PROCRIT® (epoetin alfa)

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).

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

ADVERSE REACTIONS

- 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).

DOSE 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).

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- 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 for 15 days or 600 Units/kg weekly (2.5).

DOSE 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 (5.8)
- 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 (5.5).

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.

Revised: 04/2017
PROCRIT® (epoetin alfa)

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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.

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 ≥ 11 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery.

1.5 Limitations of Use

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

1.6 Use in Patients Undergoing Radiation Therapy

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

1.7 Use in Patients Undergoing Cardiac Surgery

PROCRIT is not indicated for use:
- In patients scheduled for surgery who are willing to donate autologous blood.
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- In patients who are willing to donate autologous blood pre-operatively.

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 (5.1)].

2.2 Patients with Chronic Kidney Disease

PROCRIT is not indicated for use:
- In patients scheduled for surgery who are willing to donate autologous blood.
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- In patients who are willing to donate autologous blood pre-operatively.

2.3 Zidovudine-treated HIV-infected Patients

PROCRIT is not indicated for use:
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- In patients who are willing to donate autologous blood pre-operatively.

2.4 Patients on Cancer Chemotherapy

PROCRIT is not indicated for use:
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- In patients who are willing to donate autologous blood pre-operatively.

2.5 Surgery Patients

PROCRIT is not indicated for use:
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- In patients who are willing to donate autologous blood pre-operatively.

2.6 Preparation and Administration

PROCRIT is not indicated for use:
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- In patients who are willing to donate autologous blood pre-operatively.

2.7 Prevention of Deep Venous Thrombosis

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

2.8 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.

2.9 Prevention of Skinfold Thinning

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

2.10 Laboratory Monitoring

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 (5.1)].

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism

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

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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)].

Perioperative:

- 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.

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)].

For all patients with CKD:
- 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%.
  - 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.

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 [see Use in Specific Populations (8.1, 8.3, 8.4)].
PROCRIT® (epoetin alfa)

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 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.

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

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Normal Hematocrit Study (NHS) (N=1265)</th>
<th>CHOIR (N=1432)</th>
<th>TREAT (N=4038)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>CKD patients on hemodialysis with coexisting CHF or CAD, hematocrit 30 ± 3% on epoetin alfa</td>
<td>CKD patients not on dialysis with hemoglobin &lt; 11 g/dL not previously administered epoetin alfa</td>
<td>CKD patients not on dialysis with type II diabetes, hematocrit ≤ 11 g/dL</td>
</tr>
<tr>
<td>Hemoglobin Target; Higher vs. Lower (g/dL)</td>
<td>14.0 ± 4.0 vs. 10.0</td>
<td>13.5 ± 11.3</td>
<td>13.0 ± &gt; 9.0</td>
</tr>
<tr>
<td>Median (Q1, Q3) Achieved Hemoglobin level (g/dL)</td>
<td>12.6 (11.6, 13.3) vs. 10.3 (10.0, 10.7)</td>
<td>13.0 (12.2, 13.4) vs. 11.4 (11.1, 11.6)</td>
<td>12.5 (12.0, 12.8) vs. 10.6 (9.9, 11.3)</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>All-cause mortality or non-fatal MI</td>
<td>All-cause mortality, MI, hospitalization for CHF, or stroke</td>
<td>All-cause mortality, MI, myocardial ischemia, heart failure, and stroke</td>
</tr>
<tr>
<td>Hazard Ratio or Relative Risk (95% CI)</td>
<td>1.28 (1.06 - 1.56)</td>
<td>1.34 (1.03 - 1.74)</td>
<td>1.05 (0.94 - 1.17)</td>
</tr>
<tr>
<td>Adverse Outcome for Higher Target Group</td>
<td>All-cause mortality</td>
<td>All-cause mortality</td>
<td>Stroke</td>
</tr>
<tr>
<td>Hazard Ratio or Relative Risk (95% CI)</td>
<td>1.27 (1.04 - 1.54)</td>
<td>1.48 (0.97 - 2.27)</td>
<td>1.92 (1.38 - 2.68)</td>
</tr>
</tbody>
</table>

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 (25% vs. 23%) 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: 1.63, 1.74; p=0.03). 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. The stroke rate was 2.1% vs. 1.1%, respectively, HR 1.92, 95% CI: 1.38, 2.65; 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 2 years. 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 hemoglobin 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 of 58 patients, not receiving prophylactic antiocclusion 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 (2.6%) 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 58 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 subsets 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 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

<table>
<thead>
<tr>
<th>Study/Tumor(n)</th>
<th>Hemoglobin Target</th>
<th>Achieved Hemoglobin (Median; Q1, Q3*)</th>
<th>Primary Efficacy Outcome</th>
<th>Adverse Outcome for ESA-containing Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>Metastatic breast cancer (n=2088)</td>
<td>≤ 12 g/dL†</td>
<td>11.6 g/dL; 10.7, 12.1 g/dL</td>
<td>Progression-free survival (PFS)</td>
</tr>
<tr>
<td>Study 2</td>
<td>Metastatic breast cancer (n=339)</td>
<td>12-14 g/dL</td>
<td>12.9 g/dL; 12.2, 13.3 g/dL</td>
<td>12-month overall survival</td>
</tr>
<tr>
<td>Study 3</td>
<td>Lymphoid malignancy (n=344)</td>
<td>13-15 g/dL (M) 13-14 g/dL (F)</td>
<td>11 g/dL; 9.8, 12.1 g/dL</td>
<td>Proportion of patients achieving a hemoglobin response</td>
</tr>
<tr>
<td>Study 4</td>
<td>Early breast cancer (n=733)</td>
<td>12.5-12 g/dL</td>
<td>13.1 g/dL; 12.5, 13.7 g/dL</td>
<td>Relapse-free and overall survival</td>
</tr>
<tr>
<td>Study 5</td>
<td>Cervical cancer (n=114)</td>
<td>12-14 g/dL</td>
<td>12.7 g/dL; 12.1, 13.3 g/dL</td>
<td>Progression-free and overall survival and locoregional control</td>
</tr>
<tr>
<td>Study 6</td>
<td>Head and neck cancer (n=351)</td>
<td>≥ 15 g/dL (M) ≥ 14 g/dL (F)</td>
<td>Not available</td>
<td>Locoregional progression-free survival</td>
</tr>
<tr>
<td>Study 7</td>
<td>Head and neck cancer (n=522)</td>
<td>14-15.5 g/dL</td>
<td>Not available</td>
<td>Locoregional disease control</td>
</tr>
<tr>
<td>Study 8</td>
<td>Non-small cell lung cancer (n=70)</td>
<td>12-14 g/dL</td>
<td>Not available</td>
<td>Quality of life</td>
</tr>
<tr>
<td>Study 9</td>
<td>Non-myaloidiency (n=689)</td>
<td>12-13 g/dL</td>
<td>10.6 g/dL; 9.4, 11.8 g/dL</td>
<td>RBC transfusions</td>
</tr>
</tbody>
</table>

*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 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 83 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 2,998 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) 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: 0.83, 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. 5%). Both local recurrence (21% vs. 20%) and distant recurrence (12% vs. 7%) were lower 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. 82%; 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 8 was a randomized, placebo-controlled study in 351 head and neck cancer patients where epoetin beta or placebo was administered to achieve target hemoglobin levels ≥ 14 and ≥ 15 g/dL for women and men, respectively. Locoregional progression-free survival was significantly shorter in patients receiving epoetin betta (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

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 to 15.5 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.

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%

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

5.11 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.

5.12 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.

5.13 Additional Serious Adverse Reactions

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 3: Adverse Reactions in Patients With CKD on Dialysis

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

6.2 Adverse Reactions in Patients With CKD Not on Dialysis

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 0% 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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>PROCRIT-treated Patients (n=131)</th>
<th>Placebo-treated Patients (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>13.7%</td>
<td>10.1%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12.2%</td>
<td>7.6%</td>
</tr>
</tbody>
</table>

6.3 Adverse Reactions in Pediatric Patients

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 0% 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 5: Adverse Reactions in Zidovudine-treated HIV-infected Patients

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>PROCRIT (n=144)</th>
<th>Placebo (n=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>42%</td>
<td>34%</td>
</tr>
<tr>
<td>Cough</td>
<td>26%</td>
<td>14%</td>
</tr>
<tr>
<td>Rash</td>
<td>19%</td>
<td>7%</td>
</tr>
<tr>
<td>Injection site irritation</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Urticaria</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Respiratory tract congestion</td>
<td>1%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1%</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
PROCRIT® (epoetin alfa)

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 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 ≥ 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

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

Surgery Patients

Four hundred sixty-one patients undergoing major orthopedic surgery were studied in a placebo-controlled study (S1) and a comparative dosing study (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. For the combined PROCRIT treatment groups, a total of 90 (25%) and 268 (75%) patients (97%) randomized to placebo received at least 1 placebo dose. For the combined PROCRIT treatment groups, 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 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 ≥ 5% 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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Study S1</th>
<th>Study S2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PROCRIT 300 U/kg</td>
<td>PROCRIT 100 U/kg</td>
</tr>
<tr>
<td></td>
<td>(n=112)</td>
<td>(n=101)</td>
</tr>
<tr>
<td>Nausea</td>
<td>47%</td>
<td>43%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21%</td>
<td>12%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>16%</td>
<td>18%</td>
</tr>
<tr>
<td>Headache</td>
<td>13%</td>
<td>11%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>13%</td>
<td>9%</td>
</tr>
<tr>
<td>Chills</td>
<td>7%</td>
<td>4%</td>
</tr>
</tbody>
</table>

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of PROCRIT.

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. There was 1 infant born with pectus excavatum and hypospadias following exposure during the first trimester. Increased risk for these adverse pregnancy outcomes. There was 1 infant born with pectus excavatum and hypospadias following exposure during the first trimester.
PROCRIT® (epoetin alfa) 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 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 “gaspering 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 “gaspering syndrome“, the minimum amount of benzyl alcohol at which toxicity may occur is not known. A high proportion of 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 ages 5 years and above 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 vs 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, and 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 were age 75 years and over. No differences were noted 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)].

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 79 (20%) 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 aged 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 multiple formulations. 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)].

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.

12.3 Pharmacokinetics
In adult and pediatric patients with CKD, the elimination half-life (t1/2) of plasma erythropoietin after intravenous administration of PROCRIT ranged from 4 to 13 hours. After subcutaneous administration, Cmax was achieved within 4 to 24 hours. The t1/2 in adult patients with serum creatinine greater than 3 mg/dL was similar to those not on dialysis and those maintained on dialysis. The pharmacokinetic data indicate no apparent difference in PROCRIT t1/2 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 4-week dosing period. The pharmacokinetic parameters were similar within these 2 dosing regimens during the study period. The 40,000 Units weekly regimen had a higher Cmax (3- to 7-fold), longer T1/2 (2- to 3-fold), higher AUC0-Inf (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 t1/2 was similar (40 hours with range of 16 to 76 hours) after both dosing regimens. After the 150 Units/kg 3 times weekly dosing, the values of t1/2 and CL were similar (13.3 ± 12.4 vs. 14.2 ± 6.7 hours, and 20.2 ± 15.9 vs. 23.6 ± 5.9 ml/hr/kg) between week 1 when patients

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PROCRIT® (epoetin alfa)
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 dose with longer Tmax (38 ± 18 hours) and lower CL (9.2 ± 4.7 mL/hr/kg) during week 1 when patients were not 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

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 decreases in body weight and slight decreases in body weight gain in pregnant mice. 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.

13.2 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 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.
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 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.

### 14.3 Cancer 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>
<thead>
<tr>
<th>Table 9: Study C1: Proportion of Patients Transfused</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy Regimen</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>All Regimens</td>
</tr>
<tr>
<td>Regimens without cisplatin</td>
</tr>
<tr>
<td>Regimens containing cisplatin</td>
</tr>
</tbody>
</table>

*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 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.

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

<table>
<thead>
<tr>
<th>Chemotherapy Regimen</th>
<th>Week 5 Through Week 12 or End of Studya</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROCRIT</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>All Regimens</td>
<td>22% (11/51)</td>
</tr>
<tr>
<td>Regimens without cisplatin</td>
<td>21% (6/29)</td>
</tr>
<tr>
<td>Regimens containing cisplatin</td>
<td>23% (5/22)</td>
</tr>
</tbody>
</table>

*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 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 ≤ 12 g/dL, > 10 ≤ 13 g/dL, > 13 ≤ 15 g/dL) and then randomly assigned to receive 300 Units/kg PROCRIT, 100 Units/kg epoetin alfa, 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. 53% (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 stratum 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). Patients who received oral iron and appropriate pharmacologic anticoagulation therapy.

From pretreatment to presurgery, the mean increase in hemoglobin in the 300 Units/kg weekly group (1.44 g/dL) was greater than that observed in the 100 Units/kg daily group. The mean increase in absolute reticulocyte count 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 300 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 0.5 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 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.
- 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.

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.
• 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?”

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.
Instructions for Use
PROCRIT® (PRO’−KRIT)
(epoetin alfa)

Use these Instructions for Use if you or your caregiver has been trained to give PROCRIT injections at home. Do not give yourself the injection unless you have received training from your healthcare provider. If you are not sure about giving the injection or you have questions, ask your healthcare provider for help.

Before reading these Instructions for Use, read the Medication Guide that comes with PROCRIT for the most important information you need to know.

When you receive your PROCRIT vial and syringes make sure that:

- The name PROCRIT appears on the carton and vial label.
- The expiration date on the vial label has not passed. Do not use a vial of PROCRIT after the expiration date on the label.
- The dose strength of the PROCRIT vial (number of Units per mL on the vial label) is the same as your healthcare provider prescribed.
- You understand what the dose strength of PROCRIT means. PROCRIT vials come in several dose strengths. For example, the dose strength may be described as 10,000 Units/mL on the vial label. This strength means that 10,000 Units of medicine are contained in each 1 mL (milliliter) of liquid. Your healthcare provider may also refer to a mL as a “cc.” One mL is the same as one “cc.”
- The PROCRIT liquid in the vial is clear and colorless. Do not use PROCRIT if the liquid in the vial looks discolored or cloudy, or if the liquid has lumps, flakes, or particles.
- The PROCRIT vial has a color cap on the top of the vial. Do not use a vial of PROCRIT if the color cap on the top of the vial has been removed or is missing.
- Use only the type of disposable syringe and needle that your healthcare provider has prescribed.
- Do not shake PROCRIT. Shaking could cause PROCRIT not to work. If you shake PROCRIT, the solution in the vial may look foamy and should not be used.
- Do not freeze PROCRIT. Do not use a vial of PROCRIT that has been frozen.
- Store PROCRIT in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Keep PROCRIT away from light.
- 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.
- After removing a dose from the multidose vial, store the vial in the refrigerator (but not the freezer). Do not store the vial for more than 21 days.
- Throw away the multidose vial as directed by your healthcare provider:
  - if there is not enough medicine left in the multidose vial for another dose,
  - if it has been more than 21 days since you first put a needle into the multidose vial.

How should I prepare for an injection of PROCRIT?
- Always keep an extra syringe and needle on hand.
- Follow your healthcare provider’s instructions on how to measure your dose of PROCRIT. This dose will be measured in Units per mL or cc (1 mL is the same as 1 cc). Use a syringe that is marked in tenths of mL (for example, 0.2 mL or 0.2 cc). Using the wrong syringe can lead to a mistake in your dose and you could inject too much or too little PROCRIT.

Only use disposable syringes and needles. Use the syringes and needles only one time and then throw them away as instructed by your healthcare provider.

What do I need to know about the different types of PROCRIT vials?
PROCRIT comes in two different types of vials.
- Single-dose Vials
- Multidose Vials

The multidose vial of PROCRIT contains the preservative 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.

Important: Follow these instructions exactly to help avoid infections.

Preparing the dose:
1. Remove the vial of PROCRIT from the refrigerator. During this time, protect the solution from light.
2. Do not use a single-dose vial of PROCRIT more than one time.
3. Do not shake PROCRIT.
4. Gather the other supplies you will need for your injection (vial, syringe, alcohol wipes, cotton ball, and a puncture-proof container for throwing away the syringe and needle). See Figure 1.
5. Check the date on the PROCRIT vial to be sure that the drug has not expired.
6. Wash your hands well with soap and water before preparing the medicine. See Figure 2.

7. Flip off the protective color cap on the top of the vial. Do not remove the grey rubber stopper. Wipe the top of the grey rubber stopper with an alcohol wipe. See Figures 3 and 4.

8. Check the package containing the syringe. If the package has been opened or damaged, do not use that syringe. Throw away the syringe in the puncture-proof disposable container. If the syringe package is undamaged, open the package and remove the syringe.

9. Using a syringe and needle that has been recommended by your healthcare provider, carefully remove the needle cover. See Figure 5. Then draw air into the syringe by pulling back on the plunger. The amount of air drawn into the syringe should be equal to the amount (mL or cc) of the PROCRIT dose prescribed by your healthcare provider. See Figure 6.

10. With the vial on a flat work surface, insert the needle straight down through the grey rubber stopper of the PROCRIT vial. See Figure 7.

11. Push the plunger of the syringe down to inject the air from the syringe into the vial of PROCRIT. The air injected into the vial will allow PROCRIT to be easily withdrawn into the syringe. See Figure 7.

12. Keep the needle inside the vial. Turn the vial and syringe upside down. Be sure the tip of the needle is in the PROCRIT liquid. Keep the vial upside down. Slowly pull back on the plunger to fill the syringe with PROCRIT liquid to the number (mL or cc) that matches the dose your healthcare provider prescribed. See Figure 8.

13. Keep the needle in the vial. Check for air bubbles in the syringe. A small amount of air is harmless. Too large an air bubble will give you the wrong PROCRIT dose. To remove air bubbles, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe. Slowly push the plunger up to force the air bubbles out of the syringe. Keep the tip of the needle in the PROCRIT liquid. Pull the plunger back to the number on the syringe that matches your dose. Check again for air bubbles. If there are still air bubbles, repeat the steps above to remove them. See Figures 9 and 10.

14. Double-check that you have the correct dose in the syringe. Lay the vial down on its side with the needle still in it until after you have selected and prepared your site for injection.
Selecting and preparing the injection site:
PROCRIT can be injected into your body using two different ways (routes) as described below. Follow your healthcare provider’s instructions about how you should inject PROCRIT. In patients on hemodialysis, the intravenous (IV) route is recommended.

1. Subcutaneous Route:
   - PROCRIT can be injected directly into a layer of fat under your skin. This is called a subcutaneous injection. When giving subcutaneous injections, follow your healthcare provider’s instructions about changing the site for each injection. You may wish to write down the site where you have injected.
   - Do not inject PROCRIT into an area that is tender, red, bruised, hard, or has scars or stretch marks. Recommended sites for injection are shown in Figure 11 below, including:
     - The outer area of the upper arms
     - The abdomen (except for the 2-inch area around the navel)
     - The front of the middle thighs
     - The upper outer area of the buttocks

   - Clean the skin with an alcohol wipe where the injection is to be made. Be careful not to touch the skin that has been wiped clean. See Figure 12.

   - Double-check that the correct amount of PROCRIT is in the syringe.
   - Remove the prepared syringe and needle from the vial of PROCRIT and hold it in the hand that you will use to inject the medicine.

2. Intravenous Route:
   - PROCRIT can be injected in your vein through a special access port placed by your healthcare provider. This type of PROCRIT injection is called an intravenous (IV) injection. This route is usually for hemodialysis patients.
   - If you have a dialysis vascular access, make sure it is working by checking it as your healthcare provider has shown you. Be sure to let your healthcare provider know right away if you are having any problems, or if you have any questions.
   - Wipe off the venous port of the hemodialysis tubing with an alcohol wipe. See Figure 15.
• Insert the needle of the syringe into the cleaned venous port and push the plunger all the way down to inject all the PROCRIT. See Figure 16.

Figure 16

• Remove the syringe from the venous port. Do not recap the needle.
• Dispose of the used syringe and needle as described below.

How should I dispose of the vials, syringes, and needles?
Do not reuse the single-dose vials, syringes, or needles. Throw away the vials, syringes, and needles as instructed by your healthcare provider or by following these steps:
• Do not throw the vials, syringes, or needles in the household trash or recycle.
• Do not put the needle cover back on the needle.
• Place all used needles and syringes in a puncture-proof disposable container with a lid. Do not use glass or clear plastic containers, or any container that will be recycled or returned to a store.
• Keep the puncture-proof disposable container out of the reach of children.
• When the puncture-proof disposable container is full, tape around the cap or lid to make sure the cap or lid does not come off. Throw away the puncture-proof disposable container as instructed by your healthcare provider. There may be special state and local laws for disposing of used needles and syringes. Do not throw the puncture-proof disposable container in the household trash. Do not recycle.

Keep PROCRIT and all medicines out of reach of children.

These Instructions for Use have been approved by the U.S. Food and Drug Administration.

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