PROCRIT® EPOETIN ALFA
PROCRIT® registered trademark of distributor for INJECTION

DESCRIPTION
Erythropoietin is a glycoprotein which stimulates red blood cell production. It is produced in the kidney and stimulates the division and differentiation of committed erythroid progenitors in the bone marrow. PROCRIT® is the epoetin alfa formulation of recombinant human erythropoietin, a human α-chain amino acid glycoprotein manufactured by recombinant DNA technology, that has the same biological activity as endogenous erythropoietin, and has a molecular weight of 30,400 daltons and is produced by mammalian cells into which the human erythropoietin cDNA has been transfected. The product contains the identical amino acid sequence of isolated natural erythropoietin.

PROCRIT® is formulated as a sterile, colorless, preservative-free liquid for intravenous or subcutaneous administration. Each single-use vial contains 2,000, 3,000, 4,000, or 5,000 units of Epoetin alfa formulated in an isotonic sodium chloride/sodium citrate buffer solution (pH 6.2 ± 0.3) containing albumin (human) (2.5 mg), sodium citrate (5.8 mg), sodium chloride (8.8 mg), citric acid (0.35 mg) in Water for Injection, USP.

CLINICAL PHARMACOLOGY
Chronic Renal Failure Patients
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were treated with concomitant cisplatin containing chemotherapeutic regimens, many of whom achieved complete remissions with PROCRIT® 150 units/kg or placebo subcutaneously I.M. for 12 weeks. PROCRIT therapy was associated with a significantly (p < 0.001) greater hematocrit response than in the corresponding placebo-treated patients (see Table). HEMATOCRIT (% MEAN CHANGE FROM BASELINE TO FINAL VALUE

<table>
<thead>
<tr>
<th>STUDY</th>
<th>PROCRIT®</th>
<th>PLACEBO</th>
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<tr>
<td>Chemotherapy</td>
<td>7.6</td>
<td>1.3</td>
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<td>Cisplatin</td>
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* Significantly higher in PROCRIT® patients than in placebo patients (p < 0.001)

In two types of chemotherapy studies, utilizing a PROCRIT® dose of 150 units/kg I.M., the mean number of units of blood transfused per patient after the first month of therapy was significantly (p < 0.001) lower in PROCRIT®-treated patients (0.71 units in Months 2, 3) than in corresponding placebo-treated patients (1.84 units in Months 2, 3). Moreover, the proportion of patients transfused during Months 2 and 3 of therapy combined was significantly (p < 0.03) lower in the PROCRIT®-treated patients than in the corresponding placebo-treated patients (22% versus 43%).

Comparable intensity of chemotherapy in the PROCRIT® and placebo groups in the chemotherapy trials was suggested by a similar number of patients in each group who received concomitant cisplatin, and who were also treated as placebo patients as well as by a similar proportion of patients in PROCRIT® and placebo-treated groups whose absolute neutrophil counts fell below 1,000/μL. Available evidence suggests that patients with lymphoid and solid cancers respond to PROCRIT® therapy, and that patients with or without tumor stabilization of the bone marrow respond to PROCRIT® therapy.

CONTRADICTIONS
PROCRIT® is contraindicated in patients with:
1. Uncontrolled hypertension
2. Known hypersensitivity to mammalian cell-derived products
3. Known hypersensitivity to Albumin (Human).

WARNINGS
Chronic Renal Failure Patients
Hypertension: Patients with uncontrolled hypertension should not be treated with PROCRIT®; blood pressure should be controlled adequately before initiation of therapy. Blood pressure may rise during PROCRIT® therapy, often during the early phase of treatment with the hematocrit increasing.

For patients who respond to PROCRIT® with a rapid increase in hematocrit (e.g., more than 4 points in any two-week period), the dose of PROCRIT® should be reduced because of the possible association between a rapid increase in hematocrit and an accelerated rate of rise of hematocrit with an exacerbation of hypertension.

Seizures: Seizures have occurred in patients with CRF participating in PROCRIT® clinical trials. In patients on dialysis, there was a higher incidence of seizure occurring in the first 60 days of therapy (occurred in approximately 2.5% of patients), as compared with later timepoints.

Given the potential for an increased risk of seizures during the first 60 days of therapy, blood pressure and the presence of presynaptic neurologic symptoms should be monitored closely. Patients should be counseled to avoid potentially hazardous activities such as driving or operating heavy machinery during this period.

Thrombotic Events: During hemodialysis patients treated with PROCRIT® may present increased anticoagulation with heparin to prevent clotting of the artificial kidney. Clotting of the vascular access could impede the PROCRIT® therapy. However, patients with pre-existing vascular disease should be monitored closely.

Zidovudine-treated HIV-Infected Patients
In contrast to CRF patients, PROCRIT® therapy has not been linked to exacerbation of anemia, seizures, and thrombotic events in HIV-infected patients.

PRECAUTIONS
Chronic Renal Failure, Zidovudine-treated HIV-infected and Cancer Patients on Chemotherapy
General: The percutaneous administration of any biologic product should be attended by appropriate precautions in case allergic or anaphylactic responses occur. While transfusion reactions have occasionally been observed concomitantly with PROCRIT® therapy, there have been no allergic or anaphylactic reactions reported.

The safety and efficacy of PROCRIT® therapy have not been established in patients with a known history of a seizure disorder or underlying hematologic disorder (e.g., sickle cell anemia, myeloid dysplasia, congenital anemias, etc.). In some female patients, menopause has resumed following PROCRIT® therapy; the possibility of potential pregnancy should be discussed and the need for contraception evaluated.

Hematology: Exacerbation of porphyria has been observed rarely in PROCRIT®-treated patients with CRF. However, PROCRIT® has not caused increased urinary excretion of porphyrin metabolites in normal volunteers, even in the presence of a rapid erythropoietic response. Nevertheless, PROCRIT® should be used with caution in patients with known porphyria.

In pre-clinical studies in dogs and rats, but not in monkeys, PROCRIT® therapy was associated with subclinical bone marrow fibrosis. Bone marrow fibrosis is a known complication of CRF in humans and may be related to a secondary hyperparathyroidism of unknown factors. The incidence of bone marrow fibrosis was not increased in a study of patients on dialysis who were treated with PROCRIT® for 12-18 months, compared to the incidence of bone marrow fibrosis in a similar group of patients who had not been treated with PROCRIT®.

Hematocrit in CRF patients should be measured twice a week; zidovudine-treated HIV-infected, and cancer patients should have hematocrit measured once a week until hematocrit has been stabilized, and measured periodically thereafter.

Delayed or Diminished Response: If the patient fails to respond or to maintain a response, the following side effects should be considered and evaluated:
1. Iron deficiency: functional iron deficiency may develop with normal ferritin levels but low transferrin saturation (less than 20%), presumably due to the inability to mobilize iron stores rapidly enough to support increased erythropoiesis. Virtually all patients will eventually require supplemental iron therapy.
2. Underlying infectious, inflammatory, or malignant processes.
3. Oculocutaneous autosomal dominant retinal dystrophy.
4. Underlying hematologic diseases (i.e., thalassemia, retinoblastoma, or other myeloproliferative disorders).
5. Vitamin deficiencies: folic acid or vitamin B12.
7. Aluminum intoxication.
8. Osteitis fibrosa cystica.

Iron Evaluation: Prior to and during PROCRIT® therapy, the patient's iron stores, including transferrin saturation (serum iron in mg/dL divided by total iron binding capacity in mg/dL) should be evaluated. Transferrin saturation should be at least 20%, and ferritin should be at least 100 ng/mL. Supplementation of patients who are required to maintain transferrin saturation levels that will adequately support PROCRIT®-stimulated erythropoiesis.

Drug Interactions: No evidence of interaction of PROCRIT® with other drugs was observed in the course of clinical trials.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Carcinogenic potential of PROCRIT® has not been evaluated. PROCRIT® does not induce bacterial gene mutation (Ames test), chromosomal aberrations in mammalian cells, micronuclei in mice, or gene mutation at the HGPRT locus. In man, 3 percent of patients have undergone bone marrow biopsy and there was no evidence of increase in hematopoietic or non-hematopoietic tissues.

Pregnancy Category C: PROCRIT® has been shown to have adverse effects on fetal development. There are no adequate and well-controlled studies in pregnant women. PROCRIT® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In studies in female rats, there were decreases in body weight gain, delays in appearance of abdominal hair, delayed eyelid opening, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 units/kg group. In female rats treated intravenously, there was a slight dose-related increase in fetal weight gain of 100 and 500 units/kg. PROCRIT® has not shown any adverse effect at doses as high as 500 units/kg in pregnant rabbits from day 8 to 18 of gestation.

Nursing Mothers: Postnatal observations of the five nursing (F1 generation) female rats treated with PROCRIT® during gestation and lactation revealed no effect of PROCRIT® on dams or nursing pups. PROCRIT® does not increase body weight gain, delays in appearance of abdominal hair, eyelid opening, and decreases in the number of caudal vertebrae whose incidence is dose-related. In some groups of rats, there were no PROCRIT®-related effects on the F2 generation fetuses.

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® is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of PROCRIT® in children have not been established.

Chronic Renal Failure Patients
Patients with CRF not requiring dialysis: Blood pressure and hematuria should be monitored no less frequently than for patients maintained on dialysis. Renal function and fluid and electrolyte balance should be closely monitored, as an improved sense of well-being may obscure the need to initiate dialysis in some patients.

Hematology: In order to avoid reaching the target hematocrit too rapidly, the target range (60-70%) should be achieved over a period of 4-6 weeks. The dose of PROCRIT® should be reduced because of the possible association of excessive rate of rise of hematocrit with an exacerbation of hypertension.

The elevated blood pressure characteristic of CRF decreases toward normal after correction of anemia in PROCRIT®-treated patients. Reduction of bleeding time also occurs after correction of anemia by transfusion.

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of PROCRIT® before adjusting the dose. Because of the time required for erythropoiesis, the smallest dose that will maintain the target hematocrit level should be adjusted weekly for at least 2-6 weeks until it has been determined that the hematocrit has stabilized in response to the dose change. The hematocrit should then be monitored at regular intervals.

A complete blood count with differential and platelet count should be performed regularly. During the first two weeks of the treatment period, the dose of PROCRIT® should be increased weekly for at least 2-6 weeks until it has been determined that the hematocrit has stabilized in response to the dose change. The hematocrit should then be monitored at regular intervals.

In patients with CRF, serum chemistry values [including blood urea nitrogen (BUN), uric acid, creatinine, phosphorus, and potassium] should be monitored regularly. During clinical trials in patients on dialysis, modest increases were seen in BUN, creatinine, phosphorus, and potassium. In some patients with CRF not on dialysis, treated with PROCRIT®, modest increases in serum uric acid and phosphorus were observed. While these changes were statistically significant, they were not clinically significant and the values remained within normal ranges.

Hypertension: Patients with uncontrolled hypertension should not be treated with PROCRIT®; blood pressure should be closely monitored regularly. During clinical trials in patients on dialysis, modest increases were seen in platelet and white blood cell counts. While these changes were statistically significant, they were not clinically significant and the values remained within normal ranges.

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Hypertension: Patients with uncontrolled hypertension should not be treated with PROCRIT®; blood pressure should be closely monitored regularly. During clinical trials in patients on dialysis, modest increases were seen in platelet and white blood cell counts. While these changes were statistically significant, they were not clinically significant and the values remained within normal ranges.
Seizures: Seizures have occurred in patients with CRF participating in PROCRIT clinical trials. In patients on dialysis, there was a higher incidence of seizures during the first 30 days of therapy (occurring in approximately 2.5% of patients), as compared with later timepoints.

Given the potential for an increased risk of seizures during the first 30 days of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely. Patients should be cautioned to avoid potentially hazardous activities such as driving or operating heavy machinery during this period.

Thrombotic Events: During hemodialysis, patients treated with PROCRIT may require increased anticoagulation with heparin to prevent clotting of the artificial kidney. Clotting of the vascular access has occurred at an annualized rate of about 0.25 events per patient-year on PROCRIT therapy.

A relationship has not been established with statistical certainty between a rise in hematocrit and the rate of thrombotic events (including thrombosis of vascular access [A-V shunt]) in PROCRIT-treated patients. Overall, for patients with CRF (whether on dialysis or not), other thrombotic events (e.g., myocardial infarction, cerebrovascular accident, transient ischemic attack) have occurred at an annualized rate of less than 0.04 events per patient-year of PROCRIT therapy. Patients with pre-existing vascular disease should be monitored closely.

Diet: As the hematocrit increases and patients experience an improved sense of well-being and quality of life, the importance of compliance with dietary and dialysis prescriptions should be reinforced. In particular, hyperkalemia is not uncommon in patients with CRF. In U.S. studies in patients on dialysis, hyperkalemia has occurred at an annualized rate of approximately 0.32 episodes per patient-year of PROCRIT therapy, often in association with poor compliance to medication, dietary and/or dialysis prescriptions.

Dialysis Management: Therapy with PROCRIT results in an increase in hematocrit and a decrease in plasma volume which could affect dialysis efficiency. In studies to date, the resulting increase in hematocrit did not appear to adversely affect dialyzer function1-4 or the efficiency of high flux hemodialysis.1-4 During hemodialysis, patients treated with PROCRIT may require increased anticoagulation with heparin to prevent clotting of the artificial kidney.

Patients who are marginally dialyzed may require adjustments in their dialysis prescription. As with all patients on dialysis, the serum chemistry values (including blood urea nitrogen [BUN], creatinine, phosphorus, and potassium) in PROCRIT-treated patients should be monitored regularly to assure the adequacy of the dialysis prescription.

Renal Function: In patients with CRF not on dialysis, renal function and fluid and electrolyte balance should be closely monitored, as an improved sense of well-being may obscure the need to initiate dialysis in some patients. In patients with CRF not on dialysis, placebo-controlled studies of progression of renal dysfunction over periods of greater than one year have not been completed. In shorter-term trials in patients with CRF not on dialysis, changes in creatinine and creatinine clearance were not significantly different in PROCRIT-treated patients, compared with placebo-treated patients. Analysis of the slope of 1/serum creatinine vs. time plots in these patients indicates no significant change in the slope after the initiation of PROCRIT therapy.

Zidovudine-treated HIV-Infected Patients

Hypertension: Exacerbation of hypertension has not been observed in zidovudine-treated HIV-infected patients treated with PROCRIT. However, PROCRIT should be withheld in these patients if pre-existing hypertension is uncontrolled, and should not be started until blood pressure is controlled. In double-blind studies, a single seizure has been experienced by a PROCRIT-treated patient.14

Cancer Patients on Chemotherapy

Hypertension: Hypertension, associated with a significant increase in hematocrit, has been noted rarely in PROCRIT-treated cancer patients. Nevertheless, blood pressure in PROCRIT-treated patients should be monitored carefully, particularly in patients with an underlying history of hypertension or cardiovascular disease.

Seizures: In double-blind placebo-controlled trials, 3.2% (N=285) of PROCRIT-treated patients and 2.9% (N=365) of placebo-treated patients had seizures. Seizures in 1.6% (N=165) PROCRIT-treated patients occurred in the context of a significant increase in blood pressure and hematocrit from baseline values. However, both PROCRIT-treated patients also had underlying CNS pathology which may have been related to seizure activity.

Thrombotic Events: In double-blind placebo-controlled trials, 3.2% (N=285) of PROCRIT-treated patients and 11.8% (N=868) of placebo-treated patients had thrombotic events (e.g., pulmonary embolism, cerebrovascular accident).
PROCRI* (Epopitin alfa) 9

Seizures: In double-blind and open label trials of PROCRI in HIV-infected zidovudine-treated patients, 10 patients have experienced seizures. In general, these seizures appear to be rare and are most commonly associated with conditions such as meningitis or cerebral neoplasms, not PROCRI therapy.

Cancer Patients on Chemotherapy

PROCRI Therapy *

In patients treated: PROCRI may be dialysis-accessible given a 0.5/h flow rate. During treatment:

Pre-TI Therapy

Dose

- Wk 1: 50 units/kg T.I. (3 days on, 5 days off) for 2 weeks
- Wk 2: 75 units/kg T.I. (3 days on, 5 days off) for 2 weeks
- Wk 3: 100 units/kg T.I. (3 days on, 5 days off) for 2 weeks
- Wk 4: 150 units/kg T.I. (3 days on, 5 days off) for 2 weeks
- Wk 5: 200 units/kg T.I. (3 days on, 5 days off) for 2 weeks
- Wk 6: 250 units/kg T.I. (3 days on, 5 days off) for 2 weeks

In patients treated: 500 units/kg T.I. on 3 days every other week for 3 months. In patients on chemotherapy, adverse events with an incidence > 10% in either PROCRI-treated or placebo-treated patients were as indicated below.

Percent of Patients Reporting Event

- Pyrexia
- Diarrhea
- Nausea
- Vomiting
- Edema
- Fatigue
- Rash
- Dizziness
- Clotted Access

In the U.S. PROCRI studies in patients on dialysis (over 567 patients) the incidence (number of events per patient-year) of the most frequently reported adverse events were: hypertension (7.5%), headache (4.0%), lightheadedness (4.0%), nausea/vomiting (2.0%), clotted vascular access (2.0%), shortness of breath (0.14%), hypokalemia (0.03%), and diarrhea (0.0). Other events occurred at a rate of less than 0.10 events per patient-year.

Events reported to have occurred within several hours of administration of PROCRI were mild or transient in nature. There has been no evidence for development of antibodies to erythropoietin in patients tested to date, including those receiving intravenous PROCRI for over two years. Nevertheless, if an anaphylactoid reaction occurs, PROCRI administration should be immediately discontinued and appropriate therapy initiated.

Seizures: The relationship, if any, of PROCRI therapy to seizures is uncertain. The baseline incidence of seizures in the untreated dialysis population is difficult to determine; it appears to be in the range of 5-10% per patient-year.

Allergic Reactions: There have been no reports of serious allergic reactions or anaphylaxis associated with PROCRI administration. Skin rashes and urticaria have been observed rarely and when reported have been mild and transient in nature. There has been no evidence for development of antibodies to recombinant erythropoietin in patients tested to date, including those receiving intravenous PROCRI for over two years. Nevertheless, if an anaphylactoid reaction occurs, PROCRI administration should be immediately discontinued and appropriate therapy initiated.

Peripheral white blood cell and platelet counts are unchanged following PROCRI therapy.

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- Wk 1: 50 units/kg T.I. (3 days on, 5 days off) for 2 weeks
- Wk 2: 75 units/kg T.I. (3 days on, 5 days off) for 2 weeks
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- Wk 4: 150 units/kg T.I. (3 days on, 5 days off) for 2 weeks
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Seizures: The relationship, if any, of PROCRI therapy to seizures is uncertain. The baseline incidence of seizures in the untreated dialysis population is difficult to determine; it appears to be in the range of 5-10% per patient-year. There have been few reported seizures among patients monitored with PROCRI with an exposure of 986 patient-years for a rate of approximately 0.045 events per patient-year. However, there appeared to be a higher rate of seizure during the first 60 days of therapy (occurring in approximately 2.5% of patients), when compared to subsequent 90-day time periods. While the relationship between seizures and the rate of hematocrit is uncertain, it is recommended that the dose of PROCRI be administered in patients with hematocrits below 30% in any two-week period.

Hypertension: Up to 20% of patients with CRF have a history of hypertension. Blood pressure may rise during PROCRI therapy in patients with CRF whether or not maintained on dialysis, during the early phase of treatment when hematocrits in-
In patients on dialysis, PROCRIT® usually has been administered as an IV bolus T.I.W. While the administration of PROCRIT® is independent of the dialysis procedure, PROCRIT® may be administered into the venous line at the end of the dialysis procedure to obviate the need for additional venous access. In patients with CRF not on dialysis, PROCRIT® may be given either as an intravenous or subcutaneous injection.

During therapy, hematological parameters should be monitored regularly (see "Laboratory Monitoring").

Pre-Therapy Iron Evaluation: Prior to and during PROCRIT® therapy, the patient's iron stores, including transferrin saturation and serum ferritin, should be evaluated. Transferrin saturation should be at least 25%, and serum ferritin level should be at least 100 ng/mL. Supplemental iron may be required to increase and maintain transferrin saturation to levels that will adequately support PROCRIT®-stimulated erythropoiesis.

Dose Adjustment

- When the hematocrit reaches 30-33%, the dosage should be decreased by approximately 25 units/kg T.I.W., to avoid exceeding the target range. Since the hematocrit within this target range, the maintenance dose must be individualized for each patient (see "Maintenance Dose").
- At any time, if the hematocrit increases by more than 4 points in a two-week period, the dose should be immediately decreased. After the dose reduction, the hematocrit should be monitored twice weekly for 2-6 weeks, and further dose adjustments should be made as outlined in "Maintenance Dose."
- As the hematocrit approaches, or if it exceeds 36%, PROCRIT® should be temporarily withheld until the hematocrit decreases to the target range of 30-33%.
- If a hematocrit decrease of 5-6 points is not achieved after an eight-week period and iron stores are adequate (see "Delayed or Diminished Response"), the dose of PROCRIT® may be increased by increments of 25 units/kg T.I.W. If a hematocrit of 36% is achieved, further increases of 25 units/kg T.I.W. may be made at 4-6 week intervals until the desired response is attained.

Maintenance Dose: The maintenance dose must be individualized for each patient. As the hematocrit approaches, or if it exceeds 36%, PROCRIT® should be temporarily withheld until the hematocrit decreases to 30-33%. If the patient has not responded satisfactorily to PROCRIT® therapy, the dose should be reduced by approximately 25 units/kg T.I.W. upon re-initiation of therapy after a period of 4-6 weeks. The treatment should then be re-evaluated and the dose adjusted accordingly.

- If a hematocrit increase of 5-6 points is not achieved after an eight-week period and iron stores are adequate (see "Delayed or Diminished Response"), the dose of PROCRIT® may be increased by 25 units/kg T.I.W. Such dose increases should not be made more frequently than once a month.