target higher vs. lower hemoglobin levels. Though these trials were designed to establish a cardiovascular or renal benefit of targeting higher hemoglobin levels, in all 3 studies, patients randomized to the higher hemoglobin target experienced worse cardiovascular outcomes and showed no reduction in progression to ESRD. In each trial, the potential benefit of ESA therapy was offset by worse cardiovascular safety outcomes resulting in an unfavorable benefit-risk profile *[see Warnings and Precautions (5.1)]*.

14.2 Zidovudine-treated Patients With HIV Infection

The safety and efficacy of Epogen were evaluated in 4 placebo-controlled studies enrolling 297 anemic patients (hemoglobin < 10 g/dL) with HIV infection receiving concomitant therapy with zidovudine. In the subgroup of patients (89/125 Epogen and 88/130 placebo) with pre-study endogenous serum erythropoietin levels ≤ 500 mUnits/mL, Epogen reduced the mean cumulative number of units of blood transfused per patient by approximately 40% as compared to the placebo group. Among those patients who required RBC transfusions at baseline, 43% of patients treated with Epogen versus 18% of placebo-treated patients were RBC transfusion-independent during the second and third months of therapy. Epogen therapy also resulted in significant increases in hemoglobin in comparison to placebo. When examining the results according to the weekly dose of zidovudine received during month 3 of therapy, there was a statistically significant reduction ($p < 0.003$) in RBC transfusion

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requirements in patients treated with Epogen (n = 51) compared to placebo-treated patients (n = 54) whose mean weekly zidovudine dose was ≤ 4200 mg/week.

Approximately 17% of the patients with endogenous serum erythropoietin levels ≤ 500 mUnits/mL receiving Epogen in doses from 100 to 200 Units/kg 3 times weekly achieved a hemoglobin of 12.7 g/dL without administration of RBC transfusions or significant reduction in zidovudine dose. In the subgroup of patients whose pre-study endogenous serum erythropoietin levels were > 500 mUnits/mL, Epogen therapy did not reduce RBC transfusion requirements or increase hemoglobin compared to the corresponding responses in placebo-treated patients.

14.3 Cancer Patients on Chemotherapy

The safety and effectiveness of Epogen was assessed in two multicenter, randomized (1:1), placebo-controlled, double-blind studies (Study C1 and Study C2) and a pooled analysis of six additional randomized (1:1), multicenter, placebo-controlled, double-blind studies. All studies were conducted in patients with anemia due to concomitantly administered cancer chemotherapy. Study C1 enrolled 344 adult patients, Study C2 enrolled 222 pediatric patients, and the pooled analysis contained 131 patients randomized to epoetin alfa or placebo. In Studies C1 and C2, efficacy was demonstrated by a reduction in the proportion of patients who received an RBC transfusion, from week 5 through end of the study, with the last-known RBC transfusion status carried forward for patients who discontinued treatment. In the pooled analysis, efficacy was demonstrated by a reduction in the proportion of patients who received an RBC transfusion from week 5 through end of the study in the subset of patients who were remaining on therapy for 6 or more weeks.

Study C1

Study C1 was conducted in anemic patients (hemoglobin < 11.5 g/dL for males; < 10.5 g/dL for females) with non-myeloid malignancies receiving myelosuppressive chemotherapy. Randomization was stratified by type of malignancy (lung vs. breast vs. other), concurrent radiation therapy planned (yes or no), and baseline hemoglobin (< 9 g/dL vs. ≥ 9 g/dL); patients were randomized to epoetin alfa 40,000 Units (n = 174) or placebo (n = 170) as a weekly subcutaneous injection commencing on the first day of the chemotherapy cycle.

Ninety-one percent of patients were white, 44% were male, and the median age of patients was 66 years (range: 20 to 88 years). The proportion of patients withdrawn from the study prior to week 5 was less than 10% for placebo-treated or epoetin-treated patients. Per protocol, the last available hemoglobin values from patients who dropped out were included in the efficacy analyses. Efficacy results are shown in Table 9.

Table 9. Study C1: Proportion of Patients Transfused

	Week 5 Through Week 16 or End of Study[b]	
Chemotherapy Regimen	**Epogen (n = 174)**	**Placebo (n = 170)**
All Regimens	14% (25/174)[a]	28% (48/170)
Regimens without cisplatin	14% (21/148)	26% (35/137)
Regimens containing cisplatin	15% (4/26)	39% (13/33)

[a]Two-sided p < 0.001, logistic regression analysis adjusting for accrual rate and stratification variables
[b] Last-known RBC transfusion status carried forward for patients who discontinued treatment.

Study C2

Study C2 was conducted in 222 anemic patients, ages 5 to 18, receiving chemotherapy for the treatment of various childhood malignancies. Randomization was stratified by cancer type (solid tumors, Hodgkin's disease, acute lymphocytic leukemia, vs. non-Hodgkin's lymphoma); patients were randomized to receive epoetin alfa at 600 Units/kg maximum 40,000 Units (n = 111) or placebo (n = 111) as a weekly intravenous injection.

Sixty-nine percent of patients were white, 55% were male, and the median age of patients was 12 years (range: 5 to 18 years). Two (2%) of placebo-treated patients and 3 (3%) of epoetin alfa-treated patients dropped out of the

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study prior to week 5. There were fewer RBC transfusions from week 5 through the end-of-study in epoetin-alfa treated patients [51% (57/111)] compared to placebo-treated patients [69% (77/111)]. There was no evidence of an improvement in health-related quality of life, including no evidence of an effect on fatigue, energy, or strength in patients receiving Epogen as compared to those receiving placebo.

Pooled Analysis (Three Times Per Week Dosing)

The results of 6 studies of similar design and that randomized 131 patients to epoetin alfa or placebo were pooled to assess the safety and effectiveness of epoetin alfa. Patients were randomized to receive epoetin alfa at 150 Units/kg (n = 63) or placebo (n = 68), subcutaneously three times per week for 12 weeks in each study. Across all studies, 72 patients were treated with concomitant non cisplatin-containing chemotherapy regimens and 59 patients were treated with concomitant cisplatin-containing chemotherapy regimens. Twelve patients (19%) in the epoetin alfa arm and 10 patients (15%) in the placebo-arm dropped out prior to week 6 and are excluded from efficacy analyses.

Table 10: Proportion of Patients Transfused in the Pooled Analysis for Three Times Per Week Dosing

	Week 5 Through Week 12 or End of Study[b]	
Chemotherapy Regimen	**Epogen**	**Placebo**
All Regimens	22% (11/51)[a]	43% (25/58)
Regimens without cisplatin	21% (6/29)	33% (11/33)
Regimens containing cisplatin	23% (5/22)	56% (14/25)

[a]Two-sided $p < 0.05$, unadjusted
[b] Limited to patients remaining on study beyond week 6 and includes only RBC transfusions during weeks 5-12.

14.4 Surgery Patients

The safety and efficacy of Epogen were evaluated in a placebo-controlled, double-blind study (S1) enrolling 316 patients scheduled for major, elective orthopedic hip or knee surgery who were expected to require ≥ 2 units of blood and who were not able or willing to participate in an autologous blood donation program. Patients were stratified into 1 of 3 groups based on their pretreatment hemoglobin [≤ 10 g/dL (n = 2), > 10 to ≤ 13 g/dL (n = 96), and > 13 to ≤ 15 g/dL (n = 218)] and then randomly assigned to receive 300 Units/kg Epogen, 100 Units/kg Epogen, or placebo by subcutaneous injection for 10 days before surgery, on the day of surgery, and for 4 days after surgery. All patients received oral iron and a low-dose, postoperative warfarin regimen.

Treatment with Epogen 300 Units/kg significantly ($p = 0.024$) reduced the risk of allogeneic RBC transfusion in patients with a pretreatment hemoglobin of > 10 to ≤ 13 g/dL; 5/31 (16%) of patients treated with Epogen 300 Units/kg, 6/26 (23%) of patients treated with Epogen 100 Units/kg, and 13/29 (45%) of placebo-treated patients were transfused. There was no significant difference in the number of patients transfused between Epogen (9% 300 Units/kg, 6% 100 Units/kg) and placebo (13%) in the > 13 to ≤ 15 g/dL hemoglobin stratum. There were too few patients in the ≤ 10 g/dL group to determine if Epogen is useful in this hemoglobin strata. In the > 10 to ≤ 13 g/dL pretreatment stratum, the mean number of units transfused per Epogen-treated patient (0.45 units blood for 300 Units/kg, 0.42 units blood for 100 Units/kg) was less than the mean transfused per placebo-treated patient (1.14 units) (overall $p = 0.028$). In addition, mean hemoglobin, hematocrit, and reticulocyte counts increased significantly during the presurgery period in patients treated with Epogen.

Epogen was also evaluated in an open-label, parallel-group study (S2) enrolling 145 patients with a pretreatment hemoglobin level of ≥ 10 to ≤ 13 g/dL who were scheduled for major orthopedic hip or knee surgery and who were not participating in an autologous program. Patients were randomly assigned to receive 1 of 2 subcutaneous dosing regimens of Epogen (600 Units/kg once weekly for 3 weeks prior to surgery and on the day of surgery, or 300 Units/kg once daily for 10 days prior to surgery, on the day of surgery, and for 4 days after surgery). All patients received oral iron and appropriate pharmacologic anticoagulation therapy.

From pretreatment to presurgery, the mean increase in hemoglobin in the 600 Units/kg weekly group (1.44 g/dL) was greater than that observed in the 300 Units/kg daily group. The mean increase in absolute reticulocyte count

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was smaller in the weekly group (0.11 x $10^6/mm^3$) compared to the daily group (0.17 x $10^6/mm^3$). Mean hemoglobin levels were similar for the 2 treatment groups throughout the postsurgical period.

The erythropoietic response observed in both treatment groups resulted in similar RBC transfusion rates [11/69 (16%) in the 600 Units/kg weekly group and 14/71 (20%) in the 300 Units/kg daily group]. The mean number of units transfused per patient was approximately 0.3 units in both treatment groups.

16 HOW SUPPLIED/STORAGE AND HANDLING

Store at 36°F to 46°F (2°C to 8°C). Do not freeze.
Do not shake. Protect from light; store Epogen in the carton until use.
Do not use Epogen that has been shaken or frozen.

Single-dose, Preservative-free Vial (in citrate-buffered formulation): 1 mL of solution contains 2000 (NDC 55513-126-10), 3000 (NDC 55513-267-10), 4000 (NDC 55513-148-10), or 10,000 Units (NDC 55513-144-10) of epoetin alfa. Each strength is supplied in dispensing packs containing 10 single-dose vials.

Multiple-dose, Preserved Vial: 2 mL total volume (20,000 Units total; 10,000 Units/mL). Each 1 mL of solution contains 10,000 Units (NDC 55513-283-10) of epoetin alfa, and is supplied in dispensing packs containing 10 multiple-dose vials.

Multiple-dose, Preserved Vial: 1 mL total volume (20,000 Units/mL). Each 1 mL of solution contains 20,000 Units (NDC 55513-478-10) of epoetin alfa and is supplied in dispensing packs containing 10 multiple-dose vials.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Prior to treatment, inform patients of the risks and benefits of Epogen.

Inform patients:

- To read the Medication Guide.
- Of the increased risks of mortality, serious cardiovascular reactions, thromboembolic reactions, stroke, and tumor progression *[see Warnings and Precautions (5.1, 5.2)]*.
- To undergo regular blood pressure monitoring, adhere to prescribed anti-hypertensive regimen and follow recommended dietary restrictions.
- To contact their healthcare provider for new-onset neurologic symptoms or change in seizure frequency.
- Of the need to have regular laboratory tests for hemoglobin.
- Risks are associated with benzyl alcohol in neonates, infants, pregnant women, and nursing mothers *[see Use in Specific Populations (8.1, 8.3, 8.4)]*.

Instruct patients who self-administer Epogen of the:

- Importance of following the Instructions for Use.
- Dangers of reusing needles, syringes, or unused portions of single-dose vials.
- Proper disposal of used syringes, needles, and unused vials, and of the full container.

AMGEN®

Epogen® (epoetin alfa)

Manufactured by:
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One Amgen Center Drive
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Reference ID: 4083860

U.S. License Number 1080
Patent: http://pat.amgen.com/epogen/

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MEDICATION GUIDE

Epogen® (Ee-po-jen)
(epoetin alfa)

Read this Medication Guide:

- before you start Epogen.
- if you are told by your healthcare provider that there is new information about Epogen.
- if you are told by your healthcare provider that you may inject Epogen at home, read this Medication Guide each time you receive a new supply of medicine.

This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Talk with your healthcare provider regularly about the use of Epogen and ask if there is new information about Epogen.

What is the most important information I should know about Epogen?

Epogen may cause serious side effects that can lead to death, including:

For people with cancer:

- Your tumor may grow faster and you may die sooner if you choose to take Epogen. Your healthcare provider will talk with you about these risks.

For all people who take Epogen, including people with cancer or chronic kidney disease:

- **Serious heart problems, such as heart attack or heart failure, and stroke.** You may die sooner if you are treated with Epogen to increase red blood cells (RBCs) to near the same level found in healthy people.
- **Blood clots.** Blood clots may happen at any time while taking Epogen. If you are receiving Epogen for any reason and you are going to have surgery, talk to your healthcare provider about whether or not you need to take a blood thinner to lessen the chance of blood clots during or following surgery. Clots can form in blood vessels (veins), especially in your leg (deep venous thrombosis or DVT). Pieces of a blood clot may travel to the lungs and block the blood circulation in the lungs (pulmonary embolus).
- Call your healthcare provider or get medical help right away if you have any of these symptoms:
  - Chest pain
  - Trouble breathing or shortness of breath
  - Pain in your legs, with or without swelling
  - A cool or pale arm or leg
  - Sudden confusion, trouble speaking, or trouble understanding others' speech
  - Sudden numbness or weakness in your face, arm, or leg, especially on one side of your body
  - Sudden trouble seeing
  - Sudden trouble walking, dizziness, loss of balance or coordination
  - Loss of consciousness (fainting)
  - Hemodialysis vascular access stops working

See **"What are the possible side effects of Epogen?"** below for more information.

If you decide to take Epogen, your healthcare provider should prescribe the smallest dose of Epogen that is necessary to reduce your chance of needing RBC transfusions.

What is Epogen?

Epogen is a prescription medicine used to treat anemia. People with anemia have a lower-than-normal number of RBCs. Epogen works like the human protein called erythropoietin to help your body make more RBCs. Epogen is used to reduce or avoid the need for RBC transfusions.

Epogen may be used to treat anemia if it is caused by:

- Chronic kidney disease (you may or may not be on dialysis).
- Chemotherapy that will be used for at least two months after starting Epogen.
- A medicine called zidovudine (AZT) used to treat HIV infection.

Epogen may also be used to reduce the chance you will need RBC transfusions if you are scheduled for certain surgeries where a lot of blood loss is expected.

If your hemoglobin level stays too high or if your hemoglobin goes up too quickly, this may lead to serious health problems which may result in death. These serious health problems may happen if you take Epogen, even if you do not have an increase in your hemoglobin level.

Epogen should not be used for treatment of anemia:

- If you have cancer and you will not be receiving chemotherapy that may cause anemia.
- If you have a cancer that has a high chance of being cured. Talk with your healthcare provider about the kind of cancer you have.
- If your anemia caused by chemotherapy treatment can be managed by RBC transfusion.
- In place of emergency treatment for anemia (RBC transfusions).

Epogen has not been proven to improve quality of life, fatigue, or well-being.

Epogen should not be used to reduce the chance of RBC transfusions if:

- You are scheduled for surgery on your heart or blood vessels.
- You are able and willing to donate blood prior to surgery.

Who should not take Epogen?

Do not take Epogen if you:

- Have cancer and have not been counseled by your healthcare provider about treatment with Epogen.
- Have high blood pressure that is not controlled (uncontrolled hypertension).
- Have been told by your healthcare provider that you have or have ever had a type of anemia called Pure Red Cell Aplasia (PRCA) that starts after treatment with Epogen or other erythropoietin protein medicines.
- Have had a serious allergic reaction to Epogen.

Do not give Epogen from multiple-dose vials to:

- Pregnant or breastfeeding women
- Babies

What should I tell my healthcare provider before taking Epogen?

Epogen may not be right for you. **Tell your healthcare provider about all your health conditions,** including if you:

- Have heart disease.
- Have high blood pressure.
- Have had a seizure (convulsion) or stroke.
- Have any other medical conditions.
- Are pregnant or planning to become pregnant. It is not known if Epogen may harm your unborn baby. Talk to your healthcare provider about possible pregnancy and birth control choices that are right for you.

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If you are pregnant, discuss with your healthcare provider about enrolling in Amgen's Pregnancy Surveillance Program or call 1-800-772-6436 (1-800-77-AMGEN).

- Are breastfeeding or planning to breastfeed. It is not known if Epogen passes into breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of your medicines with you and show it to your healthcare provider when you get a new medicine.

How should I take Epogen?

- If you or your caregiver has been trained to give Epogen shots (injections) at home:
  - Be sure that you read, understand, and follow the "Instructions for Use" that come with Epogen.
  - Take Epogen exactly as your healthcare provider tells you to. Do not change the dose of Epogen unless told to do so by your healthcare provider.
  - Your healthcare provider will show you how much Epogen to use, how to inject it, how often it should be injected, and how to safely throw away the used vials, syringes, and needles.
  - If you miss a dose of Epogen, call your healthcare provider right away and ask what to do.
  - If you take more than the prescribed amount of Epogen, call your healthcare provider right away.
- During treatment with Epogen, continue to follow your healthcare provider's instructions for diet and medicines.
- Have your blood pressure checked as instructed by your healthcare provider.

What are the possible side effects of Epogen?

Epogen may cause serious side effects.

- See **"What is the most important information I should know about Epogen?"**

- **High blood pressure.** High blood pressure is a common side effect of Epogen in patients with chronic kidney disease. Your blood pressure may go up or be difficult to control with blood pressure medicine while taking Epogen. This can happen even if you have never had high blood pressure before. Your healthcare provider should check your blood pressure often. If your blood pressure does go up, your healthcare provider may prescribe new or more blood pressure medicine.

- **Seizures.** If you have any seizures while taking Epogen, get medical help right away and tell your healthcare provider.

- **Antibodies to Epogen.** Your body may make antibodies to Epogen. These antibodies can block or lessen your body's ability to make RBCs and cause you to have severe anemia. Call your healthcare provider if you have unusual tiredness, lack of energy, dizziness, or fainting. You may need to stop taking Epogen.

- **Serious allergic reactions.** Serious allergic reactions can cause a rash over your whole body, shortness of breath, wheezing, dizziness and fainting because of a drop in blood pressure, swelling around your mouth or eyes, fast pulse, or sweating. If you have a serious allergic reaction, stop using Epogen and call your healthcare provider or get medical help right away.

- **Dangers of using Epogen from multiple-dose vials in newborns, infants, and pregnant or breastfeeding women.** Do not use Epogen from multiple-dose vials in newborns, infants, pregnant or breastfeeding women because the Epogen in these vials contains benzyl alcohol. Benzyl alcohol has been shown to cause brain damage, other serious side effects, and death in newborn and premature babies. Epogen that comes in single-dose vials does not contain benzyl alcohol. **See "Who should not take Epogen?"**

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Common side effects of Epogen include:

- joint, muscle, or bone pain
- fever
- cough
- rash
- nausea
- vomiting
- soreness of mouth
- itching
- headache
- redness and pain in the skin where Epogen shots were given

These are not all of the possible side effects of Epogen. Your healthcare provider can give you a more complete list. Tell your healthcare provider about any side effects that bother you or that do not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Epogen?

- Do not shake Epogen.
- Protect Epogen from light.
- Store Epogen in the refrigerator between 36°F to 46°F (2°C to 8°C).
- **Do not freeze Epogen.** Do not use Epogen that has been frozen.
- Throw away multiple-dose vials of Epogen no later than 21 days from the first day that you put a needle into the vial.
- Single-dose vials of Epogen should be used only one time. Throw the vial away after use even if there is medicine left in the vial.

Keep Epogen and all medicines out of the reach of children.

General information about Epogen

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Use Epogen only for the condition for which it has been prescribed. Do not give Epogen to other patients even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Epogen. If you would like more information about Epogen, talk to your healthcare provider. You can ask your healthcare provider or pharmacist for information about Epogen that is written for healthcare professionals. For more information, go to the following website: www.epogen.com or call 1-800-77-AMGEN.

What are the ingredients in Epogen?

Active Ingredient: epoetin alfa

Inactive Ingredients:
- Multiple-dose vials contain benzyl alcohol.
- All vials contain albumin (human), sodium citrate, sodium chloride, and citric acid.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Manufactured by:

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Reference ID: 4083860

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROCRIT safely and effectively. See full prescribing information for PROCRIT.

PROCRIT® (epoetin alfa)
Injection, for intravenous or subcutaneous use
Initial U.S. Approval: 1989

WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE
See full prescribing information for complete boxed warning.

Chronic Kidney Disease:
- **In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL (5.1).**
- **No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.**
- **Use the lowest PROCRIT dose sufficient to reduce the need for red blood cell (RBC) transfusions (5.1).**

Cancer:
- **ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers (5.2).**
- **Use the lowest dose to avoid RBC transfusions (2.4).**
- **Use ESAs only for anemia from myelosuppressive chemotherapy (1.3).**
- **ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure (1.5).**
- **Discontinue following the completion of a chemotherapy course (2.4).**

Perisurgery:
- **Due to increased risk of deep venous thrombosis (DVT), DVT prophylaxis is recommended (5.1).**

----------RECENT MAJOR CHANGES----------
Indications and Usage, Limitations of Use (1.5) 04/2017
Warnings and Precautions, Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients With Cancer (5.2) 04/2017

----------INDICATIONS AND USAGE----------
PROCRIT is an erythropoiesis-stimulating agent (ESA) indicated for:
- Treatment of anemia due to
  - Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis (1.1).
  - Zidovudine in HIV-infected patients (1.2).
  - The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy (1.3).
- Reduction of allogeneic RBC transfusions in patients undergoing elective, noncardiac, nonvascular surgery (1.4).

Limitations of Use
PROCRIT has not been shown to improve quality of life, fatigue, or patient well-being (1.5).

PROCRIT is not indicated for use:
- In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy (1.5).
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure (1.5).
- In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion (1.5).
- In patients scheduled for surgery who are willing to donate autologous blood (1.5).
- In patients undergoing cardiac or vascular surgery (1.5).
- As a substitute for RBC transfusions in patients who require immediate correction of anemia (1.5).

----------DOSAGE AND ADMINISTRATION----------
- CKD Patients: Initial dose: 50 to 100 Units/kg 3 times weekly (adults) and 50 Units/kg 3 times weekly (children on dialysis). Individualize maintenance dose. Intravenous route recommended for patients on hemodialysis (2.2).
- Zidovudine-treated HIV-infected Patients: 100 Units/kg 3 times weekly (2.3).
- Cancer Patients on Chemotherapy: 40,000 Units weekly or 150 Units/kg 3 times weekly (adults); 600 Units/kg intravenously weekly (children ≥ 5 years) (2.4).
- Surgery Patients: 300 Units/kg per day daily for 15 days or 600 Units/kg weekly (2.5).

----------DOSAGE FORMS AND STRENGTHS----------
- Single-dose vial: 2000, 3000, 4000, 10,000, and 40,000 Units/1 mL (3)
- Multiple-dose vial containing benzyl alcohol: 20,000 Units/2 mL and 20,000 Units/1 mL (3)

----------CONTRAINDICATIONS ----------
- Uncontrolled hypertension (5.3)
- Pure red cell aplasia (PRCA) that begins after treatment with PROCRIT or other erythropoietin protein drugs (5.6)
- Serious allergic reactions to PROCRIT (5.7)
- Use of the multiple-dose vials in neonates, infants, pregnant women, and nursing mothers (8.1, 8.3, 8.4)

----------WARNINGS AND PRECAUTIONS----------
- Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism: Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit (5.1 and 14.1). Use caution in patients with coexistent cardiovascular disease and stroke (5.1).
- Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients With Cancer (5.2).
- Hypertension: Control hypertension prior to initiating and during treatment with PROCRIT (5.3).
- Seizures: PROCRIT increases the risk for seizures in patients with CKD (5.4). Increase monitoring of these patients for changes in seizure frequency or premonitory symptoms (5.4).
- PRCA: If severe anemia and low reticulocyte count develop during PROCRIT treatment, withhold PROCRIT and evaluate for PRCA (5.6).

----------ADVERSE REACTIONS----------
- Patients with CKD: Adverse reactions in ≥ 5% of PROCRIT-treated patients in clinical studies were hypertension, arthralgia, muscle spasm, pyrexia, dizziness, medical device malfunction, vascular occlusion, and upper respiratory tract infection (6.1).
- Zidovudine-treated HIV-infected Patients: Adverse reactions in ≥ 5% of PROCRIT-treated patients in clinical studies were pyrexia, cough, rash, and injection site irritation (6.1).
- Cancer Patients on Chemotherapy: Adverse reactions in ≥ 5% of PROCRIT-treated patients in clinical studies were nausea, vomiting, myalgia, arthralgia, stomatitis, cough, weight decrease, leukopenia, bone pain, rash, hyperglycemia, insomnia, headache, depression, dysphagia, hypokalemia, and thrombosis (6.1).
- Surgery Patients: Adverse reactions in ≥ 5% of PROCRIT-treated patients in clinical studies were nausea, vomiting, pruritus, headache, injection site pain, chills, deep vein thrombosis, cough, and hypertension (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Products, LP at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy, nursing mothers, neonates, and infants: Use single-dose vials only and do not mix with benzyl alcohol. Based on animal data, PROCRIT may cause fetal harm (8.1, 8.3, and 8.4).
- Pediatric Use: Safety and effectiveness have not been established in CKD patients undergoing dialysis who are less than 1 month old, pediatric patients with cancer less than 5 years old, pediatric patients with CKD not on dialysis, and pediatric patients with HIV infection (8.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE

Chronic Kidney Disease:

- **In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL *[see Warnings and Precautions (5.1)]*.**
- **No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.**
- **Use the lowest PROCRIT dose sufficient to reduce the need for red blood cell (RBC) transfusions *[see Warnings and Precautions (5.1)]*.**

Cancer:

- **ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers *[see Warnings and Precautions (5.2)]*.**
- **To decrease these risks, as well as the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid RBC transfusions *[see Dosage and Administration (2.4)]*.**
- **Use ESAs only for anemia from myelosuppressive chemotherapy *[see Indications and Usage (1.3)]*.**
- **ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure *[see Indications and Usage (1.5)]*.**
- **Discontinue following the completion of a chemotherapy course *[see Dosage and Administration (2.4)]*.**

Perisurgery:

- **Due to increased risk of Deep Venous Thrombosis (DVT), DVT prophylaxis is recommended *[see Dosage and Administration (2.5), Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

1.1 Anemia Due to Chronic Kidney Disease

PROCRIT is indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion.

1.2 Anemia Due to Zidovudine in HIV-infected Patients

PROCRIT is indicated for the treatment of anemia due to zidovudine administered at ≤ 4200 mg/week in HIV-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL.

1.3 Anemia Due to Chemotherapy in Patients With Cancer

PROCRIT is indicated for the 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 two additional months of planned chemotherapy.

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1.4 Reduction of Allogeneic Red Blood Cell Transfusions in Patients Undergoing Elective, Noncardiac, Nonvascular Surgery

PROCRIT is indicated to 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. PROCRIT is not indicated for patients who are willing to donate autologous blood pre-operatively.

1.5 Limitations of Use

PROCRIT has not been shown to improve quality of life, fatigue, or patient well-being.

PROCRIT is 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.
- In patients scheduled for surgery who are willing to donate autologous blood.
- In patients undergoing cardiac or vascular surgery.
- As a substitute for RBC transfusions in patients who require immediate correction of anemia.

2 DOSAGE AND ADMINISTRATION

2.1 Evaluation of Iron Stores and Nutritional Factors

Evaluate the iron status in all patients before and during treatment and maintain iron repletion. Correct or exclude other causes of anemia (e.g., vitamin deficiency, metabolic or chronic inflammatory conditions, bleeding, etc.) before initiating PROCRIT *[see Warnings and Precautions (5.10)]*.

2.2 Patients with Chronic Kidney Disease

In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL. No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks. Individualize dosing and use the lowest dose of PROCRIT sufficient to reduce the need for RBC transfusions *[see Warnings and Precautions (5.1)]*. Physicians and patients should weigh the possible benefits of decreasing transfusions against the increased risks of death and other serious cardiovascular adverse events *[see Boxed Warning and Clinical Studies (14)]*.

<u>For all patients with CKD:</u>

When initiating or adjusting therapy, monitor hemoglobin levels at least weekly until stable, then monitor at least monthly. When adjusting therapy consider hemoglobin rate of rise, rate of decline, ESA responsiveness and hemoglobin variability. A single hemoglobin excursion may not require a dosing change.

- Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently. Avoid frequent dose adjustments.
- If the hemoglobin rises rapidly (e.g., more than 1 g/dL in any 2-week period), reduce the dose of PROCRIT by 25% or more as needed to reduce rapid responses.
- For patients who do not respond adequately, if the hemoglobin has not increased by more than 1 g/dL after 4 weeks of therapy, increase the dose by 25%.

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- For patients who do not respond adequately over a 12-week escalation period, increasing the PROCRIT dose further is unlikely to improve response and may increase risks. Use the lowest dose that will maintain a hemoglobin level sufficient to reduce the need for RBC transfusions. Evaluate other causes of anemia. Discontinue PROCRIT if responsiveness does not improve.

For patients with CKD on dialysis:

- Initiate PROCRIT treatment when the hemoglobin level is less than 10 g/dL.
- If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of PROCRIT.
- The recommended starting dose for adult patients is 50 to 100 Units/kg 3 times weekly intravenously or subcutaneously. For pediatric patients, a starting dose of 50 Units/kg 3 times weekly intravenously or subcutaneously is recommended. The intravenous route is recommended for patients on hemodialysis.

For patients with CKD not on dialysis:

- Consider initiating PROCRIT treatment only when the hemoglobin level is less than 10 g/dL and the following considerations apply:
  - The rate of hemoglobin decline indicates the likelihood of requiring a RBC transfusion and,
  - Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal
- If the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of PROCRIT, and use the lowest dose of PROCRIT sufficient to reduce the need for RBC transfusions.
- The recommended starting dose for adult patients is 50 to 100 Units/kg 3 times weekly intravenously or subcutaneously.

When treating patients who have chronic kidney disease and cancer, physicians should refer to *Warnings and Precautions (5.1 and 5.2).*

Refer patients who self-administer PROCRIT to the Instructions for Use *[see Patient Counseling Information (17)]*.

2.3 Zidovudine-treated HIV-infected Patients

Starting Dose

The recommended starting dose in adults is 100 Units/kg as an intravenous or subcutaneous injection 3 times per week.

Dose Adjustment

- If hemoglobin does not increase after 8 weeks of therapy, increase PROCRIT dose by approximately 50 to 100 Units/kg at 4- to 8-week intervals until hemoglobin reaches a level needed to avoid RBC transfusions or 300 Units/kg.
- Withhold PROCRIT if hemoglobin exceeds 12 g/dL. Resume therapy at a dose 25% below the previous dose when hemoglobin declines to less than 11 g/dL.

Discontinue PROCRIT if an increase in hemoglobin is not achieved at a dose of 300 Units/kg for 8 weeks.

2.4 Patients on Cancer Chemotherapy

Initiate PROCRIT in patients on cancer chemotherapy only if the hemoglobin is less than 10 g/dL, and if there is a minimum of two additional months of planned chemotherapy.

Use the lowest dose of PROCRIT necessary to avoid RBC transfusions.

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Recommended Starting Dose

Adults:

- 150 Units/kg subcutaneously 3 times per week until completion of a chemotherapy course or
- 40,000 Units subcutaneously weekly until completion of a chemotherapy course.

Pediatric Patients (5 to 18 years):

- 600 Units/kg intravenously weekly until completion of a chemotherapy course.

Dose Reduction

Reduce dose by 25% if:

- Hemoglobin increases greater than 1 g/dL in any 2-week period or
- Hemoglobin reaches a level needed to avoid RBC transfusion.

Withhold dose if hemoglobin exceeds a level needed to avoid RBC transfusion. Reinitiate at a dose 25% below the previous dose when hemoglobin approaches a level where RBC transfusions may be required.

Dose Increase

After the initial 4 weeks of PROCRIT therapy, if hemoglobin increases by less than 1 g/dL and remains below 10 g/dL, increase dose to:

- 300 Units/kg three times per week in adults or
- 60,000 Units weekly in adults
- 900 Units/kg (maximum 60,000 Units) weekly in children

After 8 weeks of therapy, if there is no response as measured by hemoglobin levels or if RBC transfusions are still required, discontinue PROCRIT.

2.5 Surgery Patients

The recommended PROCRIT regimens are:

- 300 Units/kg per day subcutaneously for 15 days total: administered daily for 10 days before surgery, on the day of surgery, and for 4 days after surgery.
- 600 Units/kg subcutaneously in 4 doses administered 21, 14, and 7 days before surgery and on the day of surgery.

Deep venous thrombosis prophylaxis is recommended during PROCRIT therapy *[see Warnings and Precautions (5.1)]*.

2.6 Preparation and Administration

- Do not shake. Do not use PROCRIT that has been shaken or frozen.
- Protect vials from light.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.
- Discard unused portions of PROCRIT in preservative-free vials. Do not re-enter preservative-free vials.
- Store unused portions of PROCRIT in multiple-dose vials at 36°F to 46°F (2°C to 8°C). Discard 21 days after initial entry.
- Do not dilute. Do not mix with other drug solutions except for admixing as described below:

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- Preservative-free PROCRIT from single-dose vials may be admixed in a syringe with bacteriostatic 0.9% sodium chloride injection, USP, with benzyl alcohol 0.9% (bacteriostatic saline) in a 1:1 ratio using aseptic technique at the time of administration. Risks are associated with benzyl alcohol in neonates, infants, pregnant women, and nursing mothers *[see Use in Specific Populations (8.1, 8.3, 8.4)]*.

3 DOSAGE FORMS AND STRENGTHS

Single-dose vials: 2000, 3000, 4000, 10,000, and 40,000 Units PROCRIT /1 mL

Multiple-dose vials (contains benzyl alcohol): 20,000 Units PROCRIT /2 mL and 20,000 Units PROCRIT /1 mL

4 CONTRAINDICATIONS

PROCRIT is contraindicated in patients with:

- Uncontrolled hypertension *[see Warnings and Precautions (5.3)]*
- Pure red cell aplasia (PRCA) that begins after treatment with PROCRIT or other erythropoietin protein drugs *[see Warnings and Precautions (5.6)]*
- Serious allergic reactions to PROCRIT *[see Warnings and Precautions (5.7)]*

PROCRIT from multiple-dose vials contains benzyl alcohol and is contraindicated in:

- Neonates, infants, pregnant women, and nursing mothers. Benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients. When therapy with PROCRIT is needed in neonates and infants, use single-dose vials; do not admix with bacteriostatic saline containing benzyl alcohol *[see Use in Specific Populations (8.1, 8.3, 8.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism

- In controlled clinical trials of patients with CKD comparing higher hemoglobin targets (13 - 14 g/dL) to lower targets (9 - 11.3 g/dL), PROCRIT and other ESAs increased the risk of death, myocardial infarction, stroke, congestive heart failure, thrombosis of hemodialysis vascular access, and other thromboembolic events in the higher target groups.
- Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit *[see Clinical Studies (14.1)]*. Use caution in patients with coexistent cardiovascular disease and stroke *[see Dosage and Administration (2.2)]*. Patients with CKD and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular reactions and mortality than other patients. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may contribute to these risks.
- In controlled clinical trials of patients with cancer, PROCRIT and other ESAs increased the risks for death and serious adverse cardiovascular reactions. These adverse reactions included myocardial infarction and stroke.
- In controlled 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.

The design and overall results of the 3 large trials comparing higher and lower hemoglobin targets are shown in Table 1.

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Table 1: Randomized Controlled Trials Showing Adverse Cardiovascular Outcomes in Patients With CKD

	Normal Hematocrit Study (NHS) (N=1265)	**CHOIR (N=1432)**	**TREAT (N=4038)**
Time Period of Trial	1993 to 1996	2003 to 2006	2004 to 2009
Population	CKD patients on hemodialysis with coexisting CHF or CAD, hematocrit 30 ± 3% on epoetin alfa	CKD patients not on dialysis with hemoglobin < 11 g/dL not previously administered epoetin alfa	CKD patients not on dialysis with type II diabetes, hemoglobin ≤ 11 g/dL
Hemoglobin Target; Higher vs. Lower (g/dL)	14.0 vs. 10.0	13.5 vs. 11.3	13.0 vs. ≥ 9.0
Median (Q1, Q3) Achieved Hemoglobin level (g/dL)	12.6 (11.6, 13.3) vs. 10.3 (10.0, 10.7)	13.0 (12.2, 13.4) vs. 11.4 (11.1, 11.6)	12.5 (12.0, 12.8) vs. 10.6 (9.9, 11.3)
Primary Endpoint	All-cause mortality or non-fatal MI	All-cause mortality, MI, hospitalization for CHF, or stroke	All-cause mortality, MI, myocardial ischemia, heart failure, and stroke
Hazard Ratio or Relative Risk (95% CI)	1.28 (1.06 - 1.56)	1.34 (1.03 - 1.74)	1.05 (0.94 - 1.17)
Adverse Outcome for Higher Target Group	All-cause mortality	All-cause mortality	Stroke
Hazard Ratio or Relative Risk (95% CI)	1.27 (1.04 - 1.54)	1.48 (0.97 - 2.27)	1.92 (1.38 - 2.68)

Patients with Chronic Kidney Disease

Normal Hematocrit Study (NHS): A prospective, randomized, open-label study of 1265 patients with chronic kidney disease on dialysis with documented evidence of congestive heart failure or ischemic heart disease was designed to test the hypothesis that a higher target hematocrit (Hct) would result in improved outcomes compared with a lower target Hct. In this study, patients were randomized to epoetin alfa treatment targeted to a maintenance hemoglobin of either 14 ± 1 g/dL or 10 ± 1 g/dL. The trial was terminated early with adverse safety findings of higher mortality in the high hematocrit target group. Higher mortality (35% vs. 29%) was observed for the patients randomized to a target hemoglobin of 14 g/dL than for the patients randomized to a target hemoglobin of 10 g/dL. For all-cause mortality, the HR=1.27; 95% CI (1.04, 1.54); p=0.018. The incidence of nonfatal myocardial infarction, vascular access thrombosis, and other thrombotic events was also higher in the group randomized to a target hemoglobin of 14 g/dL.

CHOIR: A randomized, prospective trial, 1432 patients with anemia due to CKD who were not undergoing dialysis and who had not previously received epoetin alfa therapy were randomized to epoetin alfa treatment targeting a maintenance hemoglobin concentration of either 13.5 g/dL or 11.3 g/dL. The trial was terminated early with adverse safety findings. A major cardiovascular event (death, myocardial infarction, stroke, or hospitalization for congestive heart failure) occurred in 125 of the 715 patients (18%) in the higher hemoglobin group compared to 97 of the 717 patients (14%) in the lower hemoglobin group [hazard ratio (HR) 1.34, 95% CI: 1.03, 1.74; p=0.03].

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TREAT: A randomized, double-blind, placebo-controlled, prospective trial of 4038 patients with: CKD not on dialysis (eGFR of 20 – 60 mL/min), anemia (hemoglobin levels ≤ 11 g/dL), and type 2 diabetes mellitus, patients were randomized to receive either darbepoetin alfa treatment or a matching placebo. Placebo group patients also received darbepoetin alfa when their hemoglobin levels were below 9 g/dL. The trial objectives were to demonstrate the benefit of darbepoetin alfa treatment of the anemia to a target hemoglobin level of 13 g/dL, when compared to a "placebo" group, by reducing the occurrence of either of two primary endpoints: (1) a composite cardiovascular endpoint of all-cause mortality or a specified cardiovascular event (myocardial ischemia, CHF, MI, and CVA) or (2) a composite renal endpoint of all-cause mortality or progression to end stage renal disease. The overall risks for each of the two primary endpoints (the cardiovascular composite and the renal composite) were not reduced with darbepoetin alfa treatment (see Table 1), but the risk of stroke was increased nearly two-fold in the darbepoetin alfa -treated group versus the placebo group: annualized stroke rate 2.1% vs. 1.1%, respectively, HR 1.92; 95% CI: 1.38, 2.68; $p < 0.001$. The relative risk of stroke was particularly high in patients with a prior stroke: annualized stroke rate 5.2% in the darbepoetin alfa-treated group and 1.9% in the placebo group, HR 3.07; 95% CI: 1.44, 6.54. Also, among darbepoetin alfa-treated subjects with a past history of cancer, there were more deaths due to all causes and more deaths adjudicated as due to cancer, in comparison with the control group.

Patients with Cancer

An increased incidence of thromboembolic reactions, some serious and life-threatening, occurred in patients with cancer treated with ESAs.

In a randomized, placebo-controlled study (Study 2 in Table 2 *[see Warnings and Precautions (5.2)]*) of 939 women with metastatic breast cancer receiving chemotherapy, patients received either weekly epoetin alfa or placebo for up to a year. This study was designed to show that survival was superior when epoetin alfa was administered to prevent anemia (maintain hemoglobin levels between 12 and 14 g/dL or hematocrit between 36% and 42%). This study was terminated prematurely when interim results demonstrated a higher mortality at 4 months (8.7% vs. 3.4%) and a higher rate of fatal thrombotic reactions (1.1% vs. 0.2%) in the first 4 months of the study among patients treated with epoetin alfa. Based on Kaplan-Meier estimates, at the time of study termination, the 12-month survival was lower in the epoetin alfa group than in the placebo group (70% vs. 76%; HR 1.37, 95% CI: 1.07, 1.75; p=0.012).

Patients Having Surgery

An increased incidence of deep venous thrombosis (DVT) in patients receiving epoetin alfa undergoing surgical orthopedic procedures was demonstrated *[see Adverse Reactions (6.1)]*. In a randomized, controlled study, 680 adult patients, not receiving prophylactic anticoagulation and undergoing spinal surgery, were randomized to 4 doses of 600 Units/kg epoetin alfa (7, 14, and 21 days before surgery, and the day of surgery) and standard of care (SOC) treatment (n=340) or to SOC treatment alone (n=340). A higher incidence of DVTs, determined by either color flow duplex imaging or by clinical symptoms, was observed in the epoetin alfa group (16 [4.7%] patients) compared with the SOC group (7 [2.1%] patients). In addition to the 23 patients with DVTs included in the primary analysis, 19 [2.8%] patients (n=680) experienced 1 other thrombovascular event (TVE) each (12 [3.5%] in the epoetin alfa group and 7 [2.1%] in the SOC group). Deep venous thrombosis prophylaxis is strongly recommended when ESAs are used for the reduction of allogeneic RBC transfusions in surgical patients *[see Dosage and Administration (2.5)]*.

Increased mortality was observed in a randomized, placebo-controlled study of PROCRIT in adult patients who were undergoing CABG surgery (7 deaths in 126 patients randomized to PROCRIT 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.

5.2 Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients With Cancer

ESAs resulted in decreased locoregional control/progression-free survival (PFS) and/or overall survival (OS) (see Table 2). Adverse effects on PFS and/or OS were observed in studies of patients receiving chemotherapy for breast cancer (Studies 1, 2, and 4), lymphoid malignancy (Study 3), and cervical cancer (Study 5); in patients with

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advanced head and neck cancer receiving radiation therapy (Studies 6 and 7); and in patients with non-small cell lung cancer or various malignancies who were not receiving chemotherapy or radiotherapy (Studies 8 and 9).

Table 2: Randomized, Controlled Studies With Decreased Survival and/or Decreased Locoregional Control

Study/Tumor/(n)	Hemoglobin Target	Achieved Hemoglobin (Median; Q1, Q3*)	Primary Efficacy Outcome	Adverse Outcome for ESA-containing Arm
Chemotherapy				
Study 1 Metastatic breast cancer (n=2098)	≤12 g/dL†	11.6 g/dL 10.7, 12.1 g/dL	Progression-free survival (PFS)	Decreased progression-free and overall survival
Study 2 Metastatic breast cancer (n=939)	12-14 g/dL	12.9 g/dL; 12.2, 13.3 g/dL	12-month overall survival	Decreased 12-month survival
Study 3 Lymphoid malignancy (n=344)	13-15 g/dL (M) 13-14 g/dL (F)	11 g/dL; 9.8, 12.1 g/dL	Proportion of patients achieving a hemoglobin response	Decreased overall survival
Study 4 Early breast cancer (n=733)	12.5-13 g/dL	13.1 g/dL; 12.5, 13.7 g/dL	Relapse-free and overall survival	Decreased 3-year relapse-free and overall survival
Study 5 Cervical cancer (n=114)	12-14 g/dL	12.7 g/dL; 12.1, 13.3 g/dL	Progression-free and overall survival and locoregional control	Decreased 3-year progression-free and overall survival and locoregional control
Radiotherapy Alone				
Study 6 Head and neck cancer (n=351)	≥ 15 g/dL (M) ≥ 14 g/dL (F)	Not available	Locoregional progression-free survival	Decreased 5-year locoregional progression-free and overall survival
Study 7 Head and neck cancer (n=522)	14-15.5 g/dL	Not available	Locoregional disease control	Decreased locoregional disease control
No Chemotherapy or Radiotherapy				
Study 8 Non-small cell lung cancer (n=70)	12-14 g/dL	Not available	Quality of life	Decreased overall survival
Study 9 Non-myeloid malignancy (n=989)	12-13 g/dL	10.6 g/dL; 9.4, 11.8 g/dL	RBC transfusions	Decreased overall survival

*Q1=25th percentile
Q3=75th percentile
†This study did not include a defined hemoglobin target. Doses were titrated to achieve and maintain the lowest hemoglobin level sufficient to avoid transfusion and not to exceed 12 g/dL.

Decreased Overall Survival

Study 2 was described in the previous section *[see Warnings and Precautions (5.1)]*. Mortality at 4 months (8.7% vs. 3.4%) was significantly higher in the epoetin alfa arm. The most common investigator-attributed cause of death within the first 4 months was disease progression; 28 of 41 deaths in the epoetin alfa arm and 13 of 16 deaths in the

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placebo arm were attributed to disease progression. Investigator-assessed time to tumor progression was not different between the 2 groups. Survival at 12 months was significantly lower in the epoetin alfa arm (70% vs. 76%; HR 1.37, 95% CI: 1.07, 1.75; p=0.012).

Study 3 was a randomized, double-blind study (darbepoetin alfa vs. placebo) conducted in 344 anemic patients with lymphoid malignancy receiving chemotherapy. With a median follow-up of 29 months, overall mortality rates were significantly higher among patients randomized to darbepoetin alfa as compared to placebo (HR 1.36, 95% CI: 1.02, 1.82).

Study 8 was a multicenter, randomized, double-blind study (epoetin alfa vs. placebo) in which patients with advanced non-small cell lung cancer receiving only palliative radiotherapy or no active therapy were treated with epoetin alfa to achieve and maintain hemoglobin levels between 12 and 14 g/dL. Following an interim analysis of 70 patients (planned accrual 300 patients), a significant difference in survival in favor of the patients in the placebo arm of the study was observed (median survival 63 vs. 129 days; HR 1.84; p=0.04).

Study 9 was a randomized, double-blind study (darbepoetin alfa vs. placebo) in 989 anemic patients with active malignant disease, neither receiving nor planning to receive chemotherapy or radiation therapy. There was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions. The median survival was shorter in the darbepoetin alfa treatment group than in the placebo group (8 months vs. 10.8 months; HR 1.30, 95% CI: 1.07, 1.57).

Decreased Progression-free Survival and Overall Survival

Study 1 was a randomized, open label, multicenter study in 2,098 anemic women with metastatic breast cancer, who received first line or second line chemotherapy. This was a non-inferiority study designed to rule out a 15% risk increase in tumor progression or death of epoetin alfa plus standard of care (SOC) as compared with SOC alone. The median progression free survival (PFS) per investigator assessment of disease progression was 7.4 months in each arm (HR 1.09, 95% CI: 0.99, 1.20), indicating the study objective was not met. At the time of clinical data cutoff, 1337 deaths were reported. Median overall survival in the epoetin alfa plus SOC group was 17.2 months compared with 17.4 months in the SOC alone group (HR 1.06, 95% CI: 0.95, 1.18). There were more deaths from disease progression in the epoetin alfa plus SOC arm (59% vs. 56%) and more thrombotic vascular events in the epoetin alfa plus SOC arm (3% vs. 1%).

Study 4 was a randomized, open-label, controlled, factorial design study in which darbepoetin alfa was administered to prevent anemia in 733 women receiving neo-adjuvant breast cancer treatment. A final analysis was performed after a median follow-up of approximately 3 years. The 3-year survival rate was lower (86% vs. 90%; HR 1.42, 95% CI: 0.93, 2.18) and the 3-year relapse-free survival rate was lower (72% vs. 78%; HR 1.33, 95% CI: 0.99, 1.79) in the darbepoetin alfa-treated arm compared to the control arm.

Study 5 was a randomized, open-label, controlled study that enrolled 114 of a planned 460 cervical cancer patients receiving chemotherapy and radiotherapy. Patients were randomized to receive epoetin alfa to maintain hemoglobin between 12 and 14 g/dL or to RBC transfusion support as needed. The study was terminated prematurely due to an increase in thromboembolic adverse reactions in epoetin alfa-treated patients compared to control (19% vs. 9%). Both local recurrence (21% vs. 20%) and distant recurrence (12% vs. 7%) were more frequent in epoetin alfa-treated patients compared to control. Progression-free survival at 3 years was lower in the epoetin alfa-treated group compared to control (59% vs. 62%; HR 1.06, 95% CI: 0.58, 1.91). Overall survival at 3 years was lower in the epoetin alfa-treated group compared to control (61% vs. 71%; HR 1.28, 95% CI: 0.68, 2.42).

Study 6 was a randomized, placebo-controlled study in 351 head and neck cancer patients where epoetin beta or placebo was administered to achieve target hemoglobins ≥ 14 and ≥ 15 g/dL for women and men, respectively. Locoregional progression-free survival was significantly shorter in patients receiving epoetin beta (HR 1.62, 95% CI: 1.22, 2.14; p=0.0008) with medians of 406 days and 745 days in the epoetin beta and placebo arms, respectively. Overall survival was significantly shorter in patients receiving epoetin beta (HR 1.39, 95% CI: 1.05, 1.84; p=0.02).

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Decreased Locoregional Control

Study 7 was a randomized, open-label, controlled study conducted in 522 patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy alone (no chemotherapy) who were randomized to receive darbepoetin alfa to maintain hemoglobin levels of 14 to15.5 g/dL or no darbepoetin alfa. An interim analysis performed on 484 patients demonstrated that locoregional control at 5 years was significantly shorter in patients receiving darbepoetin alfa (RR 1.44, 95% CI: 1.06, 1.96; p=0.02). Overall survival was shorter in patients receiving darbepoetin alfa (RR 1.28, 95% CI: 0.98, 1.68; p=0.08).

5.3 Hypertension

PROCRIT is contraindicated in patients with uncontrolled hypertension. Following initiation and titration of PROCRIT, approximately 25% of patients on dialysis required initiation of or increases in antihypertensive therapy; hypertensive encephalopathy and seizures have been reported in patients with CKD receiving PROCRIT.

Appropriately control hypertension prior to initiation of and during treatment with PROCRIT. Reduce or withhold PROCRIT if blood pressure becomes difficult to control. Advise patients of the importance of compliance with antihypertensive therapy and dietary restrictions *[see Patient Counseling Information (17)]*.

5.4 Seizures

PROCRIT increases the risk of seizures in patients with CKD. During the first several months following initiation of PROCRIT, monitor patients closely for premonitory neurologic symptoms. Advise patients to contact their healthcare practitioner for new-onset seizures, premonitory symptoms or change in seizure frequency.

5.5 Lack or Loss of Hemoglobin Response to PROCRIT

For lack or loss of hemoglobin response to PROCRIT, initiate a search for causative factors (e.g., iron deficiency, infection, inflammation, bleeding). If typical causes of lack or loss of hemoglobin response are excluded, evaluate for PRCA *[see Warnings and Precautions (5.6)]*. In the absence of PRCA, follow dosing recommendations for management of patients with an insufficient hemoglobin response to PROCRIT therapy *[see Dosage and Administration (2.2)]*.

5.6 Pure Red Cell Aplasia

Cases of PRCA and of severe anemia, with or without other cytopenias that arise following the development of neutralizing antibodies to erythropoietin have been reported in patients treated with PROCRIT. This has been reported predominantly in patients with CKD receiving ESAs by subcutaneous administration. PRCA has also been reported in patients receiving ESAs for anemia related to hepatitis C treatment (an indication for which PROCRIT is not approved).

If severe anemia and low reticulocyte count develop during treatment with PROCRIT, withhold PROCRIT and evaluate patients for neutralizing antibodies to erythropoietin. Contact Janssen Products, LP at 1-800-JANSSEN (1-800-526-7736) to perform assays for binding and neutralizing antibodies. Permanently discontinue PROCRIT in patients who develop PRCA following treatment with PROCRIT or other erythropoietin protein drugs. Do not switch patients to other ESAs.

5.7 Serious Allergic Reactions

Serious allergic reactions, including anaphylactic reactions, angioedema, bronchospasm, skin rash, and urticaria may occur with PROCRIT. Immediately and permanently discontinue PROCRIT and administer appropriate therapy if a serious allergic or anaphylactic reaction occurs.

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5.8 Albumin (Human)

PROCRIT contains albumin, a derivative of human blood *[see Description (11)]*. 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.

5.9 Dialysis Management

Patients may require adjustments in their dialysis prescriptions after initiation of PROCRIT. Patients receiving PROCRIT may require increased anticoagulation with heparin to prevent clotting of the extracorporeal circuit during hemodialysis.

5.10 Laboratory Monitoring

Evaluate transferrin saturation and serum ferritin prior to and during PROCRIT treatment. Administer supplemental iron therapy when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20% *[see Dosage and Administration (2.1)]*. The majority of patients with CKD will require supplemental iron during the course of ESA therapy. Following initiation of therapy and after each dose adjustment, monitor hemoglobin weekly until the hemoglobin level is stable and sufficient to minimize the need for RBC transfusion.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism *[see Warnings and Precautions (5.1)]*
- Increased mortality and/or increased risk of tumor progression or recurrence in Patients With Cancer *[see Warnings and Precautions (5.2)]*
- Hypertension *[see Warnings and Precautions (5.3)]*
- Seizures *[see Warnings and Precautions (5.4)]*
- PRCA *[see Warnings and Precautions (5.6)]*
- Serious allergic reactions *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.

<u>Patients with Chronic Kidney Disease</u>

Adult Patients

Three double-blind, placebo-controlled studies, including 244 patients with CKD on dialysis, were used to identify the adverse reactions to PROCRIT. In these studies, the mean age of patients was 48 years (range: 20 to 80 years). One hundred and thirty-three (55%) patients were men. The racial distribution was as follows: 177 (73%) patients were white, 48 (20%) patients were black, 4 (2%) patients were Asian, 12 (5%) patients were other, and racial information was missing for 3 (1%) patients.

Two double-blind, placebo-controlled studies, including 210 patients with CKD not on dialysis, were used to identify the adverse reactions to PROCRIT. In these studies, the mean age of patients was 57 years (range: 24 to 79 years). One hundred and twenty-one (58%) patients were men. The racial distribution was as follows: 164 (78%) patients were white, 38 (18%) patients were black, 3 (1%) patients were Asian, 3 (1%) patients were other, and racial information was missing for 2 (1%) patients.

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The adverse reactions with a reported incidence of ≥ 5% in PROCRIT-treated patients and that occurred at a ≥ 1% higher frequency than in placebo-treated patients are shown in the table below:

Table 3: Adverse Reactions in Patients With CKD on Dialysis

Adverse Reaction	PROCRIT-treated Patients (n=148)	Placebo-treated Patients (n=96)
Hypertension	27.7%	12.5%
Arthralgia	16.2%	3.1%
Muscle spasm	7.4%	6.3%
Pyrexia	10.1%	8.3%
Dizziness	9.5%	8.3%
Medical Device Malfunction (artificial kidney clotting during dialysis)	8.1%	4.2%
Vascular Occlusion (vascular access thrombosis)	8.1%	2.1%
Upper respiratory tract infection	6.8%	5.2%

An additional serious adverse reaction that occurred in less than 5% of epoetin alfa-treated dialysis patients and greater than placebo was thrombosis (2.7% PROCRIT and 1% placebo) *[see Warnings and Precautions (5.1)]*.

The adverse reactions with a reported incidence of ≥ 5% in PROCRIT-treated patients and that occurred at a ≥ 1% higher frequency than in placebo-treated patients are shown in the table below:

Table 4: Adverse Reactions in Patients With CKD Not on Dialysis

Adverse Reactions	PROCRIT-treated Patients (n=131)	Placebo-treated Patients (n=79)
Hypertension	13.7%	10.1%
Arthralgia	12.2%	7.6%

Additional serious adverse reactions that occurred in less than 5% of epoetin alfa-treated patients not on dialysis and greater than placebo were erythema (0.8% PROCRIT and 0% placebo) and myocardial infarction (0.8% PROCRIT and 0% placebo) *[see Warnings and Precautions (5.1)]*.

Pediatric Patients

In pediatric patients with CKD on dialysis, the pattern of adverse reactions was similar to that found in adults.

Zidovudine-treated HIV-infected Patients

A total of 297 zidovudine-treated HIV-infected patients were studied in 4 placebo-controlled studies. A total of 144 (48%) patients were randomly assigned to receive PROCRIT and 153 (52%) patients were randomly assigned to receive placebo. PROCRIT was administered at doses between 100 and 200 Units/kg 3 times weekly subcutaneously for up to 12 weeks.

For the combined PROCRIT treatment groups, a total of 141 (98%) men and 3 (2%) women between the ages of 24 and 64 years were enrolled. The racial distribution of the combined PROCRIT treatment groups was as follows: 129 (90%) white, 8 (6%) black, 1 (1%) Asian, and 6 (4%) other.

In double-blind, placebo-controlled studies of 3 months duration involving approximately 300 zidovudine-treated HIV-infected patients, adverse reactions with an incidence of ≥ 1% in patients treated with PROCRIT were:

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Table 5: Adverse Reactions in Zidovudine-treated HIV-infected Patients

Adverse Reaction	PROCRIT (n=144)	Placebo (n=153)
Pyrexia	42%	34%
Cough	26%	14%
Rash	19%	7%
Injection site irritation	7%	4%
Urticaria	3%	1%
Respiratory tract congestion	1%	Not reported
Pulmonary embolism	1%	Not reported

Cancer Patients on Chemotherapy

The data below were obtained in Study C1, a 16-week, double-blind, placebo-controlled study that enrolled 344 patients with anemia secondary to chemotherapy. There were 333 patients who were evaluable for safety; 168 of 174 patients (97%) randomized to PROCRIT received at least 1 dose of study drug, and 165 of 170 patients (97%) randomized to placebo received at least 1 placebo dose. For the once weekly PROCRIT-treatment group, a total of 76 men (45%) and 92 women (55%) between the ages of 20 and 88 years were treated. The racial distribution of the PROCRIT-treatment group was 158 white (94%) and 10 black (6%). PROCRIT was administered once weekly for an average of 13 weeks at a dose of 20,000 to 60,000 IU subcutaneously (mean weekly dose was 49,000 IU).

The adverse reactions with a reported incidence of $\geq$ 5% in PROCRIT-treated patients that occurred at a higher frequency than in placebo-treated patients are shown in the table below:

Table 6: Adverse Reactions in Cancer Patients

Adverse Reaction	PROCRIT (n=168)	Placebo (n=165)
Nausea	35%	30%
Vomiting	20%	16%
Myalgia	10%	5%
Arthralgia	10%	6%
Stomatitis	10%	8%
Cough	9%	7%
Weight decrease	9%	5%
Leukopenia	8%	7%
Bone pain	7%	4%
Rash	7%	5%
Hyperglycemia	6%	4%
Insomnia	6%	2%
Headache	5%	4%
Depression	5%	4%
Dysphagia	5%	2%
Hypokalemia	5%	3%
Thrombosis	5%	3%

Surgery Patients

Four hundred sixty-one patients undergoing major orthopedic surgery were studied in a placebo-controlled study (S1) and a comparative dosing study (2 dosing regimens, S2). A total of 358 patients were randomly assigned to receive PROCRIT and 103 (22%) patients were randomly assigned to receive placebo. PROCRIT was administered daily at a dose of 100 to 300 IU/kg subcutaneously for 15 days or at 600 IU/kg once weekly for 4 weeks.

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For the combined PROCRIT treatment groups, a total of 90 (25%) and 268 (75%) women between the ages of 29 and 89 years were enrolled. The racial distribution of the combined PROCRIT treatment groups was as follows: 288 (80%) white, 64 (18%) black, 1 (< 1%) Asian, and 5 (1%) other.

The adverse reactions with a reported incidence of ≥ 1% in PROCRIT-treated patients that occurred at a higher frequency than in placebo-treated patients are shown in the table below:

Table 7: Adverse Reactions in Surgery Patients

Adverse Reaction	Study S1			Study S2	
	PROCRIT 300 U/kg	PROCRIT 100 U/kg	Placebo	PROCRIT 600 U/kg x 4 weeks	PROCRIT 300 U/kg x 15 days
	(n=112)[a]	(n=101)[a]	(n=103)[a]	(n=73)[b]	(n=72)[b]
Nausea	47%	43%	45%	45%	56%
Vomiting	21%	12%	14%	19%	28%
Pruritus	16%	16%	14%	12%	21%
Headache	13%	11%	9%	10%	18%
Injection site pain	13%	9%	8%	12%	11%
Chills	7%	4%	1%	1%	0%
Deep vein thrombosis	6%	3%	3%	0%[c]	0%[c]
Cough	5%	4%	0%	4%	4%
Hypertension	5%	3%	5%	5%	6%
Rash	2%	2%	1%	3%	3%
Edema	1%	2%	2%	1%	3%

[a]Study included patients undergoing orthopedic surgery treated with PROCRIT or placebo for 15 days.
[b]Study included patients undergoing orthopedic surgery treated with PROCRIT 600 U/kg weekly for 4 weeks or 300 U/kg daily for 15 days.
[c]DVTs were determined by clinical symptoms.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of PROCRIT.
Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Seizures *[see Warnings and Precautions (5.4)]*
- PRCA *[see Warnings and Precautions (5.6)]*
- Serious allergic reactions *[see Warnings and Precautions (5.7)]*
- Injection site reactions, including irritation and pain
- Porphyria

6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Neutralizing antibodies to epoetin alfa that cross-react with endogenous erythropoietin and other ESAs can result in PRCA or severe anemia (with or without other cytopenias) *[see Warnings and Precautions (5.6)]*.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to PROCRIT with the incidence of antibodies to other products may be misleading.

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7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with PROCRIT.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

The multiple-dose vials are formulated with benzyl alcohol. Do not administer PROCRIT from multiple-dose vials, or PROCRIT from single-dose vials admixed with bacteriostatic saline containing benzyl alcohol, to pregnant women. When therapy with PROCRIT is needed during pregnancy, use a benzyl alcohol-free formulation *[see Dosage and Administration (2) and Contraindications (4)]*.

Pregnancy Category C (single-dose vials only)

There are no adequate and well-controlled studies of PROCRIT use during pregnancy. There are limited data on PROCRIT use in pregnant women. In animal reproductive and developmental toxicity studies, adverse fetal effects occurred when pregnant rats received epoetin alfa at doses approximating the clinical recommended starting doses. Single-dose formulations of PROCRIT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There are reports of at least 33 pregnant women with anemia alone or anemia associated with severe renal disease and other hematologic disorders who received PROCRIT. Polyhydramnios and intrauterine growth restriction were reported in women with chronic renal disease, which is associated with an increased risk for these adverse pregnancy outcomes. There was 1 infant born with pectus excavatum and hypospadias following exposure during the first trimester. Due to the limited number of exposed pregnancies and multiple confounding factors (such as underlying maternal conditions, other maternal medications, and gestational timing of exposure), these published case reports and studies do not reliably estimate the frequency or absence of adverse outcomes.

When healthy rats received PROCRIT at doses of 100 Units/kg/day during mating and through early pregnancy (dosing stopped prior to organogenesis), there were slight increases in the incidences of pre- and post-implantation loss, and a decrease in live fetuses. This animal dose level of 100 Units/kg/day may approximate the clinical recommended starting dose, depending on the treatment indication. When healthy pregnant rats and rabbits received intravenous doses of up to 500 mg/kg/day of PROCRIT only during organogenesis, no teratogenic effects were observed in the offspring.

When healthy pregnant rats received PROCRIT at doses of 500 Units/kg/day late in pregnancy (after the period of organogenesis), offspring had decreased number of caudal vertebrae and growth delays *[see Nonclinical Toxicology (13.3)]*.

8.3 Nursing Mothers

The multiple-dose vials of PROCRIT are formulated with benzyl alcohol. Do not administer PROCRIT from multiple-dose vials, or PROCRIT from single-dose vials admixed with bacteriostatic saline containing benzyl alcohol, to a nursing woman. When therapy with PROCRIT is needed in nursing women, use a benzyl alcohol-free formulation *[see Dosage and Administration (2) and Contraindications (4)]*.

It is not known whether PROCRIT is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PROCRIT from single-dose vials is administered to a nursing woman.

8.4 Pediatric Use

The multiple-dose vials are formulated with benzyl alcohol. Do not administer PROCRIT from multiple-dose vials, or PROCRIT from single-dose vials admixed with bacteriostatic saline containing benzyl alcohol, to neonates or

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infants. When therapy with PROCRIT is needed in neonates and infants, use a benzyl alcohol-free formulation *[see Dosage and Administration (2) and Contraindications (4)]*.

Benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients. The "gasping syndrome," (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages > 99 mg/kg/day in neonates and low-birthweight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birthweight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

Pediatric Patients on Dialysis

PROCRIT is indicated in pediatric patients, ages 1 month to 16 years of age, for the treatment of anemia associated with CKD requiring dialysis. Safety and effectiveness in pediatric patients less than 1 month old have not been established *[see Clinical Studies (14.1)]*.

The safety data from these studies are similar to those obtained from the studies of PROCRIT in adult patients with CKD *[see Warnings and Precautions (5) and Adverse Reactions (6.1)]*.

Pediatric Cancer Patients on Chemotherapy

PROCRIT is indicated in patients 5 to 18 years old for the treatment of anemia due to concomitant myelosuppressive chemotherapy. Safety and effectiveness in pediatric patients less than 5 years of age have not been established *[see Clinical Studies (14.3)]*. The safety data from these studies are similar to those obtained from the studies of PROCRIT in adult patients with cancer *[see Warnings and Precautions (5) and Adverse Reactions (6.1)]*.

Pediatric Patients With HIV Infection Receiving Zidovudine

Published literature has reported the use of PROCRIT in 20 zidovudine-treated, anemic, pediatric patients with HIV infection, ages 8 months to 17 years, treated with 50 to 400 Units/kg subcutaneously or intravenously 2 to 3 times per week. Increases in hemoglobin levels and in reticulocyte counts and decreases in or elimination of RBC transfusions were observed.

Pharmacokinetics in Neonates

Limited pharmacokinetic data from a study of 7 preterm, very low birth weight neonates and 10 healthy adults given intravenous erythropoietin suggested that distribution volume was approximately 1.5 to 2 times higher in the preterm neonates than in the healthy adults, and clearance was approximately 3 times higher in the preterm neonates than in the healthy adults.

8.5 Geriatric Use

Of the 4553 patients who received PROCRIT in the 6 studies for treatment of anemia due to CKD not receiving dialysis, 2726 (60%) were age 65 years and over, while 1418 (31%) were 75 years and over. Of the 757 patients who received PROCRIT in the 3 studies of CKD patients on dialysis, 361 (47%) were age 65 years and over, while 100 (13%) were 75 years and over. No differences in safety or effectiveness were observed between geriatric and younger patients. Dose selection and adjustment for an elderly patient should be individualized to achieve and maintain the target hemoglobin *[see Dosage and Administration (2)]*.

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Among 778 patients enrolled in the 3 clinical studies of PROCRIT for the treatment of anemia due to concomitant chemotherapy, 419 received PROCRIT and 359 received placebo. Of the 419 who received PROCRIT, 247 (59%) were age 65 years and over, while 78 (19%) were 75 years and over. No overall differences in safety or effectiveness were observed between geriatric and younger patients. The dose requirements for PROCRIT in geriatric and younger patients within the 3 studies were similar.

Among 1731 patients enrolled in the 6 clinical studies of PROCRIT for reduction of allogeneic RBC transfusions in patients undergoing elective surgery, 1085 received PROCRIT and 646 received placebo or standard of care treatment. Of the 1085 patients who received PROCRIT, 582 (54%) were age 65 years and over, while 245 (23%) were 75 years and over. No overall differences in safety or effectiveness were observed between geriatric and younger patients. The dose requirements for PROCRIT in geriatric and younger patients within the 4 studies using the 3 times weekly schedule and 2 studies using the weekly schedule were similar.

Insufficient numbers of patients age 65 years or older were enrolled in clinical studies of PROCRIT for the treatment of zidovudine in HIV-infected patients to determine whether they respond differently from younger patients.

10 OVERDOSAGE

PROCRIT overdosage can cause hemoglobin levels above the desired level, which should be managed with discontinuation or reduction of PROCRIT dosage and/or with phlebotomy, as clinically indicated *[see Pharmacodynamics (12.2)]*. Cases of severe hypertension have been observed following overdose with ESAs *[see Warnings and Precautions (5.3)]*.

11 DESCRIPTION

PROCRIT (epoetin alfa) is a 165-amino acid erythropoiesis-stimulating glycoprotein manufactured by recombinant DNA technology. It has a molecular weight of approximately 30,400 daltons and is produced by mammalian cells into which the human erythropoietin gene has been introduced. The product contains the identical amino acid sequence of isolated natural erythropoietin.

PROCRIT is formulated as a sterile, colorless liquid in vials in multiple formulations. Single-dose vials, formulated with an isotonic sodium chloride/sodium citrate-buffered solution, are supplied in multiple strengths. Each 1 mL vial contains 2000, 3000, 4000, or 10,000 Units of epoetin alfa, Albumin (Human) (2.5 mg), citric acid (0.06 mg), sodium chloride (5.9 mg), and sodium citrate (5.8 mg) in Water for Injection, USP (pH 6.9 ± 0.3). Single-dose 1 mL vials formulated with an isotonic sodium chloride/sodium phosphate buffer contain 40,000 Units of epoetin alfa albumin (human) (2.5 mg),citric acid (0.0068 mg), sodium chloride (5.8 mg), sodium citrate (0.7 mg), sodium phosphate dibasic anhydrate (1.8 mg), and sodium phosphate monobasic monohydrate (1.2 mg) in Water for Injection, USP (pH 6.9 ± 0.3). Multiple-dose, 2 mL vials contain 10,000 Units epoetin alfa, albumin (human) (2.5 mg), benzyl alcohol (1%), sodium chloride (8.2 mg), citric acid (0.11 mg), and sodium citrate (1.3 mg) per 1 mL Water for Injection, USP (pH 6.1 ± 0.3). Multiple-dose 1 mL vials contain 20,000 Units epoetin alfa, albumin (human) (2.5 mg), benzyl alcohol (1%), sodium chloride (8.2 mg), citric acid (0.11 mg), and sodium citrate (1.3 mg), per 1 mL in Water for Injection, USP (pH 6.1 ± 0.3).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PROCRIT stimulates erythropoiesis by the same mechanism as endogenous erythropoietin.

12.2 Pharmacodynamics

PROCRIT increases the reticulocyte count within 10 days of initiation, followed by increases in the RBC count, hemoglobin, and hematocrit, usually within 2 to 6 weeks. The rate of hemoglobin increase varies among patients and is dependent upon the dose of PROCRIT administered. For correction of anemia in hemodialysis patients, a greater biologic response is not observed at doses exceeding 300 Units/kg 3 times weekly.

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12.3 Pharmacokinetics

In adult and pediatric patients with CKD, the elimination half-life ($t_{1/2}$) of plasma erythropoietin after intravenous administration of PROCRIT ranged from 4 to 13 hours. After subcutaneous administration, C_{max} was achieved within 5 to 24 hours. The $t_{1/2}$ in adult patients with serum creatinine greater than 3 mg/dL was similar between those not on dialysis and those maintained on dialysis. The pharmacokinetic data indicate no apparent difference in PROCRIT $t_{1/2}$ among adult patients above or below 65 years of age.

A pharmacokinetic study comparing 150 Units/kg subcutaneous 3 times weekly to 40,000 Units subcutaneous weekly dosing regimen was conducted for 4 weeks in healthy subjects (n=12) and for 6 weeks in anemic cancer patients (n=32) receiving cyclic chemotherapy. There was no accumulation of serum erythropoietin after the 2 dosing regimens during the study period. The 40,000 Units weekly regimen had a higher C_{max} (3- to 7-fold), longer T_{max} (2- to 3-fold), higher $AUC_{0\text{-}168\ h}$ (2- to 3-fold) of erythropoietin and lower clearance (CL) (50%) than the 150 Units/kg 3 times weekly regimen. In anemic cancer patients, the average $t_{1/2}$ was similar (40 hours with range of 16 to 67 hours) after both dosing regimens. After the 150 Units/kg 3 times weekly dosing, the values of T_{max} and CL were similar (13.3 ± 12.4 vs. 14.2 ± 6.7 hours, and 20.2 ± 15.9 vs. 23.6 ± 9.5 mL/hr/kg) between week 1 when patients were receiving chemotherapy (n=14) and week 3 when patients were not receiving chemotherapy (n=4). Differences were observed after the 40,000 Units weekly dosing with longer T_{max} (38 ± 18 hours) and lower CL (9.2 ± 4.7 mL/hr/kg) during week 1 when patients were receiving chemotherapy (n=18) compared with those (22 ± 4.5 hours, 13.9 ± 7.6 mL/hr/kg, respectively) during week 3 when patients were not receiving chemotherapy (n=7).

The pharmacokinetic profile of PROCRIT in children and adolescents appeared similar to that of adults.

The pharmacokinetics of PROCRIT has not been studied in patients with HIV infection.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

The carcinogenic potential of PROCRIT has not been evaluated.

Mutagenicity

PROCRIT was not mutagenic or clastogenic under the conditions tested: PROCRIT was negative in the *in vitro* bacterial reverse mutation assay (Ames test), in the *in vitro* mammalian cell gene mutation assay (the hypoxanthine-guanine phosphoribosyl transferase [HGPRT] locus), in an *in vitro* chromosomal aberration assay in mammalian cells, and in the *in vivo* mouse micronucleus assay.

Impairment of Fertility

When administered intravenously to male and female rats prior to and during mating, and to females through the beginning of implantation (up to gestational day 7; dosing stopped prior to the beginning of organogenesis), doses of 100 and 500 Units/kg/day of PROCRIT caused slight increases in pre-implantation loss, post-implantation loss and decreases in the incidence of live fetuses. It is not clear whether these effects reflect a drug effect on the uterine environment or on the conceptus. This animal dose level of 100 Units/kg/day approximates the clinical recommended starting dose, depending on the patient's treatment indication, but may be lower than the clinical dose in patients whose doses have been adjusted.

13.3 Reproductive and Developmental Toxicology

When pregnant rats were administered intravenous PROCRIT, 500 Units/kg/day, after the period of organogenesis (from day 17 of gestation through day 21 of lactation), their pups exhibited decreased number of caudal vertebrae, decreased body weight gain, and delayed appearance of abdominal hair, eyelid opening, and ossification. This

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animal dose level of 500 Units/kg/day is approximately 5-fold higher than the clinical recommended starting dose, depending on the patient's treatment indication.

When PROCRIT was administered intravenously during the period of organogenesis to pregnant rats (gestational days 7 to 17) and pregnant rabbits (gestational days 6 to 18), no evidence of teratogenic outcome was observed at the doses tested, up to 500 Units/kg/day. The offspring (F1 generation) of the treated rats were observed postnatally; rats from the F1 generation reached maturity and were mated; no PROCRIT-related effects were apparent for their offspring (F2 generation fetuses).

14 CLINICAL STUDIES

14.1 Patients With Chronic Kidney Disease

Adult Patients on Dialysis

Patients with chronic kidney disease on dialysis: ESA effects on rates of transfusion

In clinical studies of CKD patients on dialysis, PROCRIT increased hemoglobin levels and decreased the need for RBC transfusion. Overall, more than 95% of patients were RBC transfusion-independent after receiving PROCRIT for 3 months. In clinical studies at starting doses of 50 to 150 Units/kg 3 times weekly, adult patients responded with an average rate of hemoglobin rise as presented in Table 8.

Table 8: Average Rate of Hemoglobin Rise in 2 Weeks

Starting Dose (3 Times Weekly Intravenously)	Hemoglobin Increase in 2 Weeks
50 Units/kg	0.5 g/dL
100 Units/kg	0.8 g/dL
150 Units/kg	1.2 g/dL

The safety and efficacy of PROCRIT were evaluated in 13 clinical studies involving intravenous administration to a total of 1010 anemic patients on dialysis. Overall, more than 90% of the patients treated with PROCRIT experienced improvement in hemoglobin concentrations. In the 3 largest of these clinical studies, the median maintenance dose necessary to maintain the hemoglobin between 10 to 12 g/dL was approximately 75 Units/kg 3 times weekly. More than 95% of patients were able to avoid RBC transfusions. In the largest US multicenter study, approximately 65% of the patients received doses of 100 Units/kg 3 times weekly or less to maintain their hemoglobin at approximately 11.7 g/dL. Almost 10% of patients received a dose of 25 Units/kg or less, and approximately 10% received a dose of more than 200 Units/kg 3 times weekly to maintain their hemoglobin at this level.

In the Normal Hematocrit Study, the yearly transfusion rate was 51.5% in the lower hemoglobin group (10 g/dL) and 32.4% in the higher hemoglobin group (14 g/dL).

Other ESA trials

In a 26-week, double-blind, placebo-controlled study, 118 patients on dialysis with an average hemoglobin of approximately 7 g/dL were randomized to either PROCRIT or placebo. By the end of the study, average hemoglobin increased to approximately 11 g/dL in the PROCRIT-treated patients and remained unchanged in patients receiving placebo. PROCRIT-treated patients experienced improvements in exercise tolerance and patient-reported physical functioning at month 2 that were maintained throughout the study.

A multicenter, unit-dose study was also conducted in 119 patients receiving peritoneal dialysis who self-administered PROCRIT subcutaneously. Patients responded to PROCRIT administered subcutaneously in a manner similar to patients receiving intravenous administration.

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Pediatric Patients on Dialysis

The safety and efficacy of PROCRIT were studied in a placebo-controlled, randomized study of 113 children with anemia (hemoglobin ≤ 9 g/dL) undergoing peritoneal dialysis or hemodialysis. The initial dose of PROCRIT was 50 Units/kg intravenously or subcutaneously 3 times weekly. The dose of study drug was titrated to achieve either a hemoglobin of 10 to 12 g/dL or an absolute increase in hemoglobin of 2 g/dL over baseline.

At the end of the initial 12 weeks, a statistically significant rise in mean hemoglobin (3.1 g/dL vs. 0.3 g/dL) was observed only in the PROCRIT arm. The proportion of children achieving a hemoglobin of 10 g/dL, or an increase in hemoglobin of 2 g/dL over baseline, at any time during the first 12 weeks was higher in the PROCRIT arm (96% vs. 58%). Within 12 weeks of initiating PROCRIT therapy, 92.3% of the pediatric patients were RBC transfusion independent as compared to 65.4% who received placebo. Among patients who received 36 weeks of PROCRIT, hemodialysis patients received a higher median maintenance dose [167 Units/kg/week (n=28) vs. 76 Units/kg/week (n=36)] and took longer to achieve a hemoglobin of 10 to 12 g/dL (median time to response 69 days vs. 32 days) than patients undergoing peritoneal dialysis.

Adult Patients With CKD Not Requiring Dialysis

Four clinical studies were conducted in patients with CKD not on dialysis involving 181 patients treated with PROCRIT. These patients responded to PROCRIT therapy in a manner similar to that observed in patients on dialysis. Patients with CKD not on dialysis demonstrated a dose-dependent and sustained increase in hemoglobin when PROCRIT was administered by either an intravenous or subcutaneous route, with similar rates of rise of hemoglobin when PROCRIT was administered by either route.

Patients with chronic kidney disease not on dialysis: ESA effects on rates of transfusion
In TREAT, a randomized, double-blind trial of 4038 patients with CKD and type 2 diabetes not on dialysis, a post-hoc analysis showed that the proportion of patients receiving RBC transfusions was lower in patients administered an ESA to target a hemoglobin of 13 g/dL compared to the control arm in which an ESA was administered intermittently if hemoglobin concentration decreased to less than 9 g/dL (15% versus 25%, respectively). In CHOIR, a randomized open-label study of 1432 patients with CKD not on dialysis, use of epoetin alfa to target a higher (13.5 g/dL) versus lower (11.3 g/dL) hemoglobin goal did not reduce the use of RBC transfusions. In each trial, no benefits occurred for the cardiovascular or end-stage renal disease outcomes. In each trial, the potential benefit of ESA therapy was offset by worse cardiovascular safety outcomes resulting in an unfavorable benefit-risk profile *[see Warnings and Precautions (5.1)]*.

ESA Effects on rates of death and other serious cardiac adverse events

Three randomized outcome trials (Normal Hematocrit Study [NHS], Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease [CHOIR], and Trial of Darbepoetin Alfa in Type 2 Diabetes and CKD [TREAT]) have been conducted in patients with CKD using Epogen/PROCRIT/Aranesp to target higher vs. lower hemoglobin levels. Though these trials were designed to establish a cardiovascular or renal benefit of targeting higher hemoglobin levels, in all 3 studies, patients randomized to the higher hemoglobin target experienced worse cardiovascular outcomes and showed no reduction in progression to ESRD. In each trial, the potential benefit of ESA therapy was offset by worse cardiovascular safety outcomes resulting in an unfavorable benefit-risk profile *[see Warnings and Precautions (5.1)]*.

14.2 Zidovudine-treated Patients With HIV Infection

The safety and efficacy of PROCRIT were evaluated in 4 placebo-controlled studies enrolling 297 anemic patients (hemoglobin < 10 g/dL) with HIV infection receiving concomitant therapy with zidovudine. In the subgroup of patients (89/125 PROCRIT and 88/130 placebo) with pre-study endogenous serum erythropoietin levels ≤ 500 mUnits/mL, PROCRIT reduced the mean cumulative number of units of blood transfused per patient by approximately 40% as compared to the placebo group. Among those patients who required RBC transfusions at baseline, 43% of patients treated with PROCRIT versus 18% of placebo-treated patients were RBC transfusion-independent during the second and third months of therapy. PROCRIT therapy also resulted in significant increases in hemoglobin in comparison to placebo. When examining the results according to the weekly dose of zidovudine

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received during month 3 of therapy, there was a statistically significant reduction ($p < 0.003$) in RBC transfusion requirements in patients treated with PROCRIT (n=51) compared to placebo-treated patients (n=54) whose mean weekly zidovudine dose was ≤ 4200 mg/week.

Approximately 17% of the patients with endogenous serum erythropoietin levels ≤ 500 mUnits/mL receiving PROCRIT in doses from 100 to 200 Units/kg 3 times weekly achieved a hemoglobin of 12.7 g/dL without administration of RBC transfusions or significant reduction in zidovudine dose. In the subgroup of patients whose pre-study endogenous serum erythropoietin levels were > 500 mUnits/mL, PROCRIT therapy did not reduce RBC transfusion requirements or increase hemoglobin compared to the corresponding responses in placebo-treated patients.

14.3Cancer Patients on Chemotherapy

The safety and effectiveness of PROCRIT was assessed in two multicenter, randomized (1:1), placebo-controlled, double-blind studies (Study C1 and Study C2) and a pooled analysis of six additional randomized (1:1), multicenter, placebo-controlled, double-blind studies. All studies were conducted in patients with anemia due to concomitantly administered cancer chemotherapy. Study C1 enrolled 344 adult patients, Study C2 enrolled 222 pediatric patients, and the pooled analysis contained 131 patients randomized to epoetin alfa or placebo. In Studies C1 and C2, efficacy was demonstrated by a reduction in the proportion of patients who received an RBC transfusion, from week 5 through end of the study, with the last-known RBC transfusion status carried forward for patients who discontinued treatment. In the pooled analysis, efficacy was demonstrated by a reduction in the proportion of patients who received an RBC transfusion from week 5 through end of the study in the subset of patients who were remaining on therapy for 6 or more weeks.

Study C1

Study C1 was conducted in anemic patients (hemoglobin < 11.5 g/dL for males; < 10.5 g/dL for females) with non-myeloid malignancies receiving myelosuppressive chemotherapy. Randomization was stratified by type of malignancy (lung vs. breast vs. other), concurrent radiation therapy planned (yes or no), and baseline hemoglobin (< 9 g/dL vs. ≥ 9 g/dL); patients were randomized to epoetin alfa 40,000 Units (n=174) or placebo (n=170) as a weekly subcutaneous injection commencing on the first day of the chemotherapy cycle.

Ninety-one percent of patients were white, 44% were male, and the median age of patients was 66 years (range: 20 to 88 years). The proportion of patients withdrawn from the study prior to week 5 was less than 10% for placebo-treated or epoetin-treated patients. Per protocol, the last available hemoglobin values from patients who dropped out were included in the efficacy analyses. Efficacy results are shown in Table 9.

Table 9: Study C1: Proportion of Patients Transfused

	Week 5 Through Week 16 or End of Study[a]	
Chemotherapy Regimen	**PROCRIT (n=174)**	**Placebo (n=170)**
All Regimens	14% (25/174)[b]	28% (48/170)
Regimens without cisplatin	14% (21/148)	26% (35/137)
Regimens containing cisplatin	15% (4/26)	39% (13/33)

[a] Last-known RBC transfusion status carried forward for patients who discontinued treatment.
[b] Two-sided $p < 0.001$, logistic regression analysis adjusting for accrual rate and stratification variables.

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Study C2

Study C2 was conducted in 222 anemic patients, ages 5 to 18, receiving chemotherapy for the treatment of various childhood malignancies. Randomization was stratified by cancer type (solid tumors, Hodgkin's disease, acute lymphocytic leukemia, vs. non-Hodgkin's lymphoma); patients were randomized to receive epoetin alfa at 600 Units/kg maximum 40,000 Units (n=111) or placebo (n=111) as a weekly intravenous injection.

Sixty-nine percent of patients were white, 55% were male, and the median age of patients was 12 years (range: 5 to 18 years). Two (2%) of placebo-treated patients and 3 (3%) of epoetin alfa-treated patients dropped out of the study prior to week 5. There were fewer RBC transfusions from week 5 through the end-of-study in epoetin-alfa treated patients [51% (57/111)] compared to placebo-treated patients [69% (77/111)]. There was no evidence of an improvement in health-related quality of life, including no evidence of an effect on fatigue, energy, or strength in patients receiving PROCRIT as compared to those receiving placebo.

Pooled Analysis (Three Times Per Week Dosing)

The results of 6 studies of similar design and that randomized 131 patients to epoetin alfa or placebo were pooled to assess the safety and effectiveness of epoetin alfa. Patients were randomized to receive epoetin alfa at 150 Units/kg (n=63) or placebo (n=68), subcutaneously three times per week for 12 weeks in each study. Across all studies, 72 patients were treated with concomitant non cisplatin-containing chemotherapy regimens and 59 patients were treated with concomitant cisplatin-containing chemotherapy regimens. Twelve patients (19%) in the epoetin alfa arm and 10 patients (15%) in the placebo-arm dropped out prior to week 6 and are excluded from efficacy analyses.

Table 10: Proportion of Patients Transfused in the Pooled Analysis for Three Times Per Week Dosing

	Week 5 Through Week 12 or End of Study[a]	
Chemotherapy Regimen	**PROCRIT**	**Placebo**
All Regimens	22% (11/51)[b]	43% (25/58)
Regimens without cisplatin	21% (6/29)	33% (11/33)
Regimens containing cisplatin	23% (5/22)	56% (14/25)

[a] Limited to patients remaining on study beyond week 6 and includes only RBC transfusions during weeks 5-12.
[b] Two-sided $p < 0.05$, unadjusted.

14.4Surgery Patients

The safety and efficacy of PROCRIT were evaluated in a placebo-controlled, double-blind study (S1) enrolling 316 patients scheduled for major, elective orthopedic hip or knee surgery who were expected to require ≥ 2 units of blood and who were not able or willing to participate in an autologous blood donation program. Patients were stratified into 1 of 3 groups based on their pretreatment hemoglobin [≤ 10 g/dL (n=2), > 10 to ≤ 13 g/dL (n=96), and > 13 to ≤ 15 g/dL (n=218)] and then randomly assigned to receive 300 Units/kg PROCRIT, 100 Units/kg PROCRIT, or placebo by subcutaneous injection for 10 days before surgery, on the day of surgery, and for 4 days after surgery. All patients received oral iron and a low-dose, postoperative warfarin regimen.

Treatment with PROCRIT 300 Units/kg significantly (p=0.024) reduced the risk of allogeneic RBC transfusion in patients with a pretreatment hemoglobin of > 10 to ≤ 13 g/dL; 5/31 (16%) of patients treated with PROCRIT 300 Units/kg, 6/26 (23%) of patients treated with PROCRIT 100 Units/kg, and 13/29 (45%) of placebo-treated patients were transfused. There was no significant difference in the number of patients transfused between PROCRIT (9% 300 Units/kg, 6% 100 Units/kg) and placebo (13%) in the > 13 to ≤ 15 g/dL hemoglobin stratum. There were too few patients in the ≤ 10 g/dL group to determine if PROCRIT is useful in this hemoglobin strata. In the > 10 to ≤ 13 g/dL pretreatment stratum, the mean number of units transfused per PROCRIT-treated patient (0.45 units blood for 300 Units/kg, 0.42 units blood for 100 Units/kg) was less than the mean transfused per placebo-treated patient (1.14 units) (overall p=0.028). In addition, mean hemoglobin, hematocrit, and reticulocyte counts increased significantly during the presurgery period in patients treated with PROCRIT.

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PROCRIT was also evaluated in an open-label, parallel-group study (S2) enrolling 145 patients with a pretreatment hemoglobin level of ≥ 10 to ≤ 13 g/dL who were scheduled for major orthopedic hip or knee surgery and who were not participating in an autologous program. Patients were randomly assigned to receive 1 of 2 subcutaneous dosing regimens of PROCRIT (600 Units/kg once weekly for 3 weeks prior to surgery and on the day of surgery, or 300 Units/kg once daily for 10 days prior to surgery, on the day of surgery, and for 4 days after surgery). All patients received oral iron and appropriate pharmacologic anticoagulation therapy.

From pretreatment to presurgery, the mean increase in hemoglobin in the 600 Units/kg weekly group (1.44 g/dL) was greater than that observed in the 300 Units/kg daily group. The mean increase in absolute reticulocyte count was smaller in the weekly group ($0.11 \times 10^6/mm^3$) compared to the daily group ($0.17 \times 10^6/mm^3$). Mean hemoglobin levels were similar for the 2 treatment groups throughout the postsurgical period.

The erythropoietic response observed in both treatment groups resulted in similar RBC transfusion rates [11/69 (16%) in the 600 Units/kg weekly group and 14/71 (20%) in the 300 Units/kg daily group]. The mean number of units transfused per patient was approximately 0.3 units in both treatment groups.

16 HOW SUPPLIED/STORAGE AND HANDLING

Store at 36°F to 46°F (2°C to 8°C). Do not freeze.

Do not shake. Protect from light; store PROCRIT in the carton until use.

Do not use PROCRIT that has been shaken or frozen.

Single-dose, Preservative-free Vial: Each 1 mL of solution contains 2000 (NDC 59676-302-01), 3000 (NDC 59676-303-01), 4000 (NDC 59676-304-01), or 10,000 Units (NDC 59676-310-01) of epoetin alfa. Each strength is supplied in cartons, each carton containing 6 single-dose vials.

Single-dose, Preservative-free Vial (Tray): Each 1 mL of solution contains 10,000 Units (NDC 59676-310-02) of epoetin alfa and is supplied in dispensing packs containing 25 single-dose vials.

Single-dose, Preservative-free Vial (in phosphate-buffered formulation): Each 1 mL of solution contains 40,000 Units (NDC 59676-340-01) of epoetin alfa and is supplied in dispensing packs containing 4 single-dose vials.

Multiple-dose, Preserved Vial: 2 mL (20,000 Units total; 10,000 Units/mL). Each 1 mL of solution contains 10,000 Units (NDC 59676-312-04) of epoetin alfa and is supplied in dispensing packs containing 4 multiple-dose vials.

Multiple-dose, Preserved Vial: 1 mL (20,000 Units/mL). Each 1 mL of solution contains 20,000 Units (NDC 59676-320-04) of epoetin alfa and is supplied in dispensing packs containing 4 multiple-dose vials.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Prior to treatment, inform patients of the risks and benefits of PROCRIT.

Inform patients:

- To read the Medication Guide.
- Of the increased risks of mortality, serious cardiovascular reactions, thromboembolic reactions, stroke, and tumor progression *[see Warnings and Precautions (5.1, 5.2)]*.
- To undergo regular blood pressure monitoring, adhere to prescribed anti-hypertensive regimen and follow recommended dietary restrictions.
- To contact their healthcare provider for new-onset neurologic symptoms or change in seizure frequency.
- Of the need to have regular laboratory tests for hemoglobin.

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- Risks are associated with benzyl alcohol in neonates, infants, pregnant women, and nursing mothers *[see Use in Specific Populations (8.1, 8.3, 8.4)]*.

Instruct patients who self-administer PROCRIT of the:
- Importance of following the Instructions for Use.
- Dangers of reusing needles, syringes, or unused portions of single-dose vials.
- Proper disposal of used syringes, needles, and unused vials, and of the full container.

PROCRIT® (epoetin alfa)

Manufactured by:

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799 U.S.A.
U.S. License Number 1080

Manufactured for:

Janssen Products, LP
Horsham, Pennsylvania 19044
©Janssen Products, LP 2000
Printed in U. S. A.

Patent: www.procrit.com/patents/

MEDICATION GUIDE

PROCRIT® (PRO′–KRIT)
(epoetin alfa)

Read this Medication Guide:

- before you start PROCRIT.
- if you are told by your healthcare provider that there is new information about PROCRIT.
- if you are told by your healthcare provider that you may inject PROCRIT at home, read this Medication Guide each time you receive a new supply of medicine.

This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Talk with your healthcare provider regularly about the use of PROCRIT and ask if there is new information about PROCRIT.

What is the most important information I should know about PROCRIT?

PROCRIT may cause serious side effects that can lead to death, including:

For people with cancer:

- Your tumor may grow faster and you may die sooner if you choose to take PROCRIT. Your healthcare provider will talk with you about these risks.

For all people who take PROCRIT, including people with cancer or chronic kidney disease:

- **Serious heart problems, such as heart attack or heart failure, and stroke.** You may die sooner if you are treated with PROCRIT to increase red blood cells (RBCs) to near the same level found in healthy people.
- **Blood clots.** Blood clots may happen at any time while taking PROCRIT. If you are receiving PROCRIT for any reason and you are going to have surgery, talk to your healthcare provider about whether or not you need to take a blood thinner to lessen the chance of blood clots during or following surgery. Clots can form in blood vessels (veins), especially in your leg (deep venous thrombosis or DVT). Pieces of a blood clot may travel to the lungs and block the blood circulation in the lungs (pulmonary embolus).

- Call your healthcare provider or get medical help right away if you have any of these symptoms:
    - Chest pain
    - Trouble breathing or shortness of breath
    - Pain in your legs, with or without swelling
    - A cool or pale arm or leg
    - Sudden confusion, trouble speaking, or trouble understanding others' speech
    - Sudden numbness or weakness in your face, arm, or leg, especially on one side of your body
    - Sudden trouble seeing
    - Sudden trouble walking, dizziness, loss of balance or coordination
    - Loss of consciousness (fainting)
    - Hemodialysis vascular access stops working

See **"What are the possible side effects of PROCRIT?"** below for more information.

If you decide to take PROCRIT, your healthcare provider should prescribe the smallest dose of PROCRIT that is necessary to reduce your chance of needing RBC transfusions.

What is PROCRIT?

PROCRIT is a prescription medicine used to treat anemia. People with anemia have a lower-than-normal number of RBCs. PROCRIT works like the human protein called erythropoietin to help your body make more RBCs. PROCRIT is used to reduce or avoid the need for RBC transfusions.

PROCRIT may be used to treat anemia if it is caused by:

- Chronic kidney disease (you may or may not be on dialysis).
- Chemotherapy that will be used for at least two months after starting PROCRIT.
- A medicine called zidovudine (AZT) used to treat HIV infection.

PROCRIT may also be used to reduce the chance you will need RBC transfusions if you are scheduled for certain surgeries where a lot of blood loss is expected.

If your hemoglobin level stays too high or if your hemoglobin goes up too quickly, this may lead to serious health problems which may result in death. These serious health problems may happen if you take PROCRIT, even if you do not have an increase in your hemoglobin level.

PROCRIT should not be used for treatment of anemia:

- If you have cancer and you will not be receiving chemotherapy that may cause anemia.
- If you have a cancer that has a high chance of being cured. Talk with your healthcare provider about the kind of cancer you have.
- If your anemia caused by chemotherapy treatment can be managed by RBC transfusion.
- In place of emergency treatment for anemia (RBC transfusions).

PROCRIT has not been proven to improve quality of life, fatigue, or well-being.

PROCRIT should not be used to reduce the chance of RBC transfusions if:

- You are scheduled for surgery on your heart or blood vessels.
- You are able and willing to donate blood prior to surgery.

Who should not take PROCRIT?

Do not take PROCRIT if you:

- Have cancer and have not been counseled by your healthcare provider about treatment with PROCRIT.
- Have high blood pressure that is not controlled (uncontrolled hypertension).
- Have been told by your healthcare provider that you have or have ever had a type of anemia called Pure Red Cell Aplasia (PRCA) that starts after treatment with PROCRIT or other erythropoietin protein medicines.
- Have had a serious allergic reaction to PROCRIT.

Do not give PROCRIT from multiple-dose vials to:

- Pregnant or breastfeeding women
- Babies

What should I tell my healthcare provider before taking PROCRIT?

PROCRIT may not be right for you. **Tell your healthcare provider about all your health conditions,** including if you:

- Have heart disease.
- Have high blood pressure.
- Have had a seizure (convulsion) or stroke.

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- Have any other medical conditions.
- Are pregnant or planning to become pregnant. It is not known if PROCRIT may harm your unborn baby. Talk to your healthcare provider about possible pregnancy and birth control choices that are right for you.
- Are breastfeeding or planning to breastfeed. It is not known if PROCRIT passes into breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of your medicines with you and show it to your healthcare provider when you get a new medicine.

How should I take PROCRIT?

- If you or your caregiver has been trained to give PROCRIT shots (injections) at home:
  - Be sure that you read, understand, and follow the "Instructions for Use" that come with PROCRIT.
  - Take PROCRIT exactly as your healthcare provider tells you to. Do not change the dose of PROCRIT unless told to do so by your healthcare provider.
  - Your healthcare provider will show you how much PROCRIT to use, how to inject it, how often it should be injected, and how to safely throw away the used vials, syringes, and needles.
  - If you miss a dose of PROCRIT, call your healthcare provider right away and ask what to do.
  - If you take more than the prescribed amount of PROCRIT, call your healthcare provider right away.
- During treatment with PROCRIT, continue to follow your healthcare provider's instructions for diet and medicines.
- Have your blood pressure checked as instructed by your healthcare provider.

What are the possible side effects of PROCRIT?

PROCRIT may cause serious side effects.

- See **"What is the most important information I should know about PROCRIT?"**
- **High blood pressure.** High blood pressure is a common side effect of PROCRIT in patients with chronic kidney disease. Your blood pressure may go up or be difficult to control with blood pressure medicine while taking PROCRIT. This can happen even if you have never had high blood pressure before. Your healthcare provider should check your blood pressure often. If your blood pressure does go up, your healthcare provider may prescribe new or more blood pressure medicine.
- **Seizures.** If you have any seizures while taking PROCRIT, get medical help right away and tell your healthcare provider.
- **Antibodies to PROCRIT.** Your body may make antibodies to PROCRIT. These antibodies can block or lessen your body's ability to make RBCs and cause you to have severe anemia. Call your healthcare provider if you have unusual tiredness, lack of energy, dizziness, or fainting. You may need to stop taking PROCRIT.
- **Serious allergic reactions.** Serious allergic reactions can cause a rash over your whole body, shortness of breath, wheezing, dizziness and fainting because of a drop in blood pressure, swelling around your mouth or eyes, fast pulse, or sweating. If you have a serious allergic reaction, stop using PROCRIT and call your healthcare provider or get medical help right away.
- **Dangers of using PROCRIT from multiple-dose vials in newborns, infants, and pregnant or breastfeeding women.** Do not use PROCRIT from multiple-dose vials in newborns, infants, pregnant or breastfeeding women because the PROCRIT in these vials contains benzyl alcohol. Benzyl alcohol has been shown to cause brain damage, other serious side effects, and death in newborn and premature babies. PROCRIT that comes in single-dose vials does not contain benzyl alcohol. **See "Who should not take PROCRIT?"**

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Common side effects of PROCRIT include:

- joint, muscle, or bone pain
- fever
- cough
- rash
- nausea
- vomiting
- soreness of mouth
- itching
- headache
- redness and pain in the skin where PROCRIT shots were given

These are not all of the possible side effects of PROCRIT. Your healthcare provider can give you a more complete list. Tell your healthcare provider about any side effects that bother you or that do not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PROCRIT?

- Do not shake PROCRIT.
- Protect PROCRIT from light.
- Store PROCRIT in the refrigerator between 36°F to 46°F (2°C to 8°C).
- **Do not freeze PROCRIT.** Do not use PROCRIT that has been frozen.
- Throw away multiple-dose vials of PROCRIT no later than 21 days from the first day that you put a needle into the vial.
- Single-dose vials of PROCRIT should be used only one time. Throw the vial away after use even if there is medicine left in the vial.

Keep PROCRIT and all medicines out of the reach of children.

General information about PROCRIT

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Use PROCRIT only for the condition for which it has been prescribed. Do not give PROCRIT to other patients even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about PROCRIT. If you would like more information about PROCRIT, talk to your healthcare provider. You can ask your healthcare provider or pharmacist for information about PROCRIT that is written for healthcare professionals. For more information, go to the following website: www.PROCRIT.com or call 1-800-JANSSEN (1-800-526-7736).

What are the ingredients in PROCRIT?

Active Ingredient: epoetin alfa

Inactive Ingredients:
- Multiple-dose vials contain benzyl alcohol.
- All vials contain albumin (human), sodium citrate, sodium chloride, and citric acid.
- Single-dose vials containing 40,000 Units of PROCRIT also contain sodium phosphate monobasic monohydrate and sodium phosphate dibasic anhydrate.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Manufactured by:

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Manufactured for:

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