EPOGEN®
(Epoetin alfa)
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. EPOGEN® (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.

EPOGEN® is formulated as a sterile, colorless liquid in an isotonic sodium chloride/sodium citrate buffered solution or a sodium chloride/sodium phosphate buffered solution for intravenous (IV) or subcutaneous (SC) administration.

Single-dose, Preservative-free Vial: Each 1 mL of solution contains 2000, 3000, 4000 or 10,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 5.8 mg sodium citrate, 5.8 mg sodium chloride, and 0.06 mg citric acid in Water for Injection, USP (pH 6.9 ± 0.3). This formulation contains no preservative.

Single-dose, Preservative-free Vial: 1 mL (40,000 Units/mL). Each 1 mL of solution contains 40,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 1.2 mg sodium phosphate monobasic monohydrate, 1.8 mg sodium phosphate dibasic anhydrate, 0.7 mg sodium citrate, 5.8 mg sodium chloride, and 6.8 mcg citric acid in Water for Injection, USP (pH 6.9 ± 0.3). This formulation contains no preservative.

Multidose, Preserved Vial: 2 mL (20,000 Units, 10,000 Units/mL). Each 1 mL of solution contains 10,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 1.3 mg sodium citrate, 8.2 mg sodium chloride, 0.11 mg citric acid, and 1% benzyl alcohol as preservative in Water for Injection, USP (pH 6.1 ± 0.3).

Multidose, Preserved Vial: 1 mL (20,000 Units/mL). Each 1 mL of solution contains 20,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 1.3 mg sodium citrate, 8.2 mg sodium chloride, 0.11 mg citric acid, and 1% benzyl alcohol as preservative in Water for Injection, USP (pH 6.1 ± 0.3).

CLINICAL PHARMACOLOGY

Chronic Renal Failure Patients

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 and increase up to 100- to 1000-fold during hypoxia or anemia.[2] 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.

EPOGEN® 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 (TIW) administration of EPOGEN® is an increase in the reticulocyte count within 10 days, followed by increases in the red cell count, hemoglobin, and hematocrit, usually within 2 to 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 suggested target range (30% to 36%), that level can be sustained by EPOGEN® 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 EPOGEN®, within a therapeutic range of approximately 50 to 300 Units/kg TIW.[4] A greater biologic response is not observed at doses exceeding 300 Units/kg TIW.[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 EPOGEN® in HIV-infected patients is dependent upon the endogenous serum erythropoietin level prior to treatment. Patients with endogenous serum erythropoietin levels ≤ 500 mUnits/mL, and who are receiving a dose of zidovudine ≤ 4200 mg/week, may respond to EPOGEN® therapy. Patients with endogenous serum erythropoietin levels > 500 mUnits/mL do not appear to respond to EPOGEN® therapy. In a series of four clinical trials involving 255 patients, 60% to 80% of HIV-infected patients treated with zidovudine had endogenous serum erythropoietin levels ≤ 500 mUnits/mL.

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

Cancer Patients on Chemotherapy

A series of clinical trials enrolled 131 anemic cancer patients who received EPOGEN® TIW and 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 mUnits/mL, and approximately 4% (n = 4/110) of patients having endogenous serum erythropoietin levels > 500 mUnits/mL. In general, patients with lower baseline serum erythropoietin levels responded more vigorously to EPOGEN® than patients with higher baseline erythropoietin levels. Although no specific serum erythropoietin level can be stipulated above which patients would be unlikely to respond to EPOGEN® therapy, treatment of patients with grossly elevated serum erythropoietin levels (eg, > 200 mUnits/mL) is not recommended.

Pharmacokinetics

In adult and pediatric patients with CRF, the elimination half-life of plasma erythropoietin after intravenously administered EPOGEN® ranges from 4 to 13 hours.[14-16] The half-life is approximately 20% longer in CRF patients than that in healthy subjects. After SC administration, peak plasma levels are achieved within 5 to 24 hours. The half-life is similar between adult patients with serum creatinine level greater than 3 and not on dialysis and those maintained on dialysis.

The pharmacokinetic profile of EPOGEN® in children and adolescents appears to be similar to that of adults. Limited data are available in neonates.[17]

The pharmacokinetics of EPOGEN® have not been studied in HIV-infected patients.

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

The bioequivalence between the 10,000 Units/mL citrate-buffered Epoetin alfa formulation and the 40,000 Units/mL phosphate-buffered Epoetin alfa formulation has been demonstrated after SC administration of single 750 Units/kg doses to healthy subjects.

INDICATIONS AND USAGE

Treatment of Anemia of Chronic Renal Failure Patients

EPOGEN® is indicated for the treatment of anemia associated with CRF, including patients on dialysis (ESRD) and patients not on dialysis. EPOGEN® 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.

Non-dialysis patients with symptomatic anemia considered for therapy should have a hemoglobin less than 10 g/dL.

EPOGEN® is not intended for patients who require immediate correction of severe anemia. EPOGEN® 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 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 EPOGEN® therapy, and must be closely monitored and controlled during therapy.

EPOGEN® should be administered under the guidance of a qualified physician (see DOSAGE AND ADMINISTRATION).

Treatment of Anemia in Zidovudine-treated HIV-infected Patients

EPOGEN® is indicated for the treatment of anemia related to therapy with zidovudine in HIV-infected patients. EPOGEN® 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. EPOGEN® 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.

EPOGEN®, at a dose of 100 Units/kg TIW, 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 mUnits/mL and when patients are receiving a dose of zidovudine ≤ 4200 mg/week.

Treatment of Anemia in Cancer Patients on Chemotherapy
EPOGEN® is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. EPOGEN® is indicated to decrease the need for transfusions in patients who will be receiving concomitant chemotherapy for a minimum of 2 months. EPOGEN® 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.

Reduction of Allogeneic Blood Transfusion in Surgery Patients
EPOGEN® is indicated for the treatment of anemic patients (hemoglobin >10 to ≤ 13 g/dL) scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions.[18-20] EPOGEN® is indicated for patients at high risk for perioperative transfusions with significant, anticipated blood loss. EPOGEN® is not indicated for anemic patients who are willing to donate autologous blood. The safety of the perioperative use of EPOGEN® has been studied only in patients who are receiving anticoagulant prophylaxis.

CLINICAL EXPERIENCE: RESPONSE TO EPOGEN®
Chronic Renal Failure Patients
Response to EPOGEN® was consistent across all studies. In the presence of adequate iron stores (see 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 EPOGEN® administered and individual patient variation. In clinical trials at starting doses of 50 to 150 Units/kg TIW, adult patients responded with an average rate of hematocrit rise of:

Starting Dose	Hematocrit Increase	
(TIW IV)	Points/Day	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 2 months of therapy virtually all patients were transfusion-independent. Changes in the quality of life of adult patients treated with EPOGEN® were assessed as part of a phase 3 clinical trial.[5,8] Once the target hematocrit (32% to 38%) was achieved, statistically significant improvements were demonstrated for most quality of life parameters measured, including energy and activity level, functional ability, sleep and eating behavior, health status, satisfaction with health, sex life, well-being, psychological effect, life satisfaction, and happiness. Patients also reported improvement in their disease symptoms. They showed a statistically significant increase in exercise capacity (VO_2 max), energy, and strength with a significant reduction in aching, dizziness, anxiety, shortness of breath, muscle weakness, and leg cramps.[8,21]

Adult Patients on Dialysis: Thirteen clinical studies were conducted, involving IV administration to a total of 1010 anemic patients on dialysis for 986 patient-years of EPOGEN® therapy. In the three

largest of these clinical trials, the median maintenance dose necessary to maintain the hematocrit between 30% to 36% was approximately 75 Units/kg TIW. In the US multicenter phase 3 study, approximately 65% of the patients required doses of 100 Units/kg TIW, 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 TIW to maintain their hematocrit at this level.

A multicenter unit dose study was also conducted in 119 patients receiving peritoneal dialysis who self-administered EPOGEN® subcutaneously for approximately 109 patient-years of experience. Patients responded to EPOGEN® administered SC in a manner similar to patients receiving IV administration.[22]

Pediatric Patients on Dialysis: One hundred twenty-eight children from 2 months to 19 years of age with CRF requiring dialysis were enrolled in 4 clinical studies of EPOGEN®. The largest study was a placebo-controlled, randomized trial in 113 children with anemia (hematocrit ≤ 27%) undergoing peritoneal dialysis or hemodialysis. The initial dose of EPOGEN® was 50 Units/kg IV or SC TIW. The dose of study drug was titrated to achieve either a hematocrit of 30% to 36% or an absolute increase in hematocrit of 6 percentage points over baseline.

At the end of the initial 12 weeks, a statistically significant rise in mean hematocrit (9.4% vs 0.9%) was observed only in the EPOGEN® arm. The proportion of children achieving a hematocrit of 30%, or an increase in hematocrit of 6 percentage points over baseline, at any time during the first 12 weeks was higher in the EPOGEN® arm (96% vs 58%). Within 12 weeks of initiating EPOGEN® therapy, 92.3% of the pediatric patients were transfusion-independent as compared to 65.4% who received placebo. Among patients who received 36 weeks of EPOGEN®, hemodialysis patients required a higher median maintenance dose (167 Units/kg/week [n = 28] vs 76 Units/kg/week [n = 36]) and took longer to achieve a hematocrit of 30% to 36% (median time to response 69 days vs 32 days) than patients undergoing peritoneal dialysis.

Patients With CRF Not Requiring Dialysis

Four clinical trials were conducted in patients with CRF not on dialysis involving 181 patients treated with EPOGEN® for approximately 67 patient-years of experience. These patients responded to EPOGEN® 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 EPOGEN® was administered by either an IV or SC route, with similar rates of rise of hematocrit when EPOGEN® was administered by either route. Moreover, EPOGEN® doses of 75 to 150 Units/kg <u>per week</u> have been shown to maintain hematocrits of 36% to 38% for up to 6 months. Correcting the anemia of progressive renal failure will allow patients to remain active even though their renal function continues to decrease.[23-24]

Zidovudine-treated HIV-infected Patients

EPOGEN® 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 EPOGEN® and 88/130 placebo) with prestudy endogenous serum erythropoietin levels ≤ 500 mUnits/mL, EPOGEN® reduced the mean cumulative number of units of blood transfused per patient by approximately 40% as compared to the placebo group.[25] Among those patients who required transfusions at baseline, 43% of patients treated with EPOGEN® versus 18% of placebo-treated patients were transfusion-independent during the second and third months of therapy. EPOGEN® 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 patients treated with EPOGEN® (n = 51) compared to placebo treated patients (n = 54) whose mean weekly zidovudine dose was ≤ 4200 mg/week.[25]

Approximately 17% of the patients with endogenous serum erythropoietin levels ≤ 500 mUnits/mL receiving EPOGEN® in doses from 100 to 200 Units/kg TIW achieved a hematocrit of 38% without administration of transfusions or significant reduction in zidovudine dose. In the subgroup of patients whose prestudy endogenous serum erythropoietin levels were > 500 mUnits/mL, EPOGEN® therapy did not reduce transfusion requirements or increase hematocrit, compared to the corresponding responses in placebo-treated patients.

In a 6 month open-label EPOGEN® study, patients responded with decreased transfusion requirements and sustained increases in hematocrit and hemoglobin with doses of EPOGEN® up to 300 Units/kg TIW.[25-27]

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

Cancer Patients on Chemotherapy

Three-Times Weekly (TIW) Dosing

EPOGEN® administered TIW has been studied in a series of six placebo-controlled, double-blind trials that enrolled 131 anemic cancer patients receiving EPOGEN® or matching placebo. Across all studies, 72 patients were treated with concomitant non cisplatin-containing chemotherapy regimens and 59 patients were treated with concomitant cisplatin-containing chemotherapy regimens. Patients were randomized to EPOGEN® 150 Units/kg or placebo subcutaneously TIW for 12 weeks in each study.

The results of the pooled data from these six studies are shown in the table below. Because of the length of time required for erythropoiesis and red cell maturation, the efficacy of EPOGEN® (reduction in proportion of patients requiring transfusions) is not manifested until 2 to 6 weeks after initiation of EPOGEN®.

Proportion of Patients Transfused During Chemotherapy (Efficacy Population[a])

Chemotherapy Regimen	On Study[b]		During Months 2 and 3[c]	
	EPOGEN®	Placebo	EPOGEN®	Placebo
Regimens without cisplatin	44% (15/34)	44% (16/36)	21% (6/29)	33% (11/33)
Regimens containing cisplatin	50% (14/28)	63% (19/30)	23% (5/22)[d]	56% (14/25)
Combined	47% (29/62)	53% (35/66)	22% (11/51)[d]	43% (25/58)

[a] Limited to patients remaining on study at least 15 days (1 patient excluded from EPOGEN®, 2 patients excluded from placebo).
[b] Includes all transfusions from day 1 through the end of study.
[c] Limited to patients remaining on study beyond week 6 and includes only transfusions during weeks 5-12.
[d] Unadjusted 2-sided $p < 0.05$

Intensity of chemotherapy in the above trials was not directly assessed, however the degree and timing of neutropenia was comparable across all trials. Available evidence suggests that patients with lymphoid and solid cancers respond similarly to EPOGEN® therapy, and that patients with or without tumor infiltration of the bone marrow respond similarly to EPOGEN® therapy.

Weekly (QW) Dosing

EPOGEN® was also studied in a placebo-controlled, double-blind trial utilizing weekly dosing in a total of 344 anemic cancer patients. In this trial, 61 (35 placebo arm and 26 in the EPOGEN® arm) patients were treated with concomitant cisplatin containing regimens and 283 patients received concomitant chemotherapy regimens that did not contain cisplatinum. Patients were randomized to EPOGEN® 40,000 Units weekly (n = 174) or placebo (n = 170) SC for a planned treatment period of 16 weeks. If hemoglobin had not increased by > 1 g/dL, after 4 weeks of therapy or the patient received RBC transfusion during the first 4 weeks of therapy, study drug was increased to 60,000 Units weekly. Forty-three percent of patients in the Epoetin alfa group required and increase in EPOGEN® dose to 60,000 Units weekly.[25]

Results demonstrated that EPOGEN® therapy reduced the proportion of patients transfused in day 29 through week 16 of the study as compared to placebo. Twenty-five patients (14%) in the EPOGEN® group received transfusions compared to 48 patients (28%) in the placebo group ($p = 0.0010$) between day 29 and week 16 or the last day on study.

Comparable intensity of chemotherapy for patients enrolled in the two study arms was suggested by similarities in mean dose and frequency of administration for the 10 most commonly administered chemotherapy agents, and similarity in the incidence of changes in chemotherapy during the trial in the two arms.

Surgery Patients

EPOGEN® has been studied in a placebo-controlled, double-blind trial 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. Based on previous studies which demonstrated that pretreatment hemoglobin is a predictor of risk of receiving transfusion,[20,28] patients were stratified into one of three groups based on their pretreatment hemoglobin [≤ 10 (n = 2), > 10 to ≤ 13 (n = 96), and > 13 to ≤ 15 g/dL (n = 218)] and then randomly assigned to receive 300 Units/kg EPOGEN®, 100 Units/kg EPOGEN® or placebo by SC injection for 10 days before surgery, on the day of surgery, and for 4 days after surgery.[18] All patients received oral iron and a low-dose post-operative warfarin regimen.[18]

Treatment with EPOGEN® 300 Units/kg significantly ($p = 0.024$) reduced the risk of allogeneic transfusion in patients with a pretreatment hemoglobin of > 10 to ≤ 13; 5/31 (16%) of EPOGEN® 300 Units/kg, 6/26 (23%) of EPOGEN® 100 Units/kg, and 13/29 (45%) of placebo-treated patients were transfused.[18] There was no significant difference in the number of patients transfused between EPOGEN® (9% 300 Units/kg, 6% 100 Units/kg) and placebo (13%) in the > 13 to ≤ 15 g/dL hemoglobin stratum. There were too few patients in the ≤ 10 g/dL group to determine if EPOGEN® is useful in this hemoglobin strata. In the > 10 to ≤ 13 g/dL pretreatment stratum, the mean number of units transfused per EPOGEN®-treated patient (0.45 units blood for 300 Units/kg, 0.42 units blood for 100 Units/kg) was less than the mean transfused per placebo-treated patient (1.14 units) (overall $p = 0.028$). In addition, mean hemoglobin, hematocrit, and reticulocyte counts increased significantly during the presurgery period in patients treated with EPOGEN®.[18]

EPOGEN® was also studied in an open-label, parallel-group trial enrolling 145 subjects with a pretreatment hemoglobin level of ≥ 10 to ≤ 13 g/dL who were scheduled for major orthopedic hip or knee surgery and who were not participating in an autologous program.[19] Subjects were randomly assigned to receive one of two SC dosing regimens of EPOGEN® (600 Units/kg once weekly for 3 weeks prior to surgery and on the day of surgery, or 300 Units/kg once daily for 10 days prior to surgery, on the day of surgery and for 4 days after surgery). All subjects received oral iron and appropriate pharmacologic anticoagulation therapy.

From pretreatment to presurgery, the mean increase in hemoglobin in the 600 Units/kg weekly group (1.44 g/dL) was greater than observed in the 300 Units/kg daily group.[19] The mean increase in absolute reticulocyte count was smaller in the weekly group ($0.11 \times 10^6/mm^3$) compared to the daily group ($0.17 \times 10^6/mm^3$). Mean hemoglobin levels were similar for the two treatment groups throughout the postsurgical period.

The erythropoietic response observed in both treatment groups resulted in similar transfusion rates [11/69 (16%) in the 600 Units/kg weekly group and 14/71 (20%) in the 300 Units/kg daily group].[19] The mean number of units transfused per subject was approximately 0.3 units in both treatment groups.

CONTRAINDICATIONS

EPOGEN® is contraindicated in patients with:

1. Uncontrolled hypertension.
2. Known hypersensitivity to mammalian cell-derived products.
3. Known hypersensitivity to Albumin (Human).

WARNINGS

Pediatric Use

The multidose preserved formulation contains benzyl alcohol. Benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications in premature infants which are sometimes fatal.

Thrombotic Events and Increased Mortality

A randomized, prospective trial of 1265 hemodialysis patients with clinically evident cardiac disease (ischemic heart disease or congestive heart failure) was conducted in which patients were assigned to EPOGEN® treatment targeted to a maintenance hematocrit of either 42 ± 3% or 30 ± 3%.[42] Increased mortality was observed in 634 patients randomized to a target hematocrit of 42% [221 deaths (35% mortality)] compared to 631 patients targeted to remain at a hematocrit of 30% [185 deaths (29% mortality)]. The reason for the increased mortality observed in these studies is unknown, however, the incidence of non-fatal myocardial infarctions (3.1% vs 2.3%), vascular access thromboses (39% vs 29%), and all other thrombotic events (22% vs 18%) were also higher in the group randomized to achieve a hematocrit of 42%.

Increased mortality was also observed in a randomized placebo-controlled study of EPOGEN® in adult patients who did not have CRF who were undergoing coronary artery bypass surgery (7 deaths in 126 patients randomized to EPOGEN® versus no deaths among 56 patients receiving placebo). Four of these deaths occurred during the period of study drug administration and all four deaths were associated with thrombotic events. While the extent of the population affected is unknown, in patients at risk for thrombosis, the anticipated benefits of EPOGEN® treatment should be weighed against the potential for increased risks associated with therapy.

In a randomized, prospective trial conducted with another Epoetin alfa product, in 939 women with metastatic carcinoma of the breast who were receiving chemotherapy, patients were assigned to receive either Epoetin alfa or placebo for up to a year, in a weekly schedule, with the primary goal of showing improved survival and improved quality of life in the Epoetin alfa treatment arm.[25] This study utilized a treatment strategy designed to maintain hemoglobin levels of 12 to14 g/dL (hematocrit 36 to 42%). Increased mortality in the first 4 months after randomization was observed among 469 patients who received the erythropoietin product [41 deaths (8.7% mortality)] compared to 470 patients who received placebo [16 deaths (3.4% mortality)]. In the first four months of the study, the incidence of fatal thrombotic vascular events (1.1% vs 0.2%) and death attributed to disease progression (6.0% vs 2.8%) were both higher in the group randomized to receive Epoetin alfa as compared to placebo. Based on Kaplan-Meier estimates, the proportion of subjects surviving at 12 months after randomization was lower in the Epoetin alfa group than in the placebo group (70% vs 76%), $p = 0.012$, log rank. However, due to insufficient monitoring and data collection, reliable comparisons cannot be made concerning the effect of Epoetin alfa on overall time to disease progression, progression-free survival, and overall survival.

Pure Red Cell Aplasia
Pure red cell aplasia (PRCA), in association with neutralizing antibodies to native erythropoietin, has been observed in patients treated with recombinant erythropoietins. PRCA has been reported in a limited number of patients exposed to EPOGEN®. This has been reported predominantly in patients with CRF. Any patient with loss of response to EPOGEN® should be evaluated for the etiology of loss of effect (see PRECAUTIONS: LACK OR LOSS OF RESPONSE). EPOGEN® should be discontinued in any patient with evidence of PRCA and the patient evaluated for the presence of binding and neutralizing antibodies to EPOGEN® native erythropoietin, and any other recombinant erythropoietin administered to the patient. Amgen should be contacted to assist in this evaluation. In patients with PRCA secondary to neutralizing antibodies to erythropoietin, EPOGEN® should not be administered and such patients should not be switched to another product as anti-erythropoietin antibodies cross-react with other erythropoietins (see ADVERSE REACTIONS).

Albumin (Human)
EPOGEN® contains albumin, a derivative of human blood. 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.

Chronic Renal Failure Patients
Hypertension: Patients with uncontrolled hypertension should not be treated with EPOGEN®; blood pressure should be controlled adequately before initiation of therapy. Up to 80% of patients with CRF have a history of hypertension.[29] Although there does not appear to be any direct pressor effects of EPOGEN®, blood pressure may rise during EPOGEN® therapy. During the early phase of treatment when the hematocrit is increasing, approximately 25% of patients on dialysis may require initiation of, or increases in, antihypertensive therapy. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with EPOGEN®.

Special care should be taken to closely monitor and aggressively control blood pressure in patients treated with EPOGEN®. Patients should be advised as to the importance of compliance with antihypertensive therapy and dietary restrictions. If blood pressure is difficult to control by initiation of appropriate measures, the hemoglobin may be reduced by decreasing or withholding the dose of EPOGEN®. A clinically significant decrease in hemoglobin may not be observed for several weeks.

It is recommended that the dose of EPOGEN® be decreased if the hemoglobin increase exceeds 1 g/dL in any 2-week period, because of the possible association of excessive rate of rise of hemoglobin with an exacerbation of hypertension. In CRF patients on hemodialysis with clinically evident ischemic heart disease or congestive heart failure, the hemoglobin should be managed carefully, not to exceed 12 g/dL (see THROMBOTIC EVENTS).

Seizures: Seizures have occurred in patients with CRF participating in EPOGEN® clinical trials.

In adult 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.

While the relationship between seizures and the rate of rise of hemoglobin is uncertain, it is recommended that the dose of EPOGEN® be decreased if the hemoglobin increase exceeds 1 g/dL in any 2-week period.

Thrombotic Events: During hemodialysis, patients treated with EPOGEN® may require increased anticoagulation with heparin to prevent clotting of the artificial kidney (see ADVERSE REACTIONS for more information about thrombotic events).

Other thrombotic events (eg, myocardial infarction, cerebrovascular accident, transient ischemic attack) have occurred in clinical trials at an annualized rate of less than 0.04 events per patient year of EPOGEN® therapy. These trials were conducted in adult patients with CRF (whether on dialysis or not) in whom the target hematocrit was 32% to 40%. However, the risk of thrombotic events, including vascular access thrombosis, was significantly increased in adult patients with ischemic heart disease or congestive heart failure receiving EPOGEN® therapy with the goal of reaching a normal hematocrit (42%) as compared to a target hematocrit of 30%. Patients with pre-existing cardiovascular disease should be monitored closely.

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

PRECAUTIONS
The parenteral administration of any biologic product should be attended by appropriate precautions in case allergic or other untoward reactions occur (see CONTRAINDICATIONS).
In clinical trials, while transient rashes were occasionally observed concurrently with EPOGEN® therapy, no serious allergic or anaphylactic reactions were reported (see ADVERSE REACTIONS for more information regarding allergic reactions).

The safety and efficacy of EPOGEN® therapy have not been established in patients with a known history of a seizure disorder or underlying hematologic disease (eg, sickle cell anemia, myelodysplastic syndromes, or hypercoagulable disorders).

In some female patients, menses have resumed following EPOGEN® therapy; the possibility of pregnancy should be discussed and the need for contraception evaluated.

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

In preclinical studies in dogs and rats, but not in monkeys, EPOGEN® 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 adult patients on dialysis who were treated with EPOGEN® for 12 to 19 months, compared to the incidence of bone marrow fibrosis in a matched group of patients who had not been treated with EPOGEN®.

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

Lack or Loss of Response
If the patient fails to respond or to maintain a response to doses within the recommended dosing range, the following etiologies should be considered and evaluated:
1. Iron deficiency: Virtually all patients will eventually require supplemental iron therapy (see IRON EVALUATION).
2. Underlying infectious, inflammatory, or malignant processes.
3. Occult blood loss.
4. Underlying hematologic diseases (ie, thalassemia, refractory anemia, or other myelodysplastic disorders).
5. Vitamin deficiencies: Folic acid or vitamin B12.
6. Hemolysis.
7. Aluminum intoxication.
8. Osteitis fibrosa cystica.
9. Pure Red Cell Aplasia (PRCA): In the absence of another etiology, the patient should be evaluated for evidence of PRCA and sera should be tested for the presence of antibodies to recombinant erythropoietins.

Iron Evaluation
During EPOGEN® therapy, absolute or functional iron deficiency may develop. Functional iron deficiency, with normal ferritin levels but low transferrin saturation, is presumably due to the inability to mobilize iron stores rapidly enough to support increased erythropoiesis. Transferrin saturation should be at least 20% and ferritin should be at least 100 ng/mL.

Prior to and during EPOGEN® therapy, the patient's iron status, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, should be evaluated. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels which will adequately support erythropoiesis stimulated by EPOGEN®. All surgery patients being treated with EPOGEN® should receive adequate iron supplementation throughout the course of therapy in order to support erythropoiesis and avoid depletion of iron stores.

Drug Interaction
No evidence of interaction of EPOGEN® with other drugs was observed in the course of clinical trials.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenic potential of EPOGEN® has not been evaluated. EPOGEN® does not induce bacterial gene mutation (Ames Test), chromosomal aberrations in mammalian cells, micronuclei in mice, or gene mutation at the HGPRT locus. In female rats treated IV with EPOGEN®, there was a trend for slightly increased fetal wastage at doses of 100 and 500 Units/kg.

Pregnancy Category C

EPOGEN® has been shown to have adverse effects in rats when given in doses 5 times the human dose. There are no adequate and well-controlled studies in pregnant women. EPOGEN® 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 IV, there was a trend for slightly increased fetal wastage at doses of 100 and 500 Units/kg. EPOGEN® 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 EPOGEN® during gestation and lactation revealed no effect of EPOGEN® 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 EPOGEN®-related effects on the F2 generation fetuses.

It is not known whether EPOGEN® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when EPOGEN® is administered to a nursing woman.

Pediatric Use

See WARNINGS: PEDIATRIC USE.

Pediatric Patients on Dialysis: EPOGEN® is indicated in infants (1 month to 2 years), children (2 years to 12 years), and adolescents (12 years to 16 years) for the treatment of anemia associated with CRF requiring dialysis. Safety and effectiveness in pediatric patients less than 1 month old have not been established (see CLINICAL EXPERIENCE: CHRONIC RENAL FAILURE, PEDIATRIC PATIENTS ON DIALYSIS). The safety data from these studies show that there is no increased risk to pediatric CRF patients on dialysis when compared to the safety profile of EPOGEN® in adult CRF patients (see ADVERSE REACTIONS and WARNINGS). Published literature[30-33] provides supportive evidence of the safety and effectiveness of EPOGEN® in pediatric CRF patients on dialysis.

Pediatric Patients Not Requiring Dialysis: Published literature[33,34] has reported the use of EPOGEN® in 133 pediatric patients with anemia associated with CRF not requiring dialysis, ages 3 months to 20 years, treated with 50 to 250 Units/kg SC or IV, QW to TIW. Dose-dependent increases in hemoglobin and hematocrit were observed with reductions in transfusion requirements.

Pediatric HIV-infected Patients: Published literature [35,36] has reported the use of EPOGEN® in 20 zidovudine-treated anemic HIV-infected pediatric patients ages 8 months to 17 years, treated with 50 to 400 Units/kg SC or IV, 2 to 3 times per week. Increases in hemoglobin levels and in reticulocyte counts, and decreases in or elimination of blood transfusions were observed.

Pediatric Cancer Patients on Chemotherapy: Published literature[37,38] has reported the use of EPOGEN® in approximately 64 anemic pediatric cancer patients ages 6 months to 18 years, treated with 25 to 300 Units/kg SC or IV, 3 to 7 times per week. Increases in hemoglobin and decreases in transfusion requirements were noted.

Chronic Renal Failure Patients
Patients with CRF Not Requiring Dialysis
Blood pressure and hemoglobin 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
Sufficient time should be allowed to determine a patient's responsiveness to a dosage of EPOGEN® before adjusting the dose. Because of the time required for erythropoiesis and the red cell half-life, an interval of 2 to 6 weeks may occur between the time of a dose adjustment (initiation, increase, decrease, or discontinuation) and a significant change in hemoglobin.

In order to avoid reaching the suggested target hemoglobin too rapidly, or exceeding the suggested target range (hemoglobin of 10 g/dL to 12 g/dL), the guidelines for dose and frequency of dose adjustments (see DOSAGE AND ADMINISTRATION) should be followed.

For patients who respond to EPOGEN® with a rapid increase in hemoglobin (eg, more than 1 g/dL in any 2-week period), the dose of EPOGEN® should be reduced because of the possible association of excessive rate of rise of hemoglobin with an exacerbation of hypertension.

The elevated bleeding time characteristic of CRF decreases toward normal after correction of anemia in adult patients treated with EPOGEN®. Reduction of bleeding time also occurs after correction of anemia by transfusion.

Laboratory Monitoring
The hemoglobin should be determined twice a week until it has stabilized in the suggested target range and the maintenance dose has been established. After any dose adjustment, the hemoglobin should also be determined twice weekly for at least 2 to 6 weeks until it has been determined that the hemoglobin has stabilized in response to the dose change. The hemoglobin 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 adult patients on dialysis, modest increases were seen in BUN, creatinine, phosphorus, and potassium. In some adult patients with CRF not on dialysis treated with EPOGEN®, 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.

Diet

As the hemoglobin 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 US studies in patients on dialysis, hyperkalemia has occurred at an annualized rate of approximately 0.11 episodes per patient-year of EPOGEN® therapy, often in association with poor compliance to medication, diet, and/or dialysis.

Dialysis Management
Therapy with EPOGEN® 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 EPOGEN® 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 BUN, creatinine, phosphorus, and potassium) in patients treated with EPOGEN® should be monitored regularly to assure the adequacy of the dialysis prescription.

Information for Patients
In those situations in which the physician determines that a home dialysis patient can safely and effectively self-administer EPOGEN®, the patient should be instructed as to the proper dosage and administration. Home dialysis patients should be referred to the full "Information for Home Dialysis Patients" insert; it is not a disclosure of all possible effects. Patients should be informed of the signs and symptoms of allergic drug reaction and advised of appropriate actions. If home use is prescribed for a home dialysis patient, the patient should be thoroughly instructed in the importance of proper disposal and cautioned against the reuse of needles, syringes, or drug product. A puncture-resistant container for the disposal of used syringes and needles should be available to the patient. The full container should be disposed of according to the directions provided by the physician.

Renal Function
In adult 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 1 year have not been completed. In shorter term trials in adult patients with CRF not on dialysis, changes in creatinine and creatinine clearance were not significantly different in patients treated with EPOGEN® compared with placebo-treated patients. Analysis of the slope of 1/serum creatinine versus time plots in these patients indicates no significant change in the slope after the initiation of EPOGEN® therapy.

Zidovudine-treated HIV-infected Patients
Hypertension
Exacerbation of hypertension has not been observed in zidovudine-treated HIV-infected patients treated with EPOGEN®. However, EPOGEN® 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 patient treated with EPOGEN®.[25]

Cancer Patients on Chemotherapy
Hypertension

Hypertension, associated with a significant increase in hemoglobin, has been noted rarely in patients treated with EPOGEN®. Nevertheless, blood pressure in patients treated with EPOGEN® 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 patients treated with EPOGEN® TIW and 2.9% (n = 2/68) of placebo-treated patients had seizures. Seizures in 1.6% (n = 1/63) of patients treated with EPOGEN® TIW occurred in the context of a significant increase in blood pressure and hematocrit from baseline values. However, both patients treated with EPOGEN® also had underlying CNS pathology which may have been related to seizure activity.

In a placebo-controlled, double-blind trial utilizing weekly dosing with EPOGEN®, 1.2% (n = 2/168) of safety-evaluable patients treated with EPOGEN® and 1% (n = 1/165) of placebo-treated patients had seizures. Seizures in the patients treated with weekly EPOGEN® occurred in the context of a significant increase in hemoglobin from baseline values however significant increases in blood pressure were not seen. These patients may have had other CNS pathology.

Thrombotic Events
In double-blind, placebo-controlled trials, 3.2% (n = 2/63) of patients treated with EPOGEN® TIW and 11.8% (n = 8/68) of placebo-treated patients had thrombotic events (eg, pulmonary embolism, cerebrovascular accident), (See WARNINGS; Thrombotic Events and Increased Mortality).

In a placebo-controlled, double-blind trial utilizing weekly dosing with EPOGEN®, 6.0% (n = 10/168) of safety-evaluable patients treated with EPOGEN® and 3.6% (n = 6/165) (p = 0.444) of placebo-treated patients had clinically significant thrombotic events (deep vein thrombosis requiring anticoagulant therapy, embolic event including pulmonary embolism, myocardial infarction, cerebral ischemia, left ventricular failure and thrombotic microangiopathy). A definitive relationship between the rate of hemoglobin increase and the occurrence of clinically significant thrombotic events could not be evaluated due to the limited schedule of hemoglobin measurements in this study.

Tumor Growth Factor Potential
EPOGEN® is a growth factor that primarily stimulates red cell production. Erythropoietin receptors are also found to be present on the surface of some malignant cell lines and tumor biopsy specimens. However, it is not known if these receptors are functional. A randomized, placebo-controlled trial was conducted in 224 chemotherapy-naïve, non-anemic patients with small cell lung cancer receiving cisplatin-based combination chemotherapy, to investigate whether the concurrent use of EPOGEN® stimulated tumor growth as assessed by impact on overall response rate. Patients were randomized to receive EPOGEN® 150 Units/kg or placebo subcutaneously TIW during chemotherapy. The overall response rates, after 3 cycles of treatment, were 72% and 67%, in the EPOGEN® and placebo arms, respectively. Complete response rates (17% vs. 14%) and median overall survival (10.5 mos vs. 10.4 mos) were similar in the EPOGEN® and placebo arms.[25]

Two additional studies explored effect on survival and/or progression of administrations of other exogenous erythropoietin with higher hemoglobin targets.

In a randomized, placebo-controlled study using another Epoetin alfa product, conducted in 939 women with metastatic breast cancer, study drug dosing was titrated to attempt to maintain hemoglobin levels between 12 and 14 g/dL. At four months, death attributed to disease progression was higher (6% vs 3%) in women receiving Epoetin alfa. Overall mortality was significantly higher at 12 months in the Epoetin alfa arm (See WARNINGS; Thrombotic Events and Increased Mortality).

In a randomized, placebo-controlled study using Epoetin beta, conducted in 351 patients with head and neck cancer, study drug was administered with the aim of achieving a hemoglobin level of 14 g/dL in women and 15 g/dL in men. Locoregional progression-free survival was significantly shorter (median PFS: 406 days Epoetin beta vs 745 days placebo, $p = 0.04$) in patients receiving Epoetin beta.[43]

There is insufficient information to establish whether use of Epoetin products, including EPOGEN®, have an adverse effect on time to tumor progression or progression-free survival.

These trials permitted or required dosing to achieve hemoglobin of greater than 12 g/dL. Until further information is available, the recommended target hemoglobin should not exceed 12 g/dL in men or women.

Surgery Patients

Thrombotic/Vascular Events

In perioperative clinical trials with orthopedic patients, the overall incidence of thrombotic/vascular events was similar in Epoetin alfa and placebo-treated patients who had a pretreatment hemoglobin of > 10 g/dL to ≤ 13 g/dL. In patients with a hemoglobin of > 13 g/dL treated with 300 Units/kg of Epoetin alfa, the possibility that EPOGEN® treatment may be associated with an increased risk of postoperative thrombotic/vascular events cannot be excluded.[18-20,28]

In one study in which Epoetin alfa was administered in the perioperative period to patients undergoing coronary artery bypass graft surgery, there were 7 deaths in the group treated with Epoetin alfa ($n = 126$) and no deaths in the placebo-treated group ($n = 56$). Among the 7 deaths in the patients treated with Epoetin alfa, 4 were at the time of therapy (between study day 2 and 8). The 4 deaths at the time of therapy (3%) were associated with thrombotic/vascular events. A causative role of Epoetin alfa cannot be excluded (see WARNINGS).

Hypertension

Blood pressure may rise in the perioperative period in patients being treated with EPOGEN®. Therefore, blood pressure should be monitored carefully.

ADVERSE REACTIONS

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EPOGEN® with the incidence of antibodies to other products may be misleading.

A few cases of PRCA associated with antibodies with neutralizing activity have been reported in patients receiving EPOGEN® (see WARNINGS: PURE RED CELL APLASIA). These cases were observed in patients treated by either SC or IV routes of administration and occurred predominantly in CRF patients.

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

Percent of Patients Reporting Event

Event	Patients Treated With EPOGEN® (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-blind, 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 US EPOGEN® studies in adult 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 EPOGEN® were rare, mild, and transient, and included injection site stinging in dialysis patients and flu-like symptoms such as arthralgias and myalgias.

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

Pediatric CRF Patients: In pediatric patients with CRF on dialysis, the pattern of most adverse events was similar to that found in adults. Additional adverse events reported during the double-blind phase in >10% of pediatric patients in either treatment group were: abdominal pain, dialysis access complications including access infections and peritonitis in those receiving peritoneal dialysis, fever, upper respiratory infection, cough, pharyngitis, and constipation. The rates are similar between the treatment groups for each event.

Hypertension: Increases in blood pressure have been reported in clinical trials, often during the first 90 days of therapy. On occasion, hypertensive encephalopathy and seizures have been observed in patients with CRF treated with EPOGEN®. When data from all patients in the US phase 3 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 2-week period). However, in a double-blind, placebo-controlled trial, hypertensive adverse events were not reported at an increased rate in the group treated with EPOGEN® (150 Units/kg TIW) relative to the placebo group.

Seizures: There have been 47 seizures in 1010 patients on dialysis treated with EPOGEN® in clinical trials, 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 periods. The baseline incidence of seizures in the untreated dialysis population is difficult to determine; it appears to be in the range of 5% to 10% per patient-year.[39-41]

Thrombotic Events: In clinical trials where the maintenance hematocrit was 35 ± 3% on EPOGEN®, clotting of the vascular access (A-V shunt) has occurred at an annualized rate of about 0.25 events per patient-year, and other thrombotic events (eg, myocardial infarction, cerebral vascular accident, transient ischemic attack, and pulmonary embolism) occurred at a rate of 0.04 events per patient-year. In a separate study of 1111 untreated dialysis patients, clotting of the vascular access occurred at a rate of 0.50 events per patient-year. However, in CRF patients on hemodialysis who also had clinically evident ischemic heart disease or congestive heart failure, the risk of A-V shunt thrombosis was higher (39% vs 29%, $p < 0.001$), and myocardial infarctions, vascular ischemic events, and venous thrombosis were increased, in patients targeted to a hematocrit of 42 ± 3% compared to those maintained at 30 ± 3% (see WARNINGS).

In patients treated with commercial EPOGEN®, there have been rare reports of serious or unusual thrombo-embolic events including migratory thrombophlebitis, microvascular thrombosis, pulmonary embolus, and thrombosis of the retinal artery, and temporal and renal veins. A causal relationship has not been established.

Allergic Reactions: There have been no reports of serious allergic reactions or anaphylaxis associated with EPOGEN® administration during clinical trials. Skin rashes and urticaria have been observed rarely and when reported have generally been mild and transient in nature.

There have been rare reports of potentially serious allergic reactions including urticaria with associated respiratory symptoms or circumoral edema, or urticaria alone. Most reactions occurred in situations where a causal relationship could not be established. Symptoms recurred with rechallenge in a few instances, suggesting that allergic reactivity may occasionally be associated with EPOGEN® therapy. If an anaphylactoid reaction occurs, EPOGEN® should be immediately discontinued and appropriate therapy initiated.

Zidovudine-treated HIV-infected Patients

Adverse events reported in clinical trials with EPOGEN® 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 patients treated with EPOGEN® or placebo-treated patients were:

	Percent of Patients Reporting Event	
Event	**Patients Treated With EPOGEN® (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%

In the 297 patients studied, EPOGEN® was not associated with significant increases in opportunistic infections or mortality.[25] In 71 patients from this group treated with EPOGEN® at 150 Units/kg TIW, serum p24 antigen levels did not appear to increase.[27] Preliminary data showed no enhancement of HIV replication in infected cell lines in vitro.[25]

Peripheral white blood cell and platelet counts are unchanged following EPOGEN® 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 EPOGEN® and one was treated with placebo (EPOGEN® 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 EPOGEN® 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 EPOGEN® in zidovudine-treated HIV-infected patients, 10 patients have experienced seizures.[25] In general, these seizures appear to be related to underlying pathology such as meningitis or cerebral neoplasms, not EPOGEN® therapy.

Cancer Patients on Chemotherapy

Adverse experiences reported in clinical trials with EPOGEN® administered TIW in cancer patients were consistent with the underlying disease state. In double-blind, placebo-controlled studies of up to 3 months duration involving 131 cancer patients, adverse events with an incidence > 10% in either patients treated with EPOGEN® or placebo-treated patients were as indicated below:

Percent of Patients Reporting Event

Event	Patients Treated With EPOGEN® (n = 63)	Placebo-treated Patients (n = 68)
Pyrexia	29%	19%
Diarrhea	21%*	7%
Nausea	17%*	32%
Vomiting	17%	15%
Edema	17%*	1%
Asthenia	13%	16%
Fatigue	13%	15%
Shortness of Breath	13%	9%
Parasthesia	11%	6%
Upper Respiratory Infection	11%	4%
Dizziness	5%	12%
Trunk Pain	3%*	16%

* Statistically significant

Although some statistically significant differences between patients being treated with EPOGEN® and placebo-treated patients were noted, the overall safety profile of EPOGEN® 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 exposure to EPOGEN®) were treated for up to 32 weeks with doses as high as 927 Units/kg, the adverse experience profile of EPOGEN® was consistent with the progression of advanced cancer.

Three hundred thirty-three (333) cancer patients enrolled in a placebo-controlled double-blind trial utilizing Weekly dosing with EPOGEN® for up to 4 months were evaluable for adverse events. The incidence of adverse events was similar in both the treatment and placebo arms.

Surgery Patients
Adverse events with an incidence of ≥ 10% are shown in the following table:

	Percent of Patients Reporting Event				
Event	Patients Treated With EPOGEN® 300 U/kg (n = 112)[a]	Patients Treated With EPOGEN® 100 U/kg (n = 101)[a]	Placebo-treated Patients (n = 103)[a]	Patients Treated With EPOGEN® 600 U/kg (n = 73)[b]	Patients Treated With EPOGEN® 300 U/kg (n = 72)[b]
Pyrexia	51%	50%	60%	47%	42%
Nausea	48%	43%	45%	45%	58%
Constipation	43%	42%	43%	51%	53%
Skin Reaction, Medication Site	25%	19%	22%	26%	29%
Vomiting	22%	12%	14%	21%	29%
Skin Pain	18%	18%	17%	5%	4%
Pruritus	16%	16%	14%	14%	22%
Insomnia	13%	16%	13%	21%	18%
Headache	13%	11%	9%	10%	19%
Dizziness	12%	9%	12%	11%	21%
Urinary Tract Infection	12%	3%	11%	11%	8%
Hypertension	10%	11%	10%	5%	10%
Diarrhea	10%	7%	12%	10%	6%
Deep Venous Thrombosis	10%	3%	5%	0%[c]	0%[c]
Dyspepsia	9%	11%	6%	7%	8%
Anxiety	7%	2%	11%	11%	4%
Edema	6%	11%	8%	11%	7%

[a] Study including patients undergoing orthopedic surgery treated with EPOGEN® or placebo for 15 days
[b] Study including patients undergoing orthopedic surgery treated with EPOGEN® 600 Units/kg weekly x 4 or 300 Units/kg daily x 15
[c] Determined by clinical symptoms

Thrombotic/Vascular Events: In three double-blind, placebo-controlled orthopedic surgery studies, the rate of deep venous thrombosis (DVT) was similar among Epoetin alfa and placebo-treated patients in the recommended population of patients with a pretreatment hemoglobin of > 10 g/dL to ≤ 13 g/dL.[18,20,28] However, in 2 of 3 orthopedic surgery studies the overall rate (all pretreatment hemoglobin groups combined) of DVTs detected by postoperative ultrasonography and/or surveillance venography was higher in the group treated with Epoetin alfa than in the placebo-treated group (11% vs 6%). This finding was attributable to the difference in DVT rates observed in the subgroup of patients with pretreatment hemoglobin > 13 g/dL. However, the incidence of DVTs was within the range of that reported in the literature for orthopedic surgery patients.

In the orthopedic surgery study of patients with pretreatment hemoglobin of > 10 g/dL to ≤ 13 g/dL which compared two dosing regimens (600 Units/kg weekly x 4 and 300 Units/kg daily x 15), 4 subjects in the 600 Units/kg weekly EPOGEN® group (5%) and no subjects in the 300 Units/kg daily group had a thrombotic vascular event during the study period.[19]

In a study examining the use of Epoetin alfa in 182 patients scheduled for coronary artery bypass graft surgery, 23% of patients treated with Epoetin alfa and 29% treated with placebo experienced thrombotic/vascular events. There were 4 deaths among the Epoetin alfa-treated patients that were associated with a thrombotic/vascular event. A causative role of Epoetin alfa cannot be excluded (see WARNINGS).

OVERDOSAGE

The maximum amount of EPOGEN® that can be safely administered in single or multiple doses has not been determined. Doses of up to 1500 Units/kg TIW for 3 to 4 weeks have been administered to adults without any direct toxic effects of EPOGEN® itself.[6] Therapy with EPOGEN® can result in polycythemia if the hemoglobin is not carefully monitored and the dose appropriately adjusted. If the suggested target range is exceeded, EPOGEN® may be temporarily withheld until the hemoglobin returns to the suggested target range; EPOGEN® 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 hemoglobin.

DOSAGE AND ADMINISTRATION

Chronic Renal Failure Patients

The recommended range for the starting dose of EPOGEN® is 50 to 100 Units/kg TIW for adult patients. The recommended starting dose for pediatric CRF patients on dialysis is 50 Units/kg TIW. The dose of EPOGEN® should be reduced as the hemoglobin approaches 12 g/dL or increases by more than 1 g/dL in any 2-week period. The dosage of EPOGEN® must be individualized to maintain the hemoglobin within the suggested target range. At the physician's discretion, the suggested target hemoglobin range may be expanded to achieve maximal patient benefit.

EPOGEN® may be given either as an IV or SC injection. In patients on hemodialysis, EPOGEN® usually has been administered as an IV bolus TIW. While the administration of EPOGEN® is independent of the dialysis procedure, EPOGEN® may be administered into the venous line at the end of the dialysis procedure to obviate the need for additional venous access. In adult patients with CRF not on dialysis, EPOGEN® may be given either as an IV or SC injection.

Patients who have been judged competent by their physicians to self-administer EPOGEN® without medical or other supervision may give themselves either an IV or SC injection. The table below provides general therapeutic guidelines for patients with CRF:

Starting Dose:

Adults	50 to 100 Units/kg TIW; IV or SC
Pediatric Patients	50 Units/kg TIW; IV or SC
Reduce Dose When:	1. Hgb approaches 12 g/dL or, 2. Hgb increases > 1 g/dL in any 2-week period
Increase Dose If:	Hgb does not increase by 2 g/dL after 8 weeks of therapy, and hgb is below suggested target range
Maintenance Dose:	Individually titrate
Suggested Target Hgb Range:	10 g/dL to 12 g/dL

During therapy, hematological parameters should be monitored regularly (see LABORATORY MONITORING).

Pretherapy Iron Evaluation: Prior to and during EPOGEN® 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. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels that will adequately support erythropoiesis stimulated by EPOGEN®.

Dose Adjustment: The dose should be adjusted for each patient to achieve and maintain a target hemoglobin not to exceed 12 g/dL.

Increases in dose should not be made more frequently than once a month. If the hemoglobin is increasing and approaching 12 g/dL, the dose should be reduced by approximately 25%. If the hemoglobin continues to increase, dose should be temporarily withheld until the hemoglobin begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose. If the hemoglobin increases by more than 1 g/dL in a 2-week period, the dose should be decreased by approximately 25%.

If the increase in the hemoglobin is less than 1 g/dL over 4 weeks and iron stores are adequate (see PRECAUTIONS: Laboratory Monitoring), the dose of EPOGEN® may be increased by approximately 25% of the previous dose. Further increases may be made at 4-week intervals until the specified hemoglobin is obtained.

Maintenance Dose: The maintenance dose must be individualized for each patient on dialysis. In the US phase 3 multicenter trial in patients on hemodialysis, the median maintenance dose was 75 Units/kg TIW, with a range from 12.5 to 525 Units/kg TIW. 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 TIW to maintain their hematocrit in the suggested target range. In pediatric hemodialysis and peritoneal dialysis patients, the median maintenance dose was 167 Units/kg/week (49 to 447 Units/kg per week) and 76 Units/kg per week (24 to 323 Units/kg/week) administered in divided doses (TIW or BIW), respectively to achieve the target range of 30% to 36%.

If the hemoglobin remains below, or falls below, the suggested 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 EPOGEN® may be increased. Such dose increases should not be made more frequently than once a month, unless clinically indicated, as the

response time of the hemoglobin to a dose increase can be 2 to 6 weeks. Hemoglobin should be measured twice weekly for 2 to 6 weeks following dose increases. In adult patients with CRF not on dialysis, the maintenance dose must also be individualized. EPOGEN® doses of 75 to 150 Units/kg/week have been shown to maintain hematocrits of 36% to 38% for up to 6 months.

Lack or Loss of Response: Over 95% of patients with CRF responded with clinically significant increases in hematocrit, and virtually all patients were transfusion-independent within approximately 2 months of initiation of EPOGEN® therapy.

If a patient fails to respond or maintain a response, other etiologies should be considered and evaluated as clinically indicated (see PRECAUTIONS: LACK OR LOSS OF RESPONSE).

Zidovudine-treated HIV-infected Patients
Prior to beginning EPOGEN®, 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 mUnits/mL are unlikely to respond to therapy with EPOGEN®.

Starting Dose: For adult patients with serum erythropoietin levels ≤ 500 mUnits/mL who are receiving a dose of zidovudine ≤ 4200 mg/week, the recommended starting dose of EPOGEN® is 100 Units/kg as an IV or SC injection TIW for 8 weeks. For pediatric patients, see PRECAUTIONS: PEDIATRIC USE.

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

Maintenance Dose: After attainment of the desired response (ie, reduced transfusion requirements or increased hemoglobin), the dose of EPOGEN® 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 hemoglobin exceeds 13 g/dL, the dose should be discontinued until the hemoglobin drops to 12 g/dL. The dose should be reduced by 25% when treatment is resumed and then titrated to maintain the desired hemoglobin.

Cancer Patients on Chemotherapy
Although no specific serum erythropoietin level can be stipulated above which patients would be unlikely to respond to EPOGEN® therapy, treatment of patients with grossly elevated serum erythropoietin levels (eg, > 200 mUnits/mL) is not recommended. The hemoglobin should be monitored on a weekly basis in patients receiving EPOGEN® therapy until hemoglobin becomes stable. The dose of EPOGEN® should be titrated to maintain the desired hemoglobin.

Two EPOGEN® dosing regimens may be used in adults; 150 Units/kg SC TIW or 40,000 Units SC Weekly. For pediatric patients, see PRECAUTIONS: PEDIATRIC USE.

TIW Dosing
Starting Dose:

Adults	150 Units/kg SC TIW
Pediatric Patients	See PRECAUTIONS: Pediatric Use

Reduce Dose by 25% when:	1. Hgb approaches 12 g/dL or, 2. Hgb increases > 1 g/dL in any 2-week period
Withhold Dose if:	Hgb exceeds 13 g/dL, until the hemoglobin falls to 12 g/dL, and restart dose at 25% below the previous dose
Increase Dose to 300 Units/kg TIW if:	response is not satisfactory [no reduction in transfusion requirements or rise in hemoglobin] after 8 weeks
Suggested Target Hgb Range:	10 g/dL to 12 g/dL

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

Weekly Dosing

- The starting dose in adults is 40,000 Units SC Weekly. If after 4 weeks of therapy, the hemoglobin has not increased by ≥ 1 g/dL, in the absence of RBC transfusion, the EPOGEN® dose should be increased to 60,000 Units Weekly.
- If patients have not responded satisfactorily to an EPOGEN® dose of 60,000 Units Weekly after 4 weeks, it is unlikely that they will respond to higher doses of EPOGEN®.
- EPOGEN® should be withheld if the hemoglobin exceeds 13 g/dL and reinitiated with a 25% dose reduction when the hemoglobin is less than 12 g/dL.
- If EPOGEN® treatment produces a very rapid hemoglobin response (e.g., an increase of more than 1 g/dL in any 2-week period), the dose of EPOGEN® should be reduced by 25%.

Surgery Patients

Prior to initiating treatment with EPOGEN® a hemoglobin should be obtained to establish that it is > 10 to ≤ 13 g/dL.[18] The recommended dose of EPOGEN® is 300 Units/kg/day subcutaneously for 10 days before surgery, on the day of surgery, and for 4 days after surgery.

An alternate dose schedule is 600 Units/kg EPOGEN® subcutaneously in once weekly doses (21, 14, and 7 days before surgery) plus a fourth dose on the day of surgery.[19]

All patients should receive adequate iron supplementation. Iron supplementation should be initiated no later than the beginning of treatment with EPOGEN® and should continue throughout the course of therapy.

PREPARATION AND ADMINISTRATION OF EPOGEN®

1. Do not shake. It is not necessary to shake EPOGEN®. Prolonged vigorous shaking may denature any 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 EPOGEN®, and wipe the septum with a disinfectant. Insert the needle into the vial, and withdraw into the syringe an appropriate volume of solution.

4. **Single-dose:** 1 mL vial contains no preservative. Use one dose per vial; do not re-enter the vial. Discard unused portions.

   Multidose: 1 mL and 2 mL vials contain preservative. Store at 2° to 8° C after initial entry and between doses. Discard 21 days after initial entry.

5. Do not dilute or administer in conjunction with other drug solutions. However, at the time of SC administration, preservative-free EPOGEN® from single-use vials may be admixed in a syringe with bacteriostatic 0.9% sodium chloride injection, USP, with benzyl alcohol 0.9% (bacteriostatic saline) at a 1:1 ratio using aseptic technique. The benzyl alcohol in the bacteriostatic saline acts as a local anesthetic which may ameliorate SC injection site discomfort. Admixing is not necessary when using the multidose vials of EPOGEN® containing benzyl alcohol.

HOW SUPPLIED

EPOGEN®, containing Epoetin alfa, is available in the following packages:

1 mL **Single-dose, Preservative-free** Solution
- 2000 Units/mL (NDC 55513-126-10)
- 3000 Units/mL (NDC 55513-267-10)
- 4000 Units/mL (NDC 55513-148-10)
- 10,000 Units/mL (NDC 55513-144-10)
- 40,000 Units/mL (NDC 55513-823-10)

Supplied in dispensing packs containing 10 single-dose vials.

2 mL **Multidose, Preserved** Solution
- 10,000 Units/mL (NDC 55513-283-10)

1 mL **Multidose, Preserved** Solution
- 20,000 Units/mL (NDC 55513-478-10)

Supplied in dispensing packs containing 10 multidose vials.

STORAGE

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

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