PROCRIT®
EPOETIN ALFA

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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 (Epoetin alfa), a 165 amino acid glycoprotein manufactured by recombinant DNA technology, has the same biological effects as endogenous erythropoietin.[1] It has a molecular weight of 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, preservative-free liquid for intravenous or subcutaneous administration. Each single-use vial contains 2,000, 3,000, 4,000, or 10,000 units of Epoetin alfa formulated in an isotonic sodium chloride/sodium citrate buffered solution (pH 6.9 ± 0.3) containing Albumin (Human) (2.5 mg), sodium citrate (5.8 mg), sodium chloride (5.8 mg), citric acid (0.06 mg) in Water for Injection, USP.

CLINICAL PHARMACOLOGY

Chronic Renal Failure Patients

Erythropoietin is a glycoprotein which stimulates red blood cell production. Endogenous production of erythropoietin is normally regulated by the level of tissue oxygenation. Hypoxia and anemia generally increase the production of erythropoietin, which in turn stimulates erythropoiesis.[2] In normal subjects, plasma erythropoietin levels range from 0.01 to 0.03 units/mL,[2,3] and increase up to 100- to 1000-fold during hypoxia or anemia.[2,3] In contrast, in patients with chronic renal failure (CRF), production of erythropoietin is impaired, and this erythropoietin deficiency is the primary cause of their anemia.[3,4]

Chronic renal failure is the clinical situation in which there is a progressive and usually irreversible decline in kidney function. Such patients may manifest the sequelae of renal dysfunction, including anemia, but do not necessarily require regular dialysis. Patients with end-stage renal disease (ESRD) are those patients with CRF who require regular dialysis or kidney transplantation for survival.

PROCRIT has been shown to stimulate erythropoiesis in anemic patients with CRF, including both patients on dialysis and those who do not require regular dialysis.[4-13] The first evidence of a response to the three times weekly (T.I.W.) administration of PROCRIT is an increase in the reticulocyte count within 10 days, followed by increases in the red cell count, hemoglobin, and hematocrit, usually within 2-6 weeks.[4,5] Because of the length of time required for erythropoiesis — several days for erythroid progenitors to mature and be released into the circulation — a clinically significant increase in hematocrit is usually not observed in less than 2 weeks and may require up to 6 weeks in some patients. Once the hematocrit reaches the target range (30-33%), that level can be sustained by PROCRIT therapy in the absence of iron deficiency and concurrent illnesses.

The rate of hematocrit increase varies between patients and is dependent upon the dose of PROCRIT, within a therapeutic range of approximately 50-300 units/kg T.I.W.[4] A greater biologic response is not observed at doses exceeding 300 units/kg T.I.W.[6] Other factors affecting the rate and extent of response include availability of iron stores, the baseline hematocrit, and the presence of concurrent medical problems.

Zidovudine-treated HIV-Infected Patients

Responsiveness to PROCRIT in HIV-infected patients is dependent upon the endogenous serum erythropoietin level prior to treatment. Patients with endogenous serum erythropoietin levels ≤ 500 mU/mL and who are receiving a dose of zidovudine ≤ 4200 mg/week may respond to PROCRIT therapy. Patients with endogenous serum erythropoietin levels > 500 mU/mL do not appear to respond to PROCRIT therapy. In a series of four clinical trials involving 255 patients, 60-80 % of HIV-infected patients treated with zidovudine had endogenous serum erythropoietin levels ≤ 500 mU/mL.

Response to PROCRIT in zidovudine-treated HIV-infected patients is manifested by reduced transfusion requirements and increased hematocrit.

Cancer Patients on Chemotherapy

Anemia in cancer patients may be related to the disease itself or the effect of concomitantly administered chemotherapeutic agents. PROCRIT has been shown to increase hematocrit and decrease transfusion requirements after the first month of therapy, (months two and three of therapy), in anemic cancer patients undergoing chemotherapy.

A series of clinical trials enrolled 131 anemic cancer patients who were receiving cyclic cisplatin– or non cisplatin–containing chemotherapy. Endogenous baseline serum erythropoietin levels varied among patients in these trials with approximately 75 % (N=83/110) having endogenous serum erythropoietin levels ≤ 132 mU/mL, and approximately 4% (N=4/110) of patients having endogenous serum erythropoietin levels > 500 mU/mL. In general, patients with lower baseline serum erythropoietin levels responded more vigorously to PROCRIT than patients with higher baseline serum erythropoietin levels. Although no specific serum erythropoietin level can be stipulated above which patients would be unlikely to respond to PROCRIT therapy, treatment of patients with grossly elevated serum erythropoietin levels (e.g., > 200 mU/mL) is not recommended.

Pharmacokinetics

Intravenously administered PROCRIT is eliminated at a rate consistent with first order kinetics with a circulating half-life ranging from approximately 4 to 13 hours in patients with CRF. Within the therapeutic dose range, detectable levels of plasma erythropoietin are maintained for at least 24 hours.[7] After subcutaneous administration of PROCRIT to patients with CRF, peak serum levels are achieved within 5-24 hours after administration and decline slowly thereafter. There is no apparent difference in half-life between patients not on dialysis whose serum creatinine levels were greater than 3, and patients maintained on dialysis.

In normal volunteers, the half-life of intravenously administered PROCRIT is approximately 20% shorter than the half-life in CRF patients. The pharmacokinetics of PROCRIT have not been studied in HIV-infected patients.

INDICATIONS AND USAGE

Treatment of Anemia of Chronic Renal Failure Patients

PROCRIT is indicated in the treatment of anemia associated with chronic renal failure, including patients on dialysis (end-stage renal disease) and patients not on dialysis. PROCRIT is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients.

PROCRIT is not intended for patients who require immediate correction of severe anemia. PROCRIT may obviate the need for maintenance transfusions but is not a substitute for emergency transfusion.

Prior to initiation of therapy, the patient's iron stores, including transferrin saturation and serum ferritin, should be evaluated. Transferrin saturation should be at least 20% and ferritin at least 100 ng/mL. Blood pressure should be adequately controlled prior to initiation of PROCRIT therapy, and must be closely monitored and controlled during therapy. Non-dialysis patients with symptomatic anemia considered for therapy should have a hematocrit less than 30%. All patients on PROCRIT therapy should be regularly monitored (see "Laboratory Monitoring" and "Precautions").

PROCRIT should be administered under the guidance of a qualified physician (see "Dosage and Administration").

Treatment of Anemia in Zidovudine-treated HIV-Infected Patients

PROCRIT is indicated for the treatment of anemia related to therapy with zidovudine in HIV-infected patients. PROCRIT is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients. PROCRIT is not indicated for the treatment of anemia in HIV-infected patients due to other factors such as iron or folate deficiencies, hemolysis or gastrointestinal bleeding which should be managed appropriately.

PROCRIT, at a dose of 100 units/kg three times per week, is effective in decreasing the transfusion requirement and increasing the red blood cell level of anemic, HIV-infected patients treated with zidovudine, when the endogenous serum erythropoietin level is ≤ 500 mU/mL and when patients are receiving a dose of zidovudine ≤ 4200 mg/week.

Treatment of Anemia in Cancer Patients on Chemotherapy

PROCRIT is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. PROCRIT is indicated to decrease the need for transfusions in patients who will be receiving concomitant chemotherapy for a minimum of two months. PROCRIT is not indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis or gastrointestinal bleeding which should be managed appropriately.

Clinical Experience: Response to PROCRIT

Chronic Renal Failure Patients

Response to PROCRIT was consistent across all studies. In the presence of adequate iron stores (see "Pre-Therapy Iron

Evaluation"), the time to reach the target hematocrit is a function of the baseline hematocrit and the rate of hematocrit rise.

The rate of increase in hematocrit is dependent upon the dose of PROCRIT administered and individual patient variation. In clinical trials at starting doses of 50-150 units/kg T.I.W., patients responded with an average rate of hematocrit rise of:

HEMATOCRIT INCREASE

STARTING DOSE (T.I.W., IV)	HEMATOCRIT POINTS/DAY	HEMATOCRIT POINTS/2 WEEKS
50 units/kg	0.11	1.5
100 units/kg	0.18	2.5
150 units/kg	0.25	3.5

Over this dose range, approximately 95% of all patients responded with a clinically significant increase in hematocrit, and by the end of approximately two months of therapy virtually all patients were transfusion-independent. Once the target hematocrit was achieved, the maintenance dose was individualized for each patient.

Patients On Dialysis: Thirteen clinical studies were conducted, involving intravenous administration to a total of 1010 anemic patients on dialysis for 986 patient-years of PROCRIT therapy. In the three largest of these clinical trials, the median maintenance dose necessary to maintain the hematocrit between 30-36% was approximately 75 units/kg (T.I.W.). In the U.S. multicenter Phase III study, approximately 65% of the patients required doses of 100 units/kg T.I.W., or less, to maintain their hematocrit at approximately 35%. Almost 10% of patients required a dose of 25 units/kg, or less, and approximately 10% required a dose of more than 200 units/kg T.I.W. to maintain their hematocrit at this level.

Patients With CRF Not Requiring Dialysis: Four clinical trials were conducted in patients with CRF not on dialysis involving 181 PROCRIT-treated patients for approximately 67 patient-years of experience. These patients responded to PROCRIT therapy in a manner similar to that observed in patients on dialysis. Patients with CRF not on dialysis demonstrated a dose-dependent and sustained increase in hematocrit when PROCRIT was administered by either an intravenous (IV) or subcutaneous (SC) route, with similar rates of rise of hematocrit when PROCRIT was administered by either route. Moreover, PROCRIT doses of 75-150 units/kg per week have been shown to maintain hematocrits of 36-38% for up to six months.

Clinical Experience in Zidovudine-treated HIV-Infected Patients

PROCRIT has been studied in four placebo-controlled trials enrolling 297 anemic (hematocrit < 30%) HIV-infected (AIDS) patients receiving concomitant therapy with zidovudine, (all patients were treated with Epoetin alfa manufactured by Amgen Inc.). In the subgroup of patients (89/125 PROCRIT, and 88/130 placebo) with prestudy endogenous serum erythropoietin levels ≤ 500 mU/mL (normal endogenous serum erythropoietin levels are 4-26 mU/mL), PROCRIT reduced the mean cumulative number of units of blood transfused per patient by approximately 40%, as compared to placebo.[14] Among those patients who required transfusions at baseline, 43% of PROCRIT-treated patients versus 18% of placebo-treated patients were transfusion-independent during the second and third months of therapy. PROCRIT therapy also resulted in significant increases in hematocrit 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 ($p < 0.003$) reduction in transfusion requirements in PROCRIT-treated patients (N=51) compared to placebo-treated patients (N=54) whose mean weekly zidovudine dose was ≤ 4200 mg/week.[14] Approximately 17% of the patients with endogenous serum erythropoietin levels ≤ 500 mU/mL receiving PROCRIT in doses from 100-200 units/kg three times weekly (T.I.W.) achieved a hematocrit of 38% unrelated to transfusions or to a significant reduction in zidovudine dose. In the subgroup of patients whose prestudy endogenous serum erythropoietin levels were > 500 mU/mL, PROCRIT therapy did not reduce transfusion requirements or increase hematocrit compared to the corresponding responses in placebo-treated patients.

Responsiveness to PROCRIT therapy may be blunted by intercurrent infectious/inflammatory episodes and by an increase in zidovudine dosage. Consequently, the dose of PROCRIT must be titrated based on these factors to maintain the desired erythropoietic response.

Clinical Experience in Cancer Patients on Chemotherapy

PROCRIT has been studied in a series of placebo-controlled, double-blind trials in a total of 131 anemic cancer patients. Within this group, 72 patients were treated with concomitant non-cisplatin containing chemotherapy regimens and 59 patients

were treated with concomitant cisplatin containing chemotherapy regimens. Patients were randomized to PROCRIT 150 units/kg or placebo subcutaneously T.I.W. for 12 weeks.

PROCRIT therapy was associated with a significantly ($p<0.008$) greater hematocrit response than in the corresponding placebo-treated patients (see TABLE).[14]

HEMATOCRIT (%): MEAN CHANGE FROM BASELINE TO FINAL VALUE[a]

STUDY	PROCRIT	PLACEBO
Chemotheraphy	7.6	1.3
Cisplatin	6.9	0.6

[a] Significantly higher in PROCRIT patients than in placebo patients ($p < 0.008$)

In the two types of chemotherapy studies, (utilizing a PROCRIT dose of 150 units/kg T.I.W.), the mean number of units of blood transfused per patient after the first month of therapy was significantly ($p < 0.02$) 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%).[14]

Comparable intensity of chemotherapy in the PROCRIT and placebo groups in the chemotherapy trials was suggested by a similar area under the neutrophil time curve in PROCRIT and placebo-treated patients as well as by a similar proportion of patients in PROCRIT and placebo-treated groups whose absolute neutrophil counts fell below 1000 cells/μL. Available evidence suggests that patients with lymphoid and solid cancers respond to PROCRIT therapy, and that patients with or without tumor infiltration of the bone marrow respond to PROCRIT therapy.

CONTRAINDICATIONS

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 when the hematocrit is 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 of excessive 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 seizures during the first 90 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 90 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 (A-V shunt) has occurred at an annualized rate of about 0.25 events per patient-year on PROCRIT therapy.

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.

Zidovudine-treated HIV-Infected Patients

In contrast to CRF patients, PROCRIT therapy has not been linked to exacerbation of hypertension, seizures, and thrombotic events in HIV-infected patients.

PRECAUTIONS

Chronic Renal Failure, Zidovudine-treated HIV-Infected and Cancer Patients on Chemotherapy

General: The parenteral administration of any biologic product

should be attended by appropriate precautions in case allergic or other untoward reactions occur (see "Contraindications"). While transient rashes have occasionally been observed concurrently with PROCRIT therapy, no serious allergic or anaphylactic reactions have been 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 disease (e.g., sickle cell anemia, myelodysplastic syndromes, or hypercoagulable disorders).

In some female patients, menses have 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 secondary hyperparathyroidism or unknown factors. The incidence of bone marrow fibrosis was not increased in a study of patients on dialysis who were treated with PROCRIT for 12-19 months, compared to the incidence of bone marrow fibrosis in a matched 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 etiologies 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) Occult blood loss.
4) Underlying hematologic diseases (i.e., thalassemia, refractory anemia, or other myelodysplastic disorders).
5) Vitamin deficiencies: folic acid or vitamin B12.
6) Hemolysis.
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 divided by iron binding capacity) and serum ferritin, should be evaluated. Transferrin saturation should be at least 20%, and ferritin 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.

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 male and female rats treated intravenously with PROCRIT, there was a trend for slightly increased fetal wastage at doses of 100 and 500 units/kg.

Pregnancy Category C: PROCRIT has been shown to have adverse effects in rats when given in doses five times the human dose. There are no adequate and well-controlled studies in pregnant women. PROCRIT should be used during pregnancy only if 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, delayed ossification, 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 trend for slightly increased fetal wastage at doses 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 6 to 18 of gestation).

Nursing Mothers: Postnatal observations of the live offspring (F1 generation) of female rats treated with PROCRIT during gestation and lactation revealed no effect of PROCRIT at doses of up to 500 units/kg. There were, however, decreases in body weight gain, delays in appearance of abdominal hair, eyelid opening, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 units/kg group. 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 hematocrit 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, or exceeding the target range (hematocrit of 30-33%), the guidelines for dose and frequency of dose adjustments (see "Dosage and Administration") should be followed.

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 of excessive rate of rise of hematocrit with an exacerbation of hypertension.

The elevated bleeding time 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 and the red cell half-life, an interval of 2-6 weeks may occur between the time of a dose adjustment (initiation, increase, decrease, or discontinuation) and a significant change in hematocrit.

Laboratory Monitoring: The hematocrit should be determined twice a week until it has stabilized in the target range and the maintenance dose has been established. After any dose adjustment, the hematocrit should also be determined twice 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 clinical trials, modest increases were seen in platelets and white blood cell counts. While these changes were statistically significant, they were not clinically significant and the values remained within normal ranges.

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 changes were statistically significant, the values remained within the ranges normally seen in patients with CRF.

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 and episodes of hypertension may increase during PROCRIT therapy in all CRF patients, whether or not they require dialysis, often during the early phase of treatment when the hematocrit is increasing. To prevent hypertension and its sequelae, particular care needs to be taken in patients treated with PROCRIT to monitor and aggressively control blood pressure. During the period when hematocrit is increasing, approximately 25% of patients on dialysis may require initiation of, or increases in, antihypertensive therapy. Patients should be advised as to the importance of compliance with antihypertensive therapy and dietary restrictions. 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 of excessive rate of rise of hematocrit with an exacerbation of hypertension. If blood pressure is difficult to control, the dose of PROCRIT should be reduced; if clinically indicated, PROCRIT may be withheld until blood pressure control is re-established.

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 90 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 90 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 0.11 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 function[9,10] or the efficiency of high flux hemodialysis.[11] 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=2/63) of PROCRIT-treated patients and 2.9% (N=2/68) of placebo-treated patients had seizures. Seizures in 1.6% (N=1/63) PROCRIT-treated patient 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=2/63) of PROCRIT-treated patients and 11.8% (N=8/68) of placebo-treated patients had thrombotic events (e.g. pulmonary embolism, cerebrovascular accident).

Growth Factor Potential
PROCRIT is a growth factor that primarily stimulates red cell production. However, the possibility that PROCRIT can act as a growth factor for any tumor type, particularly myeloid malignancies, cannot be excluded.

ADVERSE REACTIONS

Chronic Renal Failure Patients
Studies analyzed to date indicate that PROCRIT is generally well-tolerated. The adverse events reported are frequent sequelae of CRF and are not necessarily attributable to PROCRIT therapy. In double-blind, placebo-controlled studies involving over 300 patients with CRF, the events reported in greater than 5% of PROCRIT-treated patients during the blinded phase were:

PERCENT OF PATIENTS REPORTING EVENT

Event	PROCRIT-Treated Patients (N=200)	PLACEBO-Treated Patients (N=135)
Hypertension	24%	19%
Headache	16%	12%
Arthralgias	11%	6%
Nausea	11%	9%
Edema	9%	10%
Fatigue	9%	14%
Diarrhea	9%	6%
Vomiting	8%	5%
Chest Pain	7%	9%
Skin Reaction (Administration Site)	7%	12%
Asthenia	7%	12%
Dizziness	7%	13%
Clotted Access	7%	2%

Significant adverse events of concern in patients with CRF treated in double-blinded, placebo-controlled trials occurred in the following percent of patients during the blinded phase of the studies:

Seizure	1.1%	1.1%
CVA/TIA	0.4%	0.6%
MI	0.4%	1.1%
Death	0	1.7%

In the U.S. PROCRIT 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 (0.75), headache (0.40), tachycardia (0.31), nausea/vomiting (0.26), clotted vascular access (0.25), shortness of breath (0.14), hyperkalemia (0.11), and diarrhea (0.11). Other reported events occurred at a rate of less than 0.10 events per patient per year.

Events reported to have occurred within several hours of administration of PROCRIT were rare, mild and transient, and included flu-like symptoms such as arthralgias and myalgias.

In all studies analyzed to date, PROCRIT administration was generally well tolerated, irrespective of the route of administration.

Allergic Reactions: There have been no reports of serious allergic reactions or anaphylaxis associated with PROCRIT 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 erythropoietin in patients tested to date, including those receiving intravenous PROCRIT for over two years. Nevertheless, if an anaphylactoid reaction occurs, PROCRIT should be immediately discontinued and appropriate therapy initiated.

Seizures: The relationship, if any, of PROCRIT 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.[15-17] There have been 47 seizures in 1010 patients on dialysis treated with PROCRIT with an exposure of 986 patient-years for a rate of approximately 0.048 events per patient-year. However, there appeared to be a higher rate of seizures during the first 90 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 rise of hematocrit is uncertain, it is recommended that the dose of PROCRIT be decreased if the hematocrit increase exceeds 4 points in any two-week period.

Hypertension: Up to 80% of patients with CRF have a history of hypertension.[18] Blood pressure may rise during PROCRIT therapy in CRF patients whether or not maintained on dialysis; during the early phase of treatment when hematocrit is increasing, approximately 25% of patients on dialysis may require initiation or increases in antihypertensive therapy. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with PROCRIT. Increases in blood pressure may be associated with the rate of increase in hematocrit. It is recommended that the dose of PROCRIT be decreased if the hematocrit increase exceeds 4 points in any two-week period.

Increases in blood pressure have been reported in clinical trials, often during the first 90 days of therapy. When data from all patients in the U.S. Phase III multicenter trial were analyzed, there was an apparent trend of more reports of hypertensive adverse events in patients on dialysis with a faster rate of rise of hematocrit (greater than 4 hematocrit points in any two week period). However, in a double-blind, placebo-controlled trial, hypertensive adverse events were not reported at an increased rate in the PROCRIT-treated group (150 units/kg T.I.W.) relative to the placebo group. There do not appear to be any direct pressor effects of PROCRIT. Care should be taken to closely monitor and control blood pressure in PROCRIT-treated patients with existing compromised cardiovasculature.

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.

Zidovudine-treated HIV-Infected Patients
Adverse experiences reported in clinical trials with PROCRIT in zidovudine-treated HIV-infected patients were consistent with the progression of HIV infection. In double-blind, placebo-controlled studies of 3-months duration involving approximately 300 zidovudine-treated HIV-infected patients, adverse events with an incidence of ≥10% in either PROCRIT-treated patients or placebo-treated patients were:

Percent of Patients Reporting Event

Event	PROCRIT-Treated Patients (N=144)	PLACEBO-Treated Patients (N=153)
Pyrexia	38%	29%
Fatigue	25%	31%
Headache	19%	14%
Cough	18%	14%
Diarrhea	16%	18%
Rash	16%	8%
Congestion, Respiratory	15%	10%
Nausea	15%	12%
Shortness of Breath	14%	13%
Asthenia	11%	14%
Skin Reaction, Medication Site	10%	7%
Dizziness	9%	10%

There were no statistically significant differences between treatment groups in the incidence of the above events.

In the 297 patients studied, PROCRIT was not associated with significant increases in opportunistic infections or mortality.[14] In 71 patients from this group treated with PROCRIT at 150 units/kgT.I.W., serum p24 antigen levels did not appear to increase.[14] Preliminary data showed no enhancement of HIV replication in infected cell lines *in vitro*.[14]

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

Allergic Reactions: Two zidovudine-treated HIV-infected patients had urticarial reactions within 48 hours of their first exposure to study medication. One patient was treated with PROCRIT and one was treated with placebo (PROCRIT vehicle alone). Both patients had positive immediate skin tests against their study medication with a negative saline control. The basis for this apparent pre-existing hypersensitivity to components of the PROCRIT formulation is unknown, but may be related to HIV-induced immunosuppression or prior exposure to blood products.

Seizures: In double-blind and open label trials of PROCRIT in HIV-infected zidovudine-treated patients, 10 patients have experienced seizures.[14] In general, these seizures appear to be related to underlying pathology such as meningitis or cerebral neoplasms, not PROCRIT therapy.

Cancer Patients on Chemotherapy
Adverse experiences reported in clinical trials with PROCRIT in cancer patients were consistent with the underlying disease state. In double-blind, placebo-controlled studies of up to three months duration involving 131 cancer patients on chemotherapy, adverse events with an incidence > 10% in either PROCRIT -treated or placebo-treated patients were as indicated below.

Percent of Patients Reporting Event

Event	PROCRIT-Treated Patients (N=63)	PLACEBO-Treated Patients (N=68)
Pyrexia	29%	19%
Diarrhea	21%[a]	7%
Nausea	17%[b]	32%
Vomiting	17%	15%
Edema	17%[c]	1%
Asthenia	13%	16%
Fatigue	13%	15%
Shortness of Breath	13%	9%
Parethesia	11%	6%
Upper Respiratory Infection	11%	4%
Dizziness	5%	12%
Trunk Pain	3%[d]	16%

a p = 0.041 c p = 0.0016
b p = 0.069 d p = 0.017

Although some statistically significant diffences between PROCRIT and placebo-treated patients were noted, the overall safety profile of PROCRIT appeared to be consistent with the disease process of advanced cancer. During double blind and subsequent open label therapy in which patients (N=72 for total PROCRIT-exposure) were treated for up to 32 weeks with doses as high as 927 units/kg, the adverse experience profile of PROCRIT was consistent with the progression of advanced cancer.

Based on comparable survival data, and on the percentage of PROCRIT and placebo-treated patients who discontinued therapy due to death, disease progression or adverse experiences (22% and 13%, respectively; p = 0.25), the clinical outcome in PROCRIT and placebo-treated patients appeared to be similar. Available data from animal tumor models and measurement of proliferation of solid tumor cells from clinical biopsy specimens in response to PROCRIT suggest that PROCRIT does not potentiate tumor growth. Nevertheless, as a growth factor, the possibility that PROCRIT may potentiate growth of some tumors, particularly myeloid tumors, cannot be excluded. A randomized controlled Phase IV study is currently ongoing to further evaluate this issue.

The mean peripheral white blood cell count was unchanged following PROCRIT therapy compared to the corresponding value in placebo-treated patients.

OVERDOSAGE

The maximum amount of PROCRIT that can be safely administered in single or multiple doses has not been determined. Doses of up to 1500 units/kg T.I.W. for three to four weeks have been administered without any direct toxic effects of PROCRIT itself.[6]

Therapy with PROCRIT can result in polycythemia if the hematocrit is not carefully monitored and the dose appropriately adjusted. If the target range is exceeded, PROCRIT may be temporarily withheld until the hematocrit returns to the target range; PROCRIT therapy may then be resumed using a lower dose (see "Dosage and Administration"). If polycythemia is of concern, phlebotomy may be indicated to decrease the hematocrit.

DOSAGE AND ADMINISTRATION

Chronic Renal Failure Patients
Starting doses of PROCRIT over the range of 50-100 units/kg three times weekly (T.I.W.) have been shown to be safe and effective in increasing hematocrit and eliminating transfusion dependency in patients with CRF (see "Clinical Experience"). The dose of PROCRIT should be reduced when the hematocrit reaches the target range of 30-33% or increases by more than 4 points in any two-week period. The dosage of PROCRIT must be individualized to maintain the hematocrit within the target range. Dose changes should generally be in the range of 25 units/kg, T.I.W. The table below provides general therapeutic guidelines.

Starting Dose	Reduce Dose When:	Increase Dose If:	Maintenance Dose	Target Hct. Range
50-100 units/kg T.I.W.; IV: Dialysis Patients; IV or SC: Non-dialysis CRF patients	1) Target range is reached, or 2) Hct. increases > 4 points in any two-week period	Hct does not increase by 5-6 points after 8 weeks of therapy, and Hct. is below target range	Individually titrate	30-33% (max: 36%)

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 (serum iron divided by iron binding capacity) and serum ferritin, should be evaluated. Transferrin saturation should be at least 20%, and ferritin 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. Once the hematocrit is within the 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%; the dose should be reduced by approximately 25 units/kg T.I.W. upon re-initiation of therapy.

- 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 in increments of 25 units/kg T.I.W. 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 is 33% or less. Upon re-initiation of therapy, the dose should be reduced by approximately 25 units/kg T.I.W., or doses omitted, and an appropriate time interval (i.e., 2-6 weeks) allowed for stabilization of response. If the hematocrit remains below, or falls below the target range, iron stores should be re-evaluated. If the transferrin saturation is less than 20%, supplemental iron should be administered. If the transferrin saturation is greater than 20%, 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, unless clinically indicated, as the response time of the hematocrit to a dose increase can be 2-6 weeks. Hematocrit should be measured twice weekly for 2-6 weeks following dose increases.

In the U.S. Phase III multicenter trial in patients on hemodialysis, the median maintenance dose was 75 units/kg T.I.W., with approximately 65% of the patients requiring doses of 100 units/kg T.I.W., or less, to maintain their hematocrit within the range of 32-38% (maintenance doses ranged from 12.5 to 525 units/kg T.I.W.). Almost 10% of the patients required a dose of 25 units/kg, or less, and approximately 10% of the patients required more than 200 units/kg T.I.W. to maintain their hematocrit in this range.

In patients with CRF not on dialysis, the maintenance dose must also be individualized. PROCRIT doses of 75-150 units/kg per week have been shown to maintain hematocrits of 36-38% for up to six months.

Delayed or Diminished Response: Over 95% of patients with CRF responded with clinically significant increases in hematocrit, and virtually all patients were transfusion-independent within approximately two months of initiation of PROCRIT therapy.

If a patient fails to respond or maintain a response, other etiologies should be considered and evaluated as clinically indicated. See "Precautions" section for discussion of delayed or diminished response.

Zidovudine-treated HIV-Infected Patients
Prior to beginning PROCRIT, it is recommended that the endogenous serum erythropoietin level be determined (prior to transfusion). Available evidence suggests that patients receiving zidovudine with endogenous serum erythropoietin levels > 500 mU/mL are unlikely to respond to therapy with PROCRIT.

Starting Dose: For patients with serum erythropoietin levels ≤ 500 mU/mL who are receiving a dose of zidovudine ≤ 4200 mg/week, the recommended starting dose of PROCRIT is 100 units/kg as an intravenous or subcutaneous injection three times weekly (T.I.W.) for 8 weeks.

Increase Dose: During the dose adjustment phase of therapy, the hematocrit should be monitored weekly. If the response is not satisfactory in terms of reducing transfusion requirements or increasing hematocrit after 8 weeks of therapy, the dose of PROCRIT can be increased by 50-100 units/kg T.I.W. Response should be evaluated every 4-8 weeks thereafter and the dose adjusted accordingly by 50-100 units/kg increments T.I.W. If patients have not responded satisfactorily to a PROCRIT dose of 300 units/kg T.I.W., it is unlikely that they will respond to higher doses of PROCRIT.

Maintenance Dose: After attainment of the desired response (i.e., reduced transfusion requirements or increased hematocrit), the dose of PROCRIT should be titrated to maintain the response based on factors such as variations in zidovudine dose and the presence of intercurrent infectious or inflammatory episodes. If the hematocrit exceeds 40%, the dose should be discontinued until the hematocrit drops to 36%. The dose should be reduced by 25% when treatment is resumed and then titrated to maintain the desired hematocrit.

Cancer Patients on Chemotherapy
Baseline endogenous serum erythropoietin levels varied among patients in these trials with approximately 75 % (N=83/110) having endogenous serum erythropoietin levels < 132 mU/mL, and approximately 4 % (N=4/110) of patients having endogenous serum erythropoietin levels > 500 mU/mL. In general, patients with lower baseline serum erythropoietin levels responded more vigorously to PROCRIT than patients with higher erythropoietin levels. Although no specific serum erythropoietin level can be stipulated above which patients would be unlikely to respond to PROCRIT therapy, treatment of patients with grossly elevated serum erythropoietin levels (e.g., > 200 mU/mL) is not recommended. The hematocrit should be monitored on a weekly basis in patients receiving PROCRIT therapy until hematocrit becomes stable.

Starting Dose: The recommended starting dose of PROCRIT is 150 units/kg subcutaneously T.I.W.

Dose Adjustment: If the response is not satisfactory in terms of reducing transfusion requirements or increasing hematocrit after 8 weeks of therapy, the dose of PROCRIT can be increased up to 300 units/kg T.I.W.. If patients have not responded satisfactorily to a PROCRIT dose of 300 units/kg T.I.W., it is unlikely that they will respond to higher doses of PROCRIT. If the hematocrit exceeds 40%, the dose of PROCRIT should be held until the hematocrit falls to 36%. The dose of PROCRIT should be reduced by 25% when treatment is resumed and titrated to maintain the desired hematocrit. If the initial dose of PROCRIT includes a very rapid hematocrit response (e.g., an increase of more than 4 percentage points in any 2 week period), the dose of PROCRIT should be reduced.

PREPARATION AND ADMINISTRATION OF PROCRIT

1. DO NOT SHAKE. Shaking may denature the glycoprotein, rendering it biologically inactive.
2. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.
3. Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from the vial containing PROCRIT, and wipe the septum with a disinfectant. Insert the needle into the vial, and withdraw into the syringe an appropriate volume of solution.
4. Use only one dose per vial; do not re-enter the vial. Discard unused portions. Contains no preservative.
5. Do not administer in conjunction with other drug solutions.

HOW SUPPLIED

PROCRIT is available in vials containing 2,000 (NDC 0062-7402-01), 3,000 (NDC 0062-7405-01), 4,000 (NDC 0062-7400-03) or 10,000 (NDC 0062-7401-03) units of Epoetin alfa in 1.0 mL of a sterile, preservative-free solution. Each dosage form is supplied in boxes containing 6 single-use vials.

STORAGE

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

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