

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

103234/5093

Trade Name: Epogen for Injection

Generic Name: Epoetin alfa

Sponsor: Amgen, Incorporated

Approval Date: October 26, 2005

Indications: 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.

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

103234/5093

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103234/5093

Amgen, Incorporated
Attention: Douglas Hunt
Director, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

OCT 26 2005

Dear Mr. Hunt:

Your request to supplement your biologics license application for Epoetin alfa to revise the Warnings: Pure Red Cell Aplasia, Adverse Reactions: Immunogenicity, and Dosage and Administration: Chronic Renal Failure sections of the package insert has been approved. Your request to revise the "What is the Most Important Information I Should Know about EPOGEN and Chronic Renal Failure" section of the patient package insert has also been approved.

We acknowledge your written agreement to disseminate the revised package insert as an attachment to a Dear Health Care Provider Letter, as described in your letter of October 24, 2005, and as outlined below:

To reach agreement regarding the content of the Dear Health Care Provider letter with the Agency by November 4, 2005. Amgen will begin to disseminate the final, signed Dear Health Care Provider letter and the approved package insert to the oncology and hematology medical communities in coordination with other erythropoiesis-stimulating protein products in the same class by December 10, 2005.

Pursuant to 21 CFR 201.57(f)(2), patient labeling must be reprinted at the end of the package insert.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy of the signed Dear Health Care Provider Letter, package inset, and patient package insert, as well as original paper copies (ten for circulars and five for other labels).

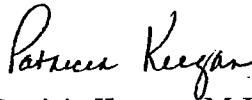
Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

This information will be included in your biologics license application file.

Sincerely,

A handwritten signature in cursive script, appearing to read "Patricia Keegan".

Patricia Keegan, M.D.

Director

Division of Biological Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

Enclosures: Package Insert and Patient Package Insert

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

103234/5093

LABELING

**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 data indicate no apparent difference in EPOGEN[®] half-life among adult patients above or below 65 years of age.

The pharmacokinetic profile of EPOGEN® in children and adolescents appears to be similar to that of adults. Limited data are available in neonates.¹⁷ A study of 7 preterm very low birth weight neonates and 10 healthy adults given IV erythropoietin suggested that distribution volume was approximately 1.5 to 2 times higher in the preterm neonates than in the healthy adults, and clearance was approximately 3 times higher in the preterm neonates than in the healthy adults.⁴⁴

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_{0-168h} (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 (TIW IV) | Hematocrit Increase | |
|-----------------------------------|----------------------------|------------------------------|
| | <u>Points/Day</u> | <u>Points/2 Weeks</u> |
| 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 (VO₂ 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 per week 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 cisplatin. 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 ($0.11 \times 10^6/\text{mm}^3$) compared to the daily group ($0.17 \times 10^6/\text{mm}^3$). 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 $42 \pm 3\%$ or $30 \pm 3\%$.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 to 14 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

Cases of pure red cell aplasia (PRCA) and of severe anemia, with or without other cytopenias, associated with neutralizing antibodies to erythropoietin have been reported in patients treated with EPOGEN®. This has been reported predominantly in patients with CRF receiving EPOGEN® by subcutaneous administration. Any patient who develops a sudden loss of response to EPOGEN®, accompanied by severe anemia and low reticulocyte count, should be evaluated for the etiology of loss of effect, including the presence of neutralizing antibodies to erythropoietin (see PRECAUTIONS: Lack or Loss of Response). If anti-erythropoietin antibody-associated anemia is suspected, withhold EPOGEN® and other erythropoietic proteins. Contact Amgen (1-800-77AMGEN) to perform assays for binding and neutralizing antibodies. EPOGEN® should be permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other erythropoietic proteins as antibodies may cross-react (see ADVERSE REACTIONS: Immunogenicity).

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) or anti-erythropoietin antibody-associated anemia: 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 erythropoietin (see WARNINGS: Pure Red Cell Aplasia).

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 literature³⁰⁻³³ 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.

Geriatric Use

Among 1051 patients enrolled in the 5 clinical trials of EPOGEN[®] for reduction of allogeneic blood transfusions in patients undergoing elective surgery 745 received EPOGEN[®] and 306 received placebo. Of the 745 patients who received EPOGEN[®], 432 (58%) were aged 65 and over, while 175 (23%) were 75 and over. No overall differences in safety or effectiveness were observed between geriatric and younger patients. The dose requirements for EPOGEN[®] in geriatric and younger patients within the 4 trials using the TIW schedule were similar. Insufficient numbers of patients were enrolled in the study using the weekly dosing regimen to determine whether the dosing requirements differ for this schedule.

Of the 882 patients enrolled in the 3 studies of chronic renal failure patients on dialysis, 757 received EPOGEN[®] and 125 received placebo. Of the 757 patients who received EPOGEN[®], 361 (47%) were aged 65 and over, while 100 (13%) were 75 and over. No differences in safety or effectiveness were observed between geriatric and younger patients. Dose selection and adjustment for an elderly patient should be individualized to achieve and maintain the target hematocrit (See DOSAGE AND ADMINISTRATION).

Insufficient numbers of patients age 65 or older were enrolled in clinical studies of EPOGEN[®] for the treatment of anemia associated with pre-dialysis chronic renal failure, cancer chemotherapy, and Zidovudine-treatment of HIV infection to determine whether they respond differently from younger subjects.

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. Neutralizing antibodies to erythropoietin, in association with PRCA or severe anemia (with or without other cytopenias), have been reported in patients receiving EPOGEN® (see WARNINGS: Pure Red Cell Aplasia) during post-marketing experience.

There has been no systematic assessment of immune responses, i.e., the incidence of either binding or neutralizing antibodies to EPOGEN®, in controlled clinical trials.

Where reported, the incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies across products within this class (erythropoietic proteins) may be misleading.

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 | 7% | 12% |
| (Administration Site) | | |
| 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% |
| CV/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 $35 \pm 3\%$ 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 $42 \pm 3\%$ compared to those maintained at $30 \pm 3\%$ (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 $\geq 10\%$ in either patients treated with EPOGEN[®] or placebo-treated patients were:

| Percent of Patients Reporting Event | | |
|-------------------------------------|--|-----------------------------|
| | Patients Treated With EPOGEN [®] | Placebo-treated Patients |
| Event | (n = 144) | (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 $\geq 10\%$ 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, the IV route is recommended*** (see WARNINGS: Pure Red Cell Aplasia) and 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: If a patient fails to respond or maintain a response, an evaluation for causative factors should be undertaken (see WARNINGS: Pure Red Cell Aplasia, PRECAUTIONS: Lack or Loss of Response, and PRECAUTIONS: Iron Evaluation).

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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EPOGEN® EPOETIN ALFA

INFORMATION FOR HOME DIALYSIS PATIENTS

WHAT IS EPOGEN® AND HOW DOES IT WORK?

EPOGEN® is a copy of human erythropoietin, a hormone produced primarily by healthy kidneys. EPOGEN® replaces the erythropoietin that the failed kidneys can no longer produce, and signals the bone marrow to make the oxygen-carrying red blood cells once again. EPOGEN® is produced in mammalian cells that have been genetically altered by the addition of a gene for the natural substance erythropoietin.

HOW SHOULD I TAKE EPOGEN®?

In those situations where your doctor has determined that you, as a home dialysis patient, can self-administer EPOGEN®, you will receive instruction on how much EPOGEN® to use, how to inject it, how often you should inject it, and how you should dispose of the unused portions of each vial.

You will be instructed to monitor your blood pressure carefully everyday and to report any changes outside of the guidelines that your doctor has given you. When the number of red blood cells increases, your blood pressure can also increase, so your doctor may prescribe some new or additional blood pressure medication. Be sure to follow your doctor's orders. You may also be instructed to have certain laboratory tests, such as additional hematocrit or iron level measurements, done more frequently. You may be asked to report these tests to your doctor or dialysis center. Also, your doctor may prescribe additional iron for you to take. Be sure to comply with your doctor's orders.

Continue to check your access, as your doctor or nurse has shown you, to make sure it is working. Be sure to let your health care professional know right away if there is a problem.

Allergy to EPOGEN®

Patients occasionally experience redness, swelling, or itching at the site of injection of EPOGEN®. This may indicate an allergy to the components of EPOGEN®, or it may indicate a local reaction. If you have a local reaction, consult your doctor. A potentially more serious reaction would be a generalized allergy to EPOGEN®, which could cause a rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life-threatening. If you think you are having a generalized allergic reaction, stop taking EPOGEN® and notify a doctor or emergency medical personnel immediately.

HOW WILL I KNOW IF EPOGEN® IS WORKING?

The effectiveness of EPOGEN® is measured by the increase in hematocrit (the amount of red blood cells in the blood) that results from EPOGEN® therapy. The rise in hematocrit is not immediate. It usually takes about 2 to 6 weeks before the hematocrit starts to rise. The amount of time it takes, and the dose of EPOGEN® that is needed to make the hematocrit increase, varies from patient to patient.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT EPOGEN® AND CHRONIC RENAL FAILURE?

EPOGEN® has been prescribed for you by your doctor because you:

1. Have anemia due to your kidney disease.
2. Are able to dialyze at home.
3. Have been determined to be able to administer EPOGEN® without direct medical or other supervision.

A lack of energy or feeling of tiredness is the major symptom of anemia. Additional symptoms include shortness of breath, chest pain, and feeling cold all the time. The reason for these symptoms is that there is a lack of red blood cells. Red blood cells carry oxygen, which is important for all of the body's functions. When there are fewer red blood cells, the body does not get all the oxygen it needs.

Kidneys remove toxins from the blood; they also measure the amount of oxygen in the blood. If there is not enough oxygen, the kidneys will produce a hormone called erythropoietin. Erythropoietin is released into the bloodstream and travels to the bone marrow where red blood cells are made. Erythropoietin signals the bone marrow to make more oxygen-carrying red blood cells.

As the kidneys fail, they stop cleansing toxins from your body. They also make less erythropoietin than they should. Therefore, the bone marrow does not receive a strong-enough signal to make the oxygen-carrying red blood cells. Fewer red blood cells are produced so the muscles, brain, and other parts of the body do not get the oxygen they need to function properly.

Most patients treated with EPOGEN® no longer need blood transfusions. However, certain medical conditions, or unexpected blood loss, may result in the need for a transfusion.

It is possible that your body may make antibodies against EPOGEN®. Antibodies to EPOGEN® can block or reduce your body's ability to make red blood cells, causing severe anemia. Symptoms of severe anemia include unusual tiredness and lack of energy. If you experience these symptoms, ***call your doctor.***

WHAT DO I NEED TO KNOW IF I AM GIVING MYSELF EPOGEN® INJECTIONS?

When you receive your EPOGEN® from the dialysis center, doctor's office or home dialysis supplier, always check to see that:

1. The name EPOGEN® appears on the carton and vial label.
2. You will be able to use EPOGEN® before the expiration date stamped on the package.

The EPOGEN® solution in the vial should always be clear and colorless. Do not use EPOGEN® if the contents of the vial appear discolored or cloudy, or if the vial appears to contain lumps, flakes, or particles. In addition, if the vial has been shaken vigorously, the solution may appear to be frothy and should not be used. Therefore, care should be taken not to shake the EPOGEN® vial vigorously before use.

Single Use Vials-S

If you have been prescribed EPOGEN® vials for single use, your vial will have a capital "S" with a number next to it identifying the concentration of EPOGEN® in the vial, printed in a colored dot on the front left side of the label (for example, "S2" identifies a single use vial with 2000 Units/mL). Single

use means the vial cannot be used more than once, and any unused portion of the vial should be discarded as directed by your doctor or dialysis center.

Multidose Use Vials-M

If you have been prescribed EPOGEN[®] Multidose vials, your vial will have a capital "M" with a number under it identifying the concentration of EPOGEN[®] in the vial, printed in a colored dot on the front left side of the label (for example, "M10" identifies a Multidose vial with 10,000 Units/mL). Multidose EPOGEN[®] can be used to inject multiple doses as prescribed by your doctor, and may be stored in the refrigerator (but not the freezing compartment) between doses for up to 21 days. Follow your doctor's or dialysis center's instructions on what to do with the used vials.

HOW SHOULD I STORE EPOGEN[®]?

EPOGEN[®] should be stored in the refrigerator, but not in the freezing compartment. Do not let the vial freeze and do not leave it in direct sunlight. Do not use a vial of EPOGEN[®] that has been frozen or after the expiration date that is stamped on the label. If you have any questions about the safety of a vial of EPOGEN[®] that has been subjected to temperature extremes, be sure to check with your dialysis unit staff.

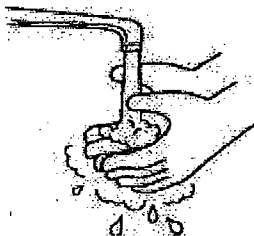
Always use the correct syringe.

Your doctor has instructed you on how to give yourself the correct dosage of EPOGEN[®]. This dosage will usually be measured in Units per milliliter or cc's. It is important to use a syringe that is marked in tenths of milliliters (for example, 0.2 mL or cc). Failure to use the proper syringe can lead to a mistake in dosage, and you may receive too much or too little EPOGEN[®]. Too little EPOGEN[®] may not be effective in increasing your hematocrit, and too much EPOGEN[®] may lead to a hematocrit that is too high. Only use disposable syringes and needles as they do not require sterilization; they should be used once and disposed of as instructed by your doctor.

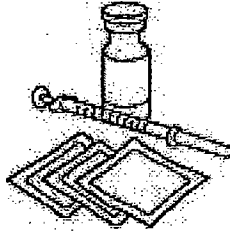
IMPORTANT: TO HELP AVOID CONTAMINATION AND POSSIBLE INFECTION, FOLLOW THESE INSTRUCTIONS EXACTLY.

Preparing the Dose

1. Wash your hands thoroughly with soap and water before preparing the medication.



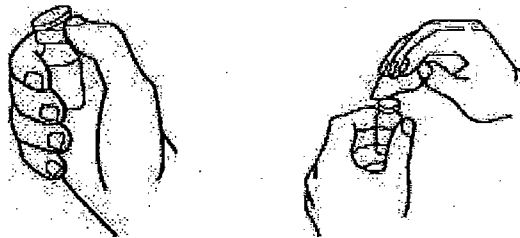
2. Check the date on the EPOGEN[®] vial to be sure that the drug has not expired.
3. Remove the vial of EPOGEN[®] from the refrigerator and allow it to reach room temperature. Unless you are using a Multidose vial, each EPOGEN[®] vial is designed to be used only once. It is not necessary to shake EPOGEN[®]. Prolonged vigorous shaking may damage the product. Assemble the other supplies you will need for your injection.



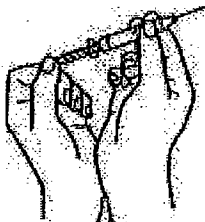
4. Hemodialysis patients should wipe off the venous port of the hemodialysis tubing with an antiseptic swab. Peritoneal dialysis patients should cleanse the skin with an antiseptic swab where the injection is to be made.



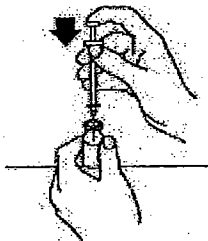
5. Flip off the red protective cap but do not remove the gray rubber stopper. Wipe the top of the gray rubber stopper with an antiseptic swab.



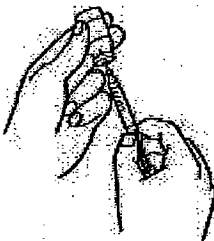
6. Using a syringe and needle designed for subcutaneous injection, draw air into the syringe by pulling back on the plunger. The amount of air should be equal to your EPOGEN[®] dose.



7. Carefully remove the needle cover. Put the needle through the gray rubber stopper of the EPOGEN[®] vial.
8. Push the plunger in to discharge air into the vial. The air injected into the vial will allow EPOGEN[®] to be easily withdrawn into the syringe.



9. Turn the vial and syringe upside down in one hand. Be sure the tip of the needle is in the EPOGEN[®] solution. Your other hand will be free to move the plunger. Draw back on the plunger slowly to draw the correct dose of EPOGEN[®] into the syringe.

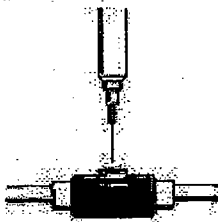


10. Check for air bubbles. The air is harmless, but too large an air bubble will reduce the EPOGEN[®] dose. To remove air bubbles, gently tap the syringe to move the air bubbles to the top of the syringe, then use the plunger to push the solution and the air back into the vial. Then remeasure your correct dose of EPOGEN[®].
11. Double check your dose. Remove the needle from the vial. Do not lay the syringe down or allow the needle to touch anything.

Injecting the Dose

Patients on Home Hemodialysis Using the Intravenous Injection Route:

1. Insert the needle of the syringe into the previously cleansed venous port and inject the EPOGEN[®].

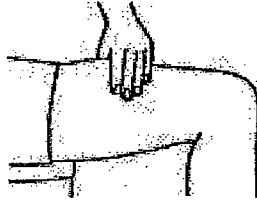


2. Remove the syringe and dispose of the whole unit. Use the disposable syringe only once. Dispose of syringes and needles as directed by your doctor, by following these simple steps:
 - Place all used needles and syringes in a hard plastic container with a screw-on-cap, or a metal container with a plastic lid, such as a coffee can properly labeled as to content. If a metal container is used, cut a small hole in the plastic lid and tape the lid to the metal container. If a hard-plastic container is used, always screw the cap on tightly after each use. When the container is full, tape around the cap or lid, and dispose of according to your doctor's instructions.
 - Do not use glass or clear plastic containers, or any container that will be recycled or returned to a store.

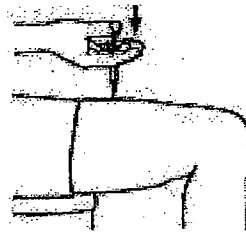
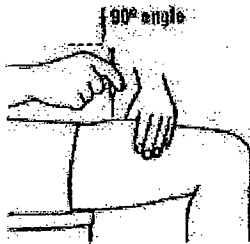
- Always store the container out of the reach of children.
- Please check with your doctor, nurse, or pharmacist for other suggestions. There may be special state and local laws that they will discuss with you.

Patients on Home Peritoneal Dialysis or Home Hemodialysis Using the Subcutaneous Route:

1. With one hand, stabilize the previously cleansed skin by spreading it or by pinching up a large area with your free hand.

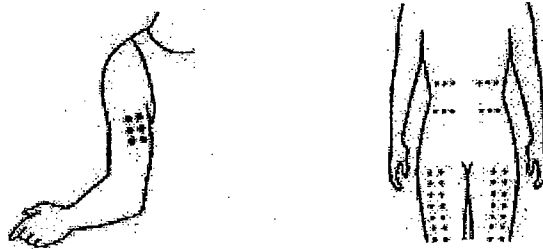


2. Hold the syringe with the other hand, as you would a pencil. Double check that the correct amount of EPOGEN[®] is in the syringe. Insert the needle straight into the skin (90 degree angle). Pull the plunger back slightly. If blood comes into the syringe, do not inject EPOGEN[®], as the needle has entered a blood vessel; withdraw the syringe and inject at a different site. Inject the EPOGEN[®] by pushing the plunger all the way down.



3. Hold an antiseptic swab near the needle and pull the needle straight out of the skin. Press the antiseptic swab over the injection site for several seconds.
4. Use the disposable syringe only once. Dispose of syringes and needles as directed by your doctor, by following these simple steps:
 - Place all used needles and syringes in a hard plastic container with a screw-on-cap, or a metal container with a plastic lid, such as a coffee can properly labeled as to content. If a metal container is used, cut a small hole in the plastic lid and tape the lid to the metal container. If a hard-plastic container is used, always screw the cap on tightly after each use. When the container is full, tape around the cap or lid, and dispose of according to your doctor's instructions.
 - Do not use glass or clear plastic containers, or any container that will be recycled or returned to a store.
 - Always store the container out of the reach of children.
 - Please check with your doctor, nurse, or pharmacist for other suggestions. There may be special state and local laws that they will discuss with you.

5. Always change the site for each injection as directed. Occasionally a problem may develop at the injection site. If you notice a lump, swelling, or bruising that doesn't go away, contact your doctor. You may wish to record the site just used so that you can keep track.



Usage in Pregnancy

If you are pregnant or nursing a baby, consult your doctor before using EPOGEN®.

Important Notes

Since you are a home dialysis patient and your doctor allows you to self-administer EPOGEN®, please note the following:

1. Always follow the instructions of your doctor concerning the dosage and administration of EPOGEN®. Do not change the dose or instructions for administration of EPOGEN® without consulting your doctor.
2. Your doctor will tell you what to do if you miss a dose of EPOGEN®. Always keep a spare syringe and needle on hand.
3. Always consult your doctor if you notice anything unusual about your condition or your use of EPOGEN®.

Amgen

Manufactured by:

Amgen Inc.

Amgen Center

Thousand Oaks, California 91320-1789

US EPO PI Copy

Issue date: xx/xx/xxxx

V1.2.1

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
103234/5093


LABELING REVIEW

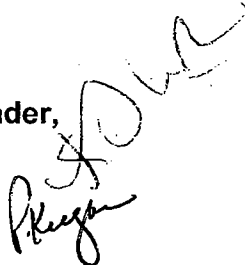
STN 103234.5093
LABELING SUPPLEMENT REVIEW

9/13/05 KSG

STN: 103234.5093
SUBMISSION DATE: June 28, 2005.
ACTION DATE: December 28, 2005.
SPONSOR: Amgen, Inc.
DRUG: EPOGEN/PROCRIT (epoetin alfa)

PROPOSED LABELING CHANGE: Addition of language to WARNINGS, Pure Red Cell Aplasia: PRECAUTIONS, Lack or Loss of Response; ADVERSE REACTIONS, Immunogenicity, DOSAGE AND ADMINISTRATION, Chronic Renal Failure Patients, Lack or Loss of Response.

CLINICAL REVIEW: Harvey Luksenburg, M.D., Clinical Reviewer, Office of Oncology Drug Products, Division of Biologic Oncology Products 

THROUGH: Kaushik Shastri, M.D. Team Leader, Patricia Keegan, M.D., Director, CDER, Office of Oncology Drug Products, Division of Biologic Oncology Products 

RPM: Monica Hughes

I. BACKGROUND

The Sponsors have submitted 2 spontaneous pharmacovigilance reports for patients with hepatitis C, who were treated with Procrit during a course of ribavirin (RBV) and interferon (IFN) and who developed clinical evidence of EPO antibody-mediated PRCA. Procrit is used as an off-label therapy for the treatment of anemia that develops during the course of RBV/IFN administration. These cases were atypical with respect to previously described cases of antibody-mediated PRCA in that they were associated with marrow hypocellularity and cytopenias.

In a teleconference between FDA and the Sponsor on May 25, 2005, FDA requested that Amgen and J&JPRD work together to develop class labeling for pure red cell aplasia to include reference to atypical cases.

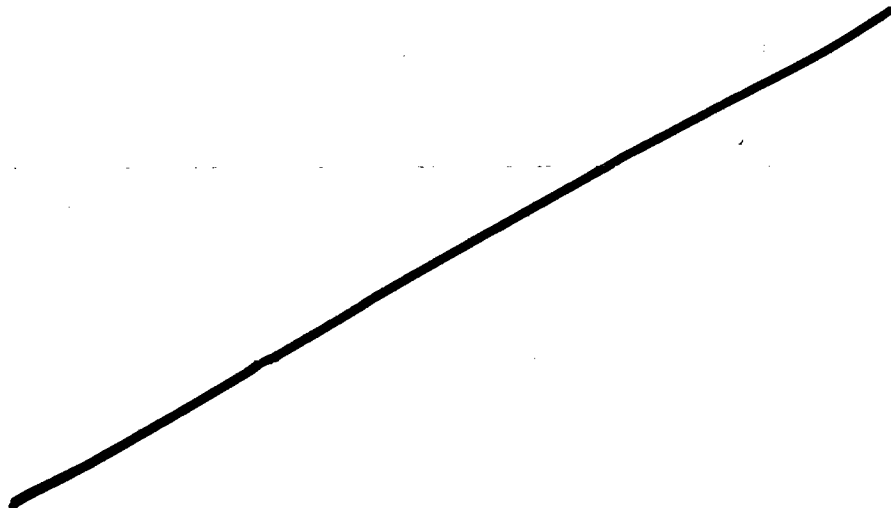
This submission, a Changes Being Effected (CBE) Labeling Supplement, includes the Sponsors' proposed labeling, a draft of a Dear Health Care Provider Letter, draft Envelopes for this Letter, and a draft of the Patient Product Information.

II. SPONSORS' PROPOSED CHANGES

(New language is underlined)

WARNINGS

Pure Red Cell Aplasia



PRECAUTIONS

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 (see WARNINGS: PURE RED CELL APLASIA).

ADVERSE REACTIONS

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. _____

(see WARNINGS: PURE RED CELL APLASIA).

The observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies _____ may be misleading.

*Appears This Way
On Original*

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, the IV route is recommended and 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.

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 WARNINGS: PURE RED CELL APLASIA and PRECAUTIONS: LACK OR LOSS OF RESPONSE).

III. FDA REVIEW OF THE DATA

Case #1

Patient 1 (US076416)

50 y/o male with severe hepatitis C without cirrhosis who completed a first course of RBV/IFN with Procrit. Approximately one year later (October 2003), the patient experienced a relapse and resumed treatment with RBV/IFN, and Procrit. Baseline Hgb was 14.8, WBC 3.4, platelet 211K. In 2/04, the patient developed a decreased therapeutic response: Hgb 9.5, WBC 2.5, platelet 68K. Procrit was increased to 60,000 s.c. weekly, RBV was withheld and interferon was reduced by 25%. Two weeks later, both RBV and interferon were discontinued. On — the patient was hospitalized for decreased therapeutic response: Hgb 5.6, WBC 3.6, platelet 84K. Patient was treated with RBC transfusion and Neupogen. Procrit was discontinued and the patient became transfusion dependent.

Work-up was negative for bleeding. Parvovirus serology was positive (IgG). An assay for anti-erythropoietin antibodies (4/7/04) was positive for neutralizing antibodies against epoetin alfa. Circulating EPO values were <7.8 mU/ml (normal 10-30).

Bone marrow biopsy (5/4/04) revealed "hypocellular marrow (15%), with a myeloid:erythroid ratio of 5:1."

Treatment with danazol was started. Over the next 4 months, the patient was transfusion independent: Hgb ranged between 9.1 to 10.5. Anti-erythropoietin antibodies assay on 12/15/04 was positive.

FDA Reviewer's Comment:

While the clinical and serological results are consistent with PRCA, the bone marrow biopsy is atypical for this conditions, since the myeloid:erythroid ratio was 5:1, and the marrow was hypocellular.

The normal range for M:E ratios is between 3:1 and 5:1. In classic PRCA, the number of erythroid precursors is vanishingly small, and the M:E ratio is 50 to 100:1.

Patient 2 (US103432)

44 y/o male with hepatitis C was started on RBV/IFN for 9 months (date uncertain). Treatment was discontinued due to the patient's indigent status. In 6/03, the patient was restarted on RBV/IFN. In 7/03, the patient developed a WBC of 3.1, and a platelet count of 128K. About one month later, the patient developed anemia, and Procrit was started (8/03)--Hgb was 12.6 at this time. In 2/04, the patient developed anemia while on Procrit: Hgb 8.8, WBC 2.8. Procrit dose was increased. In 5/04 the Hgb decreased to 6.5, WBC 3.2, platelet count 85,000. RBC treatment was given. RBV/IFN was discontinued. In —, the patient was hospitalized for anemia: Hgb 5.0, reticulocyte count was 0.1%. Procrit therapy was withheld because of the clinical suspicion of PRCA. Patient had a positive parvovirus IgG serology. Procrit was resumed 3 weeks later, but the patient remained transfusion dependent. Serum anti-erythropoietin antibodies collected on 11/30/04 was positive. The patient's anemia apparently improved without specific therapy.

A bone marrow biopsy on — revealed a hypocellular marrow (20-30%), with all cell lines represented, including erythroid precursors. M:E ratio was 1:1

Reviewer's Comment:

This patient had a clinical and serological picture compatible with PRCA. However the bone marrow biopsy was not typical for PRCA: the M:E ratio was low for this condition, and the marrow was hypocellular. The bone marrow biopsy was possibly performed after the patient was recovering from PRCA—a Hgb value of 10.3 was recorded one month prior to the marrow biopsy. However, there is no information provided as to whether this Hgb was due to transfusion support or not.

Other Cases Submitted by Amgen:

Amgen has submitted three sets of adverse events associated with epoetin alfa. The first includes 38 EPOGEN adverse events, consisting of 29 reports of pure red cell aplasia

confirmed by bone marrow biopsy. Only three of these reports were binding and antibody positive. These cases are summarized below.

US016124: 50 year old female with a history of renal transplant who started EPOGEN 4,000 Units IV t.i.w. on August 7, 1996. the baseline hct was 35.6%. In September 1998, the patient was found to have severe anemia with thrombocytopenia: the Hgb was 6.6 g/dl and the platelet count was 95,000. EPOGEN was reportedly increased in dosage. In [REDACTED] bone marrow biopsy revealed a marked decrease in erythroid precursors. The Hgb was 8.0 g/dl, platelets 93,000. From [REDACTED] the patient required transfusions approximately every 2 weeks. On [REDACTED], a bone marrow biopsy showed: mild hypocellularity, with markedly decreased erythroid precursors, M:E ratio of 40:1. Megakaryocytes and granulocytic precursors were present. Work-up was negative for autoimmune disease, viral illnesses, thymoma, and other possible causes. In 2000 (date not specified), EPOGEN was discontinued.

Serum assay was positive for the presence of neutralizing antibodies for against EPOGEN. The relative anti-epoetin antibody concentration was 0.31 mcg/ml. Cross-reactivity was also observed against darbepoetin alfa.

US038385: 65 year old female on hemodialysis, who started Procrit on August 20, 2002. The baseline hematocrit was 33%. In December 2002, the patient developed a decreased therapeutic response. The hematocrit was 31%. In May 2003, the hematocrit was 17%, reticulocyte count was 0%. The patient received RBC transfusion, and upper and lower endoscopy was negative. A bone marrow aspirate and biopsy performed on [REDACTED], revealed a hypocellular marrow (approximately 10%), M:E ratio 210:1, rare erythroblasts, and normal myeloid maturation. The Hgb was 8.3 g/dl, WBC 5.2 and platelet count 148,000. EPOGEN was discontinued on July 20, 2003. a serum assay collected on July 10, 2003 was positive for neutralizing antibodies against epoetin alfa. The relative concentration was 10.18 mcg/ml. During the next 5 months, the patient required approximately 50 units of PRBCs.

US067580: 55 year old male, a dialysis patient status post renal transplant, with a history of hematuria and positive hepatitis B surface antigen, was started on EPOGEN 6,000 Units t.i.w. on November 20, 2002. Baseline Hgb was 9.5 g/dl. In November 2003, the patient was noted to be having a decrease therapeutic response: the Hgb was 6.1 g/dl. over the next 4 months, the patient required multiple transfusions despite increases in the EPOGEN to 12,000 units t.i.w. Bone marrow aspirate and biopsy were consistent with pure red cell aplasia. Serum collected on March 2, 2004 was positive for neutralizing antibodies against epoetin alfa. The relative anti-epoetin alfa antibody concentration was 5.05 mcg/ml.

There is one report of a patient who was binding antibody positive with PRCA confirmed by bone marrow biopsy, but the neutralizing antibody status had not been determined. There were 6 reports of patients with positive binding antibodies, but the bone marrow biopsies in these patients did not confirm PRCA.

Amgen also has submitted 4 reports of patients who received Procrit with bone marrow confirmed PRCA with positive binding antibodies, 2 of which had neutralizing activity.

FDA Reviewers Comments:

These cases are illustrative of the patterns seen in antibody-positive PRCA associated with EPREX: severe anemia, typical bone marrow picture (normal or mild hypocellularity, with very high M:E ratio), and positivity for neutralizing antibodies to erythropoietin.

Thus the aggregate of experience indicates that antibody-positive PRCA may be seen in patients who have received EPOGEN/PROCrit, as well as Aranesp (darbepoetin alfa) and EPREX (epoetin alfa). In some patients who received EPOGEN/PROCrit, the clinical picture, in addition to severe anemia, also included neutropenia and/or thrombocytopenia, and a severely hypocellular bone marrow.

IV. ACTIONS

1. FDA PROPOSED LABELING LANGUAGE

WARNINGS

Pure Red Cell Aplasia

Cases of pure red cell aplasia (PRCA) **and** of severe anemia, with or without other cytopenias, associated with neutralizing antibodies to erythropoietin **have** been reported in patients treated with EPOGEN®. This has been reported predominantly in patients with CRF receiving EPOGEN® by subcutaneous administration. Any patient who develops a sudden loss of response to EPOGEN®, accompanied by severe anemia and low reticulocyte count, should be evaluated for the etiology of loss of effect, including the presence of neutralizing antibodies to erythropoietin (see PRECAUTIONS: Lack or Loss of Response). If anti-erythropoietin antibody-associated anemia is suspected, withhold EPOGEN® and other erythropoietic proteins. Contact Amgen (1-800-77AMGEN) to perform assays for binding and neutralizing antibodies. EPOGEN® should be **permanently** discontinued in patients with antibody-mediated anemia. Patients should not be switched to other erythropoietic proteins as antibodies may cross-react (see ADVERSE REACTIONS: Immunogenicity).

PRECAUTIONS

Lack or Loss of Response

9. Pure Red Cell Aplasia (PRCA) or¹ anti-erythropoietin antibody-associated anemia: 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 erythropoietin (see WARNINGS: Pure Red Cell Aplasia).

ADVERSE REACTIONS

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. Neutralizing antibodies to erythropoietin, in association with PRCA or severe anemia (with or without other cytopenias), have been reported in patients receiving EPOGEN® (see WARNINGS: Pure Red Cell Aplasia) during post-marketing experience.

There has been no systematic assessment of immune responses, i.e., the incidence of either binding or neutralizing antibodies to EPOGEN®, in controlled clinical trials.

Where reported, the incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies across products within this class (erythropoietic proteins) may be misleading.

DOSAGE AND ADMINISTRATION


Chronic Renal Failure Patients

EPOGEN® may be given either as an IV or SC injection. ***In patients on hemodialysis, the IV route is recommended*** (see WARNINGS: Pure Red Cell Aplasia) and 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.

Lack or Loss of Response:

If a patient fails to respond or maintain a response, an evaluation for causative factors should be undertaken (see WARNINGS: Pure Red Cell Aplasia, PRECAUTIONS: Lack or Loss of Response, and PRECAUTIONS: Iron Evaluation).

2. Dear Health Care Provider Letter:

FDA requested that Amgen submit a copy of a Dear Health Care Provider Letter (DHCP) with the accompanying envelope, which should be labeled "IMPORTANT DRUG WARNING". The purpose of this letter is to apprise physicians of the new safety information concerning red cell aplasia and of the preference to be given to the intravenous route of administration  in patients with chronic renal failure.

FDA made revisions to Amgen's Letter, which consisted of more specific language describing the atypical features of antibody-associated red cell aplasia. In addition, the FDA added language outlining steps that clinicians are advised to take if antibody-associated PRCA is suspected for any erythropoietic protein:

(1) If a patient _____ response, an evaluation for causative factors should be undertaken and if anti-erythropoietin antibody-associated anemia is suspected, physicians should withhold PROCRIT® and other erythropoietic proteins and contact _____ to perform assays for binding and neutralizing antibodies.

(2) PROCRIT® should be permanently discontinued in patients with antibody-mediated anemia.

(3) Patients should not be switched to other erythropoietic proteins as there is a potential for the antibodies to cross-react

the Letter, below, contains the changes recommended by FDA (underlined):

_____ 2005

Dear Health Care Professional:

_____ EPOGEN® (Epoetin alfa).
The WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND
ADMINISTRATION sections

PRCA has been previously reported in patients treated with recombinant erythropoietic proteins. As the potential for PRCA and anti-EPO antibody associated anemia applies to all marketed recombinant erythropoietic proteins, product labeling for all drugs in this class have been updated in a consistent manner to state the following:

(1) If a patient _____ response, an evaluation for causative factors should be undertaken and if anti-erythropoietin antibody-associated anemia is suspected, physicians should withhold PROCRIT® and other erythropoietic proteins and contact _____ to perform assays for binding and neutralizing antibodies.

(2) PROCRIT® should be permanently discontinued in patients with antibody-mediated anemia.

(3) Patients should not be switched to other erythropoietic proteins as there is a potential for the antibodies to cross-react.

Specifically, the revised sections of the label are as follows:

WARNINGS

Pure Red Cell Aplasia

Cases of pure red cell aplasia (PRCA) and of severe anemia, with or without other cytopenias, associated with neutralizing antibodies to erythropoietin have been reported in patients treated with [REDACTED]. This has been reported predominantly in patients with CRF receiving [REDACTED] by subcutaneous administration. Any patient who develops a sudden loss of response to [REDACTED] accompanied by severe anemia and low reticulocyte count, should be evaluated for the etiology of loss of effect, including the presence of neutralizing antibodies to erythropoietin (see PRECAUTIONS: Lack or Loss of Response). If anti-erythropoietin antibody-associated anemia is suspected, withhold [REDACTED] and other erythropoietic proteins. Contact [REDACTED] to perform assays for binding and neutralizing antibodies. [REDACTED] should be permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other erythropoietic proteins as antibodies may cross-react (see ADVERSE REACTIONS: Immunogenicity).

PRECAUTIONS

Lack or Loss of Response

10. Pure Red Cell Aplasia (PRCA) or anti-erythropoietin antibody-associated anemia: 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 erythropoietin (see WARNINGS: Pure Red Cell Aplasia).

ADVERSE REACTIONS

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. Neutralizing antibodies to erythropoietin, in association with PRCA or severe anemia (with or without other cytopenias), have been reported in patients receiving [REDACTED] (see WARNINGS: Pure Red Cell Aplasia) during post-marketing experience.

There has been no systematic assessment of immune responses, i.e., the incidence of either binding or neutralizing antibodies to [REDACTED], in controlled clinical trials.

Where reported, the incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies across products within this class (erythropoietic proteins) ⁽¹⁾ may be misleading.

DOSAGE AND ADMINISTRATION

Chronic Renal Failure Patients

_____ may be given either as an IV or SC injection. **In patients on hemodialysis, the IV route is recommended** (see WARNINGS: Pure Red Cell Aplasia) and _____ usually has been administered as an IV bolus TIW. While the administration of _____ is independent of the dialysis procedure, _____ 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, _____ may be given either as an IV or SC injection.

Lack or Loss of Response:

If a patient fails to respond or maintain a response, an evaluation for causative factors should be undertaken (see WARNINGS: Pure Red Cell Aplasia, PRECAUTIONS: Lack or Loss of Response, and PRECAUTIONS: Iron Evaluation).

You are encouraged to report adverse events in association with _____ to _____. Alternatively, this information may be reported to FDA's MedWatch reporting system by phone (1-800-FDA-1088), facsimile (1-800-FDA-0178), the MedWatch website at <https://www.accessdata.fda.gov/scripts/medwatch/>, or mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787. Both health care professionals and consumers should use Form 3500 (available at the MedWatch website) for reporting adverse events.

A copy of the revised prescribing information for _____ is enclosed. When utilized in accordance with the approved prescribing information, the benefit/risk profile of _____ continues to be favorable. Should you have any questions or require further information regarding the use of _____, please contact _____ at the number above.

Sincerely,

3. Patient Product Information (PPI)

FDA requested that Amgen submit a revised copy of the Patient Product Information (PPI) for EPOGEN/Procrit. The revised PPI was submitted with the new label. The requested revisions were to incorporate language informing patients of the new safety information.

The revised PPI, with Amgen's proposed changes, is below (new language is underlined):

EPOGEN® EPOETIN ALFA

INFORMATION FOR HOME DIALYSIS PATIENTS

What is EPOGEN® and how does it work?

EPOGEN® is a copy of human erythropoietin, a hormone produced primarily by healthy kidneys. EPOGEN® replaces the erythropoietin that the failed kidneys can no longer produce, and signals the bone marrow to make the oxygen-carrying red blood cells once again. EPOGEN® is produced in mammalian cells that have been genetically altered by the addition of a gene for the natural substance erythropoietin.

How Should I Take EPOGEN®?

In those situations where your doctor has determined that you, as a home dialysis patient, can self-administer EPOGEN®, you will receive instruction on how much EPOGEN® to use, how to inject it, how often you should inject it, and how you should dispose of the unused portions of each vial.

You will be instructed to monitor your blood pressure carefully everyday and to report any changes outside of the guidelines that your doctor has given you. When the number of red blood cells increases, your blood pressure can also increase, so your doctor may prescribe some new or additional blood pressure medication. Be sure to follow your doctor's orders. You may also be instructed to have certain laboratory tests, such as additional hematocrit or iron level measurements, done more frequently. You may be asked to report these tests to your doctor or dialysis center. Also, your doctor may prescribe additional iron for you to take. Be sure to comply with your doctor's orders. Continue to check your access, as your doctor or nurse has shown you, to make sure it is working. Be sure to let your health care professional know right away if there is a problem.

Allergy to EPOGEN®

Patients occasionally experience redness, swelling, or itching at the site of injection of EPOGEN®. This may indicate an allergy to the components of EPOGEN®, or it may indicate a local reaction. If you have a local reaction, consult your doctor. A potentially more serious reaction would be a generalized allergy to EPOGEN®, which could cause a rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life-threatening. If you think you are having a generalized allergic reaction, stop taking EPOGEN® and notify a doctor or emergency medical personnel immediately.

HOW WILL I KNOW IF EPOGEN® IS WORKING?

The effectiveness of EPOGEN® is measured by the increase in hematocrit (the amount of red blood cells in the blood) that results from EPOGEN® therapy. The rise in hematocrit is not immediate. It usually takes about 2 to 6 weeks before the hematocrit starts to rise. The amount of time it takes, and the dose of EPOGEN® that is needed to make the hematocrit increase, varies from patient to patient.

What is the most important information I should know about EPOGEN[®] and CHRONIC RENAL FAILURE?

EPOGEN[®] has been prescribed for you by your doctor because you:

1. Have anemia due to your kidney disease.
2. Are able to dialyze at home.
3. Have been determined to be able to administer EPOGEN[®] without direct medical or other supervision.

A lack of energy or feeling of tiredness is the major symptom of anemia. Additional symptoms include shortness of breath, chest pain, and feeling cold all the time. The reason for these symptoms is that there is a lack of red blood cells. Red blood cells carry oxygen, which is important for all of the body's functions. When there are fewer red blood cells, the body does not get all the oxygen it needs.

Kidneys remove toxins from the blood; they also measure the amount of oxygen in the blood. If there is not enough oxygen, the kidneys will produce a hormone called erythropoietin. Erythropoietin is released into the bloodstream and travels to the bone marrow where red blood cells are made. Erythropoietin signals the bone marrow to make more oxygen-carrying red blood cells.

As the kidneys fail, they stop cleansing toxins from your body. They also make less erythropoietin than they should. Therefore, the bone marrow does not receive a strong-enough signal to make the oxygen-carrying red blood cells. Fewer red blood cells are produced so the muscles, brain, and other parts of the body do not get the oxygen they need to function properly.

Most patients treated with EPOGEN[®] no longer need blood transfusions. However, certain medical conditions, or unexpected blood loss, may result in the need for a transfusion.

It is possible that your body may make antibodies against EPOGEN[®]. Antibodies to EPOGEN[®] can block or reduce your body's ability to make red blood cells, causing severe anemia. Symptoms of severe anemia include unusual tiredness and lack of energy. If you experience these symptoms, **call your doctor.**

What do I Need to Know if I am Giving Myself EPOGEN[®] Injections?

When you receive your EPOGEN[®] from the dialysis center, doctor's office or home dialysis supplier, always check to see that:

1. The name EPOGEN[®] appears on the carton and vial label.
2. You will be able to use EPOGEN[®] before the expiration date stamped on the package.

The EPOGEN[®] solution in the vial should always be clear and colorless. Do not use EPOGEN[®] if the contents of the vial appear discolored or cloudy, or if the vial appears to contain lumps, flakes, or particles. In addition, if the vial has been shaken vigorously, the solution may appear to be frothy and should not be used. Therefore, care should be taken not to shake the EPOGEN[®] vial vigorously before use.

Single Use Vials-S

If you have been prescribed EPOGEN[®] vials for single use, your vial will have a capital “S” with a number next to it identifying the concentration of EPOGEN[®] in the vial, printed in a colored dot on the front left side of the label (for example, “S2” identifies a single use vial with 2000 Units/mL). Single use means the vial cannot be used more than once, and any unused portion of the vial should be discarded as directed by your doctor or dialysis center.

Multidose Use Vials-M

If you have been prescribed EPOGEN[®] Multidose vials, your vial will have a capital “M” with a number under it identifying the concentration of EPOGEN[®] in the vial, printed in a colored dot on the front left side of the label (for example, “M10” identifies a Multidose vial with 10,000 Units/mL). Multidose EPOGEN[®] can be used to inject multiple doses as prescribed by your doctor, and may be stored in the refrigerator (but not the freezing compartment) between doses for up to 21 days. Follow your doctor’s or dialysis center’s instructions on what to do with the used vials.

How Should I Store EPOGEN[®]?

EPOGEN[®] should be stored in the refrigerator, but not in the freezing compartment. Do not let the vial freeze and do not leave it in direct sunlight. Do not use a vial of EPOGEN[®] that has been frozen or after the expiration date that is stamped on the label. If you have any questions about the safety of a vial of EPOGEN[®] that has been subjected to temperature extremes, be sure to check with your dialysis unit staff.

Always use the correct syringe.

Your doctor has instructed you on how to give yourself the correct dosage of EPOGEN[®]. This dosage will usually be measured in Units per milliliter or cc’s. It is important to use a syringe that is marked in tenths of milliliters (for example, 0.2 mL or cc). Failure to use the proper syringe can lead to a mistake in dosage, and you may receive too much or too little EPOGEN[®]. Too little EPOGEN[®] may not be effective in increasing your hematocrit, and too much EPOGEN[®] may lead to a hematocrit that is too high. Only use disposable syringes and needles as they do not require sterilization; they should be used once and disposed of as instructed by your doctor.

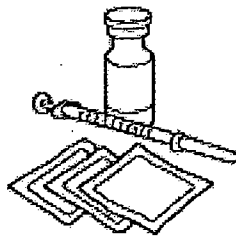
IMPORTANT: TO HELP AVOID CONTAMINATION AND POSSIBLE INFECTION, FOLLOW THESE INSTRUCTIONS EXACTLY.

Preparing the Dose

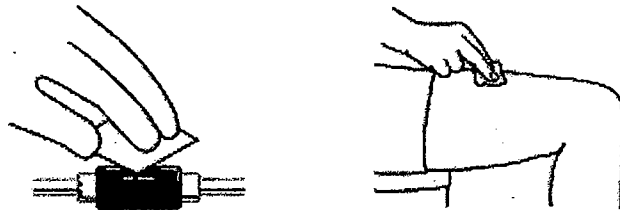
1. Wash your hands thoroughly with soap and water before preparing the medication.



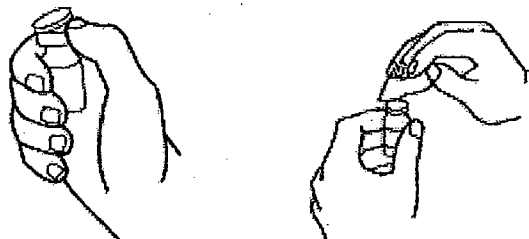
2. Check the date on the EPOGEN[®] vial to be sure that the drug has not expired.
3. Remove the vial of EPOGEN[®] from the refrigerator and allow it to reach room temperature. Unless you are using a Multidose vial, each EPOGEN[®] vial is designed to be used only once. It is not necessary to shake EPOGEN[®]. Prolonged vigorous shaking may damage the product. Assemble the other supplies you will need for your injection.



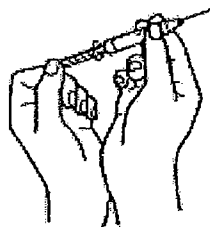
4. Hemodialysis patients should wipe off the venous port of the hemodialysis tubing with an antiseptic swab. Peritoneal dialysis patients should cleanse the skin with an antiseptic swab where the injection is to be made.



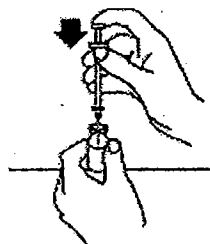
5. Flip off the red protective cap but do not remove the gray rubber stopper. Wipe the top of the gray rubber stopper with an antiseptic swab.



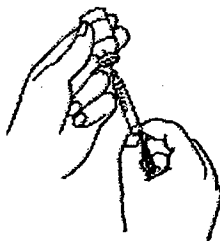
6. Using a syringe and needle designed for subcutaneous injection, draw air into the syringe by pulling back on the plunger. The amount of air should be equal to your EPOGEN[®] dose.



7. Carefully remove the needle cover. Put the needle through the gray rubber stopper of the EPOGEN[®] vial.
8. Push the plunger in to discharge air into the vial. The air injected into the vial will allow EPOGEN[®] to be easily withdrawn into the syringe.



9. Turn the vial and syringe upside down in one hand. Be sure the tip of the needle is in the EPOGEN[®] solution. Your other hand will be free to move the plunger. Draw back on the plunger slowly to draw the correct dose of EPOGEN[®] into the syringe.

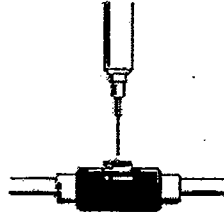


10. Check for air bubbles. The air is harmless, but too large an air bubble will reduce the EPOGEN[®] dose. To remove air bubbles, gently tap the syringe to move the air bubbles to the top of the syringe, then use the plunger to push the solution and the air back into the vial. Then remeasure your correct dose of EPOGEN[®].
11. Double check your dose. Remove the needle from the vial. Do not lay the syringe down or allow the needle to touch anything.

Injecting the Dose

Patients on Home Hemodialysis Using the Intravenous Injection Route:

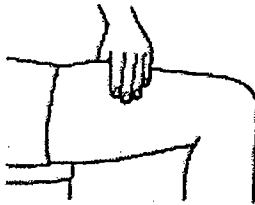
1. Insert the needle of the syringe into the previously cleansed venous port and inject the EPOGEN[®].



2. Remove the syringe and dispose of the whole unit. Use the disposable syringe only once. Dispose of syringes and needles as directed by your doctor, by following these simple steps:
 - V. Place all used needles and syringes in a hard plastic container with a screw-on-cap, or a metal container with a plastic lid, such as a coffee can properly labeled as to content. If a metal container is used, cut a small hole in the plastic lid and tape the lid to the metal container. If a hard-plastic container is used, always screw the cap on tightly after each use. When the container is full, tape around the cap or lid, and dispose of according to your doctor's instructions.
 - VI. Do not use glass or clear plastic containers, or any container that will be recycled or returned to a store.
 - VII. Always store the container out of the reach of children.
 - VIII. Please check with your doctor, nurse, or pharmacist for other suggestions. There may be special state and local laws that they will discuss with you.

Patients on Home Peritoneal Dialysis or Home Hemodialysis Using the Subcutaneous Route:

1. With one hand, stabilize the previously cleansed skin by spreading it or by pinching up a large area with your free hand.



2. Hold the syringe with the other hand, as you would a pencil. Double check that the correct amount of EPOGEN[®] is in the syringe. Insert the needle straight into the skin (90 degree angle). Pull the plunger back slightly. If blood comes into the syringe, do not inject EPOGEN[®], as the needle has entered a blood vessel; withdraw the syringe and inject at a different site. Inject the EPOGEN[®] by pushing the plunger all the way down.



3. Hold an antiseptic swab near the needle and pull the needle straight out of the skin. Press the antiseptic swab over the injection site for several seconds.
4. Use the disposable syringe only once. Dispose of syringes and needles as directed by your doctor, by following these simple steps:

IX. Place all used needles and syringes in a hard plastic container with a screw-on-cap, or a metal container with a plastic lid, such as a coffee can properly labeled as to content. If a metal container is used, cut a small hole in the plastic lid and tape the lid to the metal container. If a hard-plastic container is used, always screw the cap on tightly after each use. When the container is full, tape around the cap or lid, and dispose of according to your doctor's instructions.

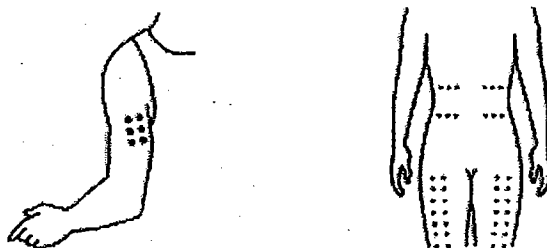
X. Do not use glass or clear plastic containers, or any container that will be recycled or returned to a store.

XI. Always store the container out of the reach of children.

XII. Please check with your doctor, nurse, or pharmacist for other suggestions.

There may be special state and local laws that they will discuss with you.

5. Always change the site for each injection as directed. Occasionally a problem may develop at the injection site. If you notice a lump, swelling, or bruising that doesn't go away, contact your doctor. You may wish to record the site just used so that you can keep track.



Usage in Pregnancy

If you are pregnant or nursing a baby, consult your doctor before using EPOGEN®.

Important Notes

Since you are a home dialysis patient and your doctor allows you to self-administer EPOGEN®, please note the following:

1. Always follow the instructions of your doctor concerning the dosage and administration of EPOGEN®. Do not change the dose or instructions for administration of EPOGEN® without consulting your doctor.
2. Your doctor will tell you what to do if you miss a dose of EPOGEN®. Always keep a spare syringe and needle on hand.
3. Always consult your doctor if you notice anything unusual about your condition or your use of EPOGEN®.

Amgen

Manufactured by:

Amgen Inc.

Amgen Center

Thousand Oaks, California 91320-1789

US EPO PI Copy

Issue date: xx/xx/xxxx

V1.2

V. Recommendations

FDA recommends that the above changes be incorporated into the EPOGEN/PROCRIT Product Label, and the Patient Product Information.

FDA accepts the text, with revisions of the Dear Health Care Provider Letter.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

103234/5093

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

RECEIVED

APPLICANT INFORMATION

NAME OF APPLICANT

Amgen Inc.

DATE OF SUBMISSION

27 June 2005

TELEPHONE NO. (Include Area Code)

805-447-1000

FACSIMILE (FAX) Number (Include Area Code)

805-498-9377

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, Ca 91320-1799

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) BL 103234

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

Epoetin alfa

PROPRIETARY NAME (trade name) IF ANY

EPOGEN®, PROCRIT®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)

rHuEPO

CODE NAME (If any)

DOSAGE FORM:

Injectable

STRENGTHS: 2,000; 3,000; 4,000; 10,000;
20,000; 40,000 Units/mL

ROUTE OF ADMINISTRATION:

IV; SC

(PROPOSED) INDICATION(S) FOR USE: Patients with chronic renal failure (CRF) on dialysis, CRF not on dialysis, cancer patients on chemotherapy, and non-cardiac, non-vascular surgery patients.

APPLICATION INFORMATION

APPLICATION TYPE

(check one)

☐ NEW DRUG APPLICATION (21 CFR 314.50)

☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

☒ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

☐ 505 (b)(1)

☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug

Holder of Approved Application

TYPE OF SUBMISSION (check one)

☐ ORIGINAL APPLICATION

☐ AMENDMENT TO PENDING APPLICATION

☐ RESUBMISSION

☐ PRESUBMISSION

☐ ANNUAL REPORT

☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT

☐ EFFICACY SUPPLEMENT

☒ LABELING SUPPLEMENT

☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

☒ CBE

☐ CBE-30

☐ Prior Approval (PA)

REASON FOR SUBMISSION

Revised labeling - PRCA

PROPOSED MARKETING STATUS (check one)

☒ PRESCRIPTION PRODUCT (Rx)

☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

1

THIS APPLICATION IS

☐ PAPER

☐ PAPER AND ELECTRONIC

☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

| | | | |
|---|--|--|---|
| This application contains the following items: (Check all that apply) | | | |
| <input checked="" type="checkbox"/> | 1. Index | | |
| <input checked="" type="checkbox"/> | 2. Labeling (check one) | <input checked="" type="checkbox"/> Draft Labeling | <input type="checkbox"/> Final Printed Labeling |
| <input type="checkbox"/> | 3. Summary (21 CFR 314.50 (c)) | | |
| <input type="checkbox"/> | 4. Chemistry section | | |
| <input type="checkbox"/> | A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2) | | |
| <input type="checkbox"/> | B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request) | | |
| <input type="checkbox"/> | C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2) | | |
| <input type="checkbox"/> | 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2) | | |
| <input type="checkbox"/> | 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2) | | |
| <input type="checkbox"/> | 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4)) | | |
| <input type="checkbox"/> | 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2) | | |
| <input type="checkbox"/> | 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2) | | |
| <input type="checkbox"/> | 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2) | | |
| <input type="checkbox"/> | 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2) | | |
| <input type="checkbox"/> | 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2) | | |
| <input type="checkbox"/> | 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c)) | | |
| <input type="checkbox"/> | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A)) | | |
| <input type="checkbox"/> | 15. Establishment description (21 CFR Part 600, if applicable) | | |
| <input type="checkbox"/> | 16. Debarment certification (FD&C Act 306 (k)(1)) | | |
| <input type="checkbox"/> | 17. Field copy certification (21 CFR 314.50 (j)(3)) | | |
| <input checked="" type="checkbox"/> | 18. User Fee Cover Sheet (Form FDA 3397) | | |
| <input type="checkbox"/> | 19. Financial Information (21 CFR Part 54) | | |
| <input checked="" type="checkbox"/> | 20. OTHER (Specify) Dear Healthcare Provider Letters and Envelopes, Medwatch reports and additional safety information | | |

CERTIFICATION

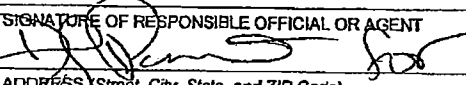
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

| | | |
|---|---|------------------------------------|
| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT  | TYPED NAME AND TITLE Douglas Hunt, Director Regulatory Affairs | DATE 27 June 2005 |
| ADDRESS (Street, City, State, and ZIP Code) One Amgen Center Drive, Thousand Oaks, CA 91320-1799 | | Telephone Number (805) 447-1000 |

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

BL 103234

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☐ YES ☒ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(805) 447-1000

3. PRODUCT NAME

Epoetin alfa

6. USER FEE I.D. NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☐ NO

(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

TITLE

Doug Hunt
Director, Regulatory Affairs

DATE

6/27/2005



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

JUL 11 2005

Amgen, Incorporated
Attention: Douglas Hunt
Director, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Hunt:

SUBMISSION TRACKING NUMBER (STN) BL 103234/5093 has been assigned to your recent supplement to your biologics license application for Epoetin alfa received on June 28, 2005, to revise the warnings section: Pure Red Cell Aplasia adverse reactions: Immunogenicity section and Dosage and Administration: Chronic Renal Failure section of the package insert.

This acknowledgment recognizes that your submission is in the form of a "Special Labeling Supplement--Changes Being Effectuated" as described under 21 CFR 601.12(f)(2). Continued use of the changes is subject to final approval of this supplement.

Unless we notify you within 60 days of the receipt date that the supplement is not sufficiently complete to permit substantive review, this supplement will be considered filed.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions. Effective October 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

If you have any questions, please contact the Regulatory Project Manager,
Monica Hughes, M.S., at (301) 827-5101.

Sincerely,

A handwritten signature in black ink, appearing to read 'Wendy Aaronson', with a long horizontal flourish extending to the right.

Wendy Aaronson, M.S.

Deputy Director

Division of Review Management and Policy

Office of Drug Evaluation VI

Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 19, 2005
From: Monica Hughes, DBOP/CDER
Subject: 103234-5093, First Committee Meeting

This first committee meeting was a face-to-face, internal, FDA meeting. Attendees included Pat Keegan, Harvey Luksenburg, Melanie Pierce, Jennie Chang (ODS/DDRE), and Catherine Gray (DDMAC).


This is a CBE-30 labeling supplement to revise the Warnings section: Pure Red Cell Aplasia Adverse Reactions: Immunogenicity section and Dosage and Administration: Chronic Renal Failure section of the package insert.

The meeting started out with introductions of the review committee members. Next, timelines and dates for all future meetings were discussed, they are as follows:

| | |
|-------------------------|-----------|
| First Committee Meeting | 19-Jul-05 |
| Filing Meeting | 12-Aug-05 |
| Filing Action | 27-Aug-05 |
| Deficiencies Identified | 10-Sep-05 |
| First Action Due | 28-Dec-05 |

This submission consists of a revised physician insert (PI), patient package insert (PPI), Dear Health Care Letter (DHCP), Mailing Envelope for DHCP.

Discussion and Action Items:

1. 
2. Team decided that the patient package insert needs to be reviewed by ODS/DSRCS and specifically asked where this information would fit best in the current PPI and to comment on the language. The RPM will forward a formal consult for the PPI to ODS/DSRCS.

3. Team discussed the current thoughts on proposed revisions to the PI (attached). This supplement is being reviewed simultaneously with the PRCA labeling for Aranesp (103951-5096) and suggested wording is being applied to both supplements to have a more uniform "class labeling" effect. Following team discussions, Dr. Luksenburg agreed to make agreed upon changes and forward them to the RPM to incorporate them into the appropriate PI's and forward to Amgen.

The filing meeting is scheduled for July 26, 2005.

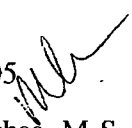
The meeting ended with agreement that all action items will be followed-up on.

**Appears This Way
On Original**



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 26, 2005 
From: Monica Hughes, M.S., DBOP/OODP
Subject: 103234/5093 Filing Meeting

FDA Attendees:

Monica Hughes
Patricia Keegan
Melanie Pierce
Harvey Luksenburg
Catherine Gray

The team agreed that this supplement is filable. The acknowledgement letter stated that the supplement would be considered filed unless notified, so a separate filing letter is not needed.

Dr. Luksenburg is currently working on proposed revised language for the package insert.

A formal consult was submitted to DSRCs for the PPI. Diane Yaplee notified me there would be a 30 day timeframe for us to receive comments.

The team agreed to send the revised PI in the meantime to Amgen and to let them know comments for the PPI will be sent separately.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 28, 2005

TO: Monica Hughes, Regulatory Project Manager
Division of Review Management Policy (DRMP)

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for Epogen/Procrit (epoetin alfa) and Aranesp (darbepoetin alfa), BLAs 103234/5093 and 103951/5096

Background and Summary

The sponsor submitted Changes being Effected-30 labeling supplements for Epogen/Procrit (epoetin alfa) and Aranesp (darbepoetin alfa), BLAs 103234/5093 and 103951/5096 for the inclusion of a Warning for Pure Red Cell Aplasia (PRCA) in the PI and PPI.

Comments and Recommendations for the Patient Labeling (PPIs)

For Aranesp:

Move the PRCA Warning up to the second bullet under the section, "What are the possible or reasonably likely side effects of Aranesp®?" and revise as follows:

"It is possible that your body may make antibodies against Aranesp®. _____ antibodies to Aranesp® can block or reduce your body's ability to make red blood cells, causing severe anemia. Symptoms of severe anemia include unusual tiredness and lack of energy. If you experience these symptoms, ~~call your doctor~~ call your doctor.

For Epogen/Procrit:

1. We recommend revising the PRCA Warning as above.
2. We recommend revising and simplifying the PPI to make it similar to the Aranesp PPI, with regard to headings and information contained in the various sections. The user of Epogen is never given a list of side effects. The section headed with "What is the most important

information I should know about Epogen and chronic renal failure?" is located in the middle half of the leaflet, minimizing its importance and leading many readers to forget the information due to serial position effect.

Please call us if you have any questions.

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUGS
OFFICE OF DRUG EVALUATION VI
DIVISION OF REVIEW MANAGEMENT AND POLICY

Woodmont Office Complex II, 6th Floor
1451 Rockville Pike
Rockville, Maryland 20852-1448
FAX #: 301-827-5397

FACSIMILE TRANSMISSION RECORD

TOTAL NUMBER OF PAGES: 33 (Including Cover Page)

FAX TO: Donna Peterson at Amgen

Facsimile Telephone No. 202-585-9729 **Voice Telephone No.** 202-589-9729

FROM: Monica Hughes, M.S., Regulatory Project Manager

Facsimile Telephone No. 301-827-5397 **Voice Telephone No.** 301-827-1528

DATE: 7-28-05 **TIME:** _____

MESSAGE: Donna,

Attached are our proposed revisions for the Package Insert for 103234-5093.

Please call me to confirm receipt of this facsimile.

Thank you,

Monica

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31 Page(s) Withheld

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 Deliberative Process

Withheld Track Number: Administrative-1

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUGS
OFFICE OF DRUG EVALUATION VI
DIVISION OF REVIEW MANAGEMENT AND POLICY

Woodmont Office Complex II, 6th Floor
1451 Rockville Pike
Rockville, Maryland 20852-1448
FAX #: 301-827-5397

FACSIMILE TRANSMISSION RECORD

TOTAL NUMBER OF PAGES: 38 (Including Cover Page)

FAX TO: Donna Peterson at Amgen

Facsimile Telephone No. (202) 585-9729 **Voice Telephone No.** _____

FROM: Monica Hughes, M.S., Regulatory Project Manager

Facsimile Telephone No. 301-827-5397 **Voice Telephone No.** 301-827-1528

DATE: 9-1-05 **TIME:** _____

MESSAGE: Donna,

Attached are our proposed PI and PPI revisions for 103234-5093 in response to your

August 26, 2005, submission.

Please call me to confirm receipt of this facsimile.

Thank you,

Monica

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38 Page(s) Withheld

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✓ Draft Labeling

 Deliberative Process

CENTER FOR DRUG EVALUATION AND RESEARCH

FOOD AND DRUG ADMINISTRATION

OFFICE OF ONCOLOGY DRUG PRODUCTS

DIVISION OF BIOLOGIC ONCOLOGY PRODUCTS

**Woodmont II Office Complex
1451 Rockville Pike
Rockville, Maryland 20852-1448
FAX # (301)827-5397**

FACSIMILE TRANSMISSION RECORD

TOTAL NUMBER OF PAGES: 11 (Including Cover Page)

FAX TO: Donna Peterson at Amgen, Inc.

Facsimile Telephone No. (202) 585-9729 **Voice Telephone No.**

FROM: Monica Hughes, M.S., Regulatory Project Manager

Facsimile Telephone No. (301) 827-5397 **Voice Telephone No.** (301) 827-1528

DATE: 9-7-05 **TIME:**

MESSAGE: Donna,

Attached are the proposed revisions to the DHCP letters under the PRCA supplement

103234/5093. Please note, the footnotes that appear in the DHCP LTRs will need to be removed

these inserted when I extracted language from Amgen's revised PI submission.

Please call me to confirm receipt of this facsimile.

Thank you, Monica

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

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 Deliberative Process

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: July 25, 2005

DESIRED COMPLETION

ODS CONSULT #: 05-0203

DATE OF DOCUMENT:

DATE: August 19, 2005

June 27, 2005 (103234/5093)

June 29, 2005 (103951/5096)

TO: Patricia Keegan, M.D.
Director, Division of Biologic Oncology Products
HFD-107

THROUGH: Monica Hughes
Project Manager
HFD-109

PRODUCT NAME:

Aranesp® (Darbepoetin Alfa) Injection
25 mcg/0.42 mL, 25 mcg/mL, 40 mcg/0.4 mL,
40 mcg/mL, 60 mcg/0.3 mL, 60 mcg/mL,
100 mcg/0.5 mL, 100 mcg/mL, 150 mcg/0.3 mL,
150 mcg/0.75 mL, 200 mcg/0.4 mL, 200 mcg/mL,
300 mcg/0.6 mL, 300 mcg/mL, 500 mcg/mL

BLA#: 103951/5096

BLA SPONSOR:

Amgen Inc.

Epogen®/Procrit® (Epoetin Alfa) Injection
2000 units/mL, 3000 units/mL, 4000 units/mL,
10000 units/mL, 20000 units/mL, 40000 units/mL

BLA#: 103234/5093

SAFETY EVALUATOR: Todd D. Bridges, R.Ph.

RECOMMENDATIONS:

DMETS recommends implementation of the package insert and patient package insert labeling revisions outlined in Section III of this review in order to minimize potential user error. Additionally, DMETS has reviewed and made recommendations regarding the proposed Pure red cell aplasia (PRCA) language and the placement thereof in the package insert and patient package insert labeling.

Denise P. Toyer, Pharm.D.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Carol Holquist 10/3/05

Carol Holquist, R.Ph.
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

LABEL AND LABELING REVIEW

DATE OF REVIEW: August 15, 2005

BLAS#: 103234/5093 (Epogen®/Procrit®)
103951/5096 (Aranesp®)

NAME OF DRUG: Epogen®/Procrit® (Epoetin Alfa) Injection
2000 units/mL, 3000 units/mL, 4000 units/mL,
10000 units/mL, 20000 units/mL, 40000 units/mL

Aranesp® (Darbepoetin Alfa) Injection
25 mcg/0.42 mL, 25 mcg/mL, 40 mcg/0.4 mL, 40 mcg/mL, 60 mcg/0.3 mL,
60 mcg/mL, 100 mcg/0.5 mL, 100 mcg/mL, 150 mcg/0.3 mL, 150 mcg/0.75 mL,
200 mcg/0.4 mL, 200 mcg/mL, 300 mcg/0.6 mL, 300 mcg/mL, 500 mcg/mL

BLA HOLDER: Amgen Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Biologic Oncology Products (HFD-107) to review and comment on the package insert and patient package insert labeling of Epogen®/Procrit® and Aranesp®, which were submitted on June 27, 2005 and June 29, 2005, respectively. Per an email from Project Manager Monica Hughes dated August 29, 2005, it was communicated that because Amgen Inc. is the BLA holder and manufacturer of both Epogen and Procrit, the package insert and patient package insert labeling are the exact same for both products except the marketing names (i.e., Epogen and Procrit). Epogen and Aranesp are marketed by Amgen whereas Procrit is marketed by Ortho Biotech. The sponsor submitted these BLA supplements to reflect the incorporation of Pure red cell aplasia (PRCA) language into the package insert and patient package insert labeling.

PRODUCT INFORMATION

Epogen®/Procrit® is a glycoprotein which stimulates red blood cell production. Epogen®/Procrit® is indicated for the treatment of anemia associated with chronic renal failure, anemia related to therapy with zidovudine in HIV infected patients, and anemia in cancer patients on chemotherapy. Additionally, Epogen®/Procrit® is used for the treatment of anemic patients scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need for allogenic blood transfusions. The usual adult starting dose is 50 units/kg to 100 units/kg administered as a single intravenously or subcutaneously injection three times a week. The maintenance dose is individually titrated to maintain a hemoglobin range of 10 g/dL to 12 g/dL. Epogen®/Procrit® is supplied in the package configurations listed in Table 1 (see page 3).

Table 1. Epogen®/Procrit® package configurations.

| PACKAGE DESCRIPTION | CONCENTRATION |
|-----------------------|---|
| 1 mL single-dose vial | 2000 units/mL, 3000 units/mL, 4000 units/mL, 10000 units/mL, 40000 units/mL |
| 1 mL multidose vial | 20000 units/mL |
| 2 mL multidose vial | 10000 units/mL |

Aranesp is an erythropoiesis stimulating protein. Aranesp is indicated for the treatment of anemia associated with chronic renal failure and for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. The recommended starting dose for the correction of anemia in chronic renal failure patients is 0.45 mcg/kg, administered as a single intravenous or subcutaneous injection once weekly. For cancer patients receiving chemotherapy, the recommended starting dose is 2.25 mcg/kg administered as a single weekly subcutaneous injection. Due to the longer serum half-life, Aranesp is administered less frequently than Epogen. Aranesp, which is available in an albumin solution and a polysorbate solution, is supplied in the packaging configurations listed in Table 2 (see below). To reduce the risk of accidental needlesticks to users, each prefilled syringe is equipped with a needle guard that covers the needle during disposal.

Table 2. Aranesp package configurations.

| PACKAGE DESCRIPTION | CONCENTRATION |
|-------------------------------|--|
| 0.75 mL single-dose vial | 150 mcg/0.75 mL |
| 1 mL single-dose vial | 25 mcg/mL, 40 mcg/mL, 60 mcg/mL, 100 mcg/mL, 200 mcg/mL, 300 mcg/mL, 500 mcg/mL |
| Single-dose prefilled syringe | 25 mcg/0.42 mL, 40 mcg/0.4 mL, 60 mcg/0.3 mL, 100 mcg/0.5 mL, 150 mcg/0.3 mL, 200 mcg/0.4 mL, 300 mcg/0.6 mL, 500 mcg/mL |

II. ADVERSE EVENT REPORTING SYSTEM (AERS)

A. ARANESP SEARCH

DMETS searched the FDA Adverse Event Reporting System (AERS) database to identify any post-marketing safety reports of medication errors associated with Aranesp. The MedDRA Preferred Terms (PT), "Medication Error", "Accidental Overdose", and "Pharmaceutical Product Complaint" were used to perform the searches along with the tradename "Aranesp", verbatim entry "Aranesp%", and the active ingredient "Darbepoetin". The search strategy retrieved five cases pertaining to the labeling and packaging of Aranesp. In the first case the reporter states that all strengths of Aranesp have a tamper evident seal except for the 40 mcg strength. The next two cases note the inappropriate use of trailing zeros in the labels and labeling of Aranesp. Another case describes confusion over the total drug content of the vial and prefilled syringe of Aranesp 60 mcg. The strength of Aranesp contained in the 60 mcg vial and prefilled syringe is 60 mcg/mL and 60 mcg/0.3 mL, respectively. The report does not discuss whether the patient was administered the overdose, thus, harm to the patient is unknown. The remaining case describes a situation in which an order written for Aranesp 100 mcg subcutaneously was filled with a 100 mcg/mL vial of Aranesp. However, the pharmacy generated label attached to the vial incorrectly stated the strength as 100 mcg/0.5 mL. No patient harm occurred because a nurse discovered the error before the medication was administered to the patient.

B. EPOGEN SEARCH

DMETS searched the FDA Adverse Event Reporting System (AERS) database to identify any post-marketing safety reports of medication errors associated with Epogen. The MedDRA Preferred Terms (PT), “Medication Error”, “Accidental Overdose”, and “Pharmaceutical Product Complaint” were used to perform the searches along with the tradename “Epogen”, verbatim entry “Epogen%”, and the active ingredient “Epoetin”. The search strategy retrieved six cases pertaining to the labeling and packaging of Epogen, two of which involved confusion between the 10,000 units/mL single-dose and multidose vials. The 10,000 units/mL multidose vial is labeled as 10,000 units/mL (20,000 units/2 mL) and is being mistaken for the 10,000 units/mL single-dose vial (see Figures 1 & 2 below). Neither of the two cases resulted in patient harm. The third case involved confusion concerning the expression of strength on the carton labeling of the 10,000 units/mL multidose vials. One statement on the carton labeling reads “10 x 10,000 units/2 mL Multidose Vials” and a second statement reads “10,000 units/1 mL (20,000 units/2 mL) 2 mL Multidose Vials”. The fourth case involves instances of Epogen vials being returned to stock and incorrectly placed in the wrong pharmacy storage bin. The fifth case expressed concerns about unconventional designations (e.g., M10) used to express type (i.e., single-dose vial vs. multidose vial) and concentration of Epogen vials. The report continues in saying these designations “could possibly cause problems such as 2 vials or 2 mL being used with S2 designation” and that these designations promote “shortcut to product identification as opposed to careful label reading”. The sixth case involved the look-alike properties of Epogen 10,000 units/mL and 20,000 units/mL multidose vials. The report states that “several patients received the wrong strength because a nurse gave dose from vial of 20,000 units/mL instead of 10,000 units/mL”. Patient harm was not discussed in this report. See Figures 1 & 2 below for side-by-side comparison of the two different strengths.

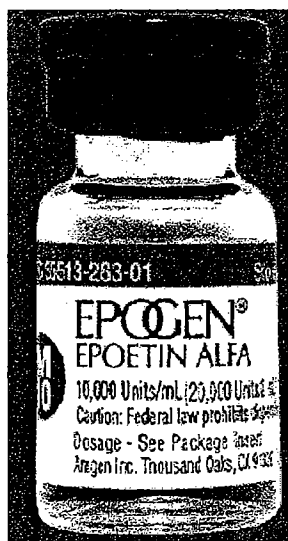


Figure 1. Epogen 10,000 units/mL multidose vial.

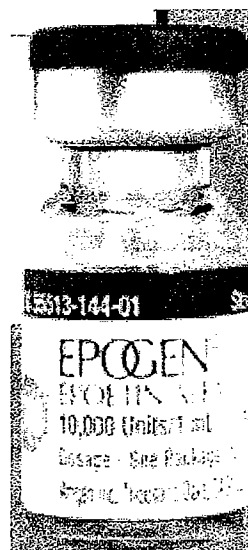


Figure 2. Epogen 10,000 units/mL single-dose vial.

C. PROCrit SEARCH

DMETS searched the FDA Adverse Event Reporting System (AERS) database to identify any post-marketing safety reports of medication errors associated with Procrit. The MedDRA Preferred Terms (PT), "Medication Error", "Accidental Overdose", and "Pharmaceutical Product Complaint" were used to perform the searches along with the tradename "Procrit", verbatim entry "Procrit%", and the active ingredient "Epoetin". The search strategy retrieved one case pertaining to the labeling and packaging of Procrit. The case involved a nurse selecting the 3,000 units/mL vial from unit stock when she intended to select the 2,000 units/mL vial. The report states that the color of the 2,000 units/mL vial is very similar to the color of the 3,000 units/mL vial (see Figures 3 & 4 below). The error was discovered when the vial selected from stock (3,000 units/mL) was compared to the physician's order. Since the incorrect dose was not administered, there was no patient harm.

Best Possible Copy

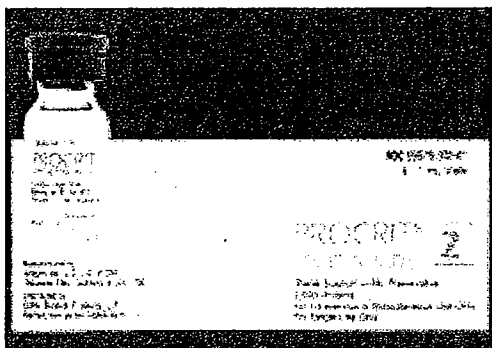


Figure 3. Procrit 2000 units/mL vial and carton.

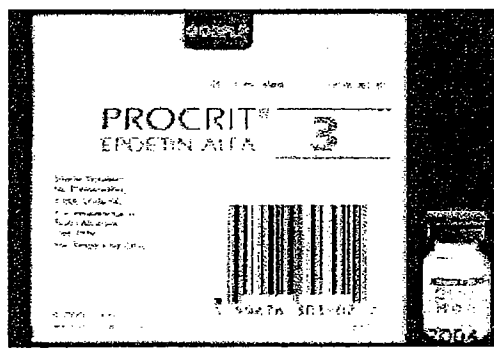


Figure 4. Procrit 3000 units/mL vial and carton.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the package insert and patient package insert labeling of Epogen/Procrit and Aranesp, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which may minimize potential user error.

A. ARANESP

1. GENERAL COMMENTS

- a. Delete the use of trailing zeros throughout the labels and labeling. DMETS notes that the Joint Commission for Accreditation of Hospitals (JCAHO), 2005 Hospitals National Patient Safety Goals includes the goal: Improve the effectiveness of communication among caregivers. A requirement to meet this goal is that each hospital must 'Standardize a list of abbreviations, acronyms and symbols that are not to be used throughout the organization. The use of trailing zeroes is specifically listed as a dangerous abbreviation, acronym, or symbol. Other healthcare organizations, such as ISMP have also published similar lists containing symbols that can lead to medication errors.
- b. Delete the use of the dangerous abbreviation "u" throughout the labels and labeling. DMETS is aware from postmarketing reports of confusion resulting from the confusion of the abbreviation "u" for units. We further note that the Joint Commission for Accreditation of Hospitals, 2005 Hospitals National Patient Safety Goals includes the goal: Improve the effectiveness of communication among caregivers. A requirement to meet this goal is that

each hospital must 'Standardize a list of abbreviations, acronyms and symbols that are not to be used throughout the organization. The use of "u" is specifically listed as a dangerous symbol. Other healthcare organizations, such as ISMP have also published similar lists containing symbols that can lead to medication errors. Thus, where "u" appears in the labeling, revise to read "units".

- c. Avoid the use of abbreviations and acronyms (e.g., CJD, TTP, OS, CRF, etc.) throughout the labels and labeling. Abbreviations and acronyms may be misinterpreted.
- d. _____ In its February 2004 report entitled *Combating Counterfeit Drugs: A Report of the Food and Drug Administration*, the FDA concluded that tamper evident packaging may be beneficial in fighting counterfeiting of prescription drugs. The report points out that it would be beneficial for manufacturers and re-packagers to consider using tamper evident packaging for prescription product containers, starting with products likely to be counterfeited or newly approved products, where the benefits are equal to or outweigh the cost. Therefore, DMETS recommends that all of the Aranesp products be safety sealed with a tamper seal.

2. PACKAGE INSERT LABELING

- a. See General Comments A(1)a through A(1)c.
- b. In accordance with 21 CFR 201.57(f)(2), reprint the "Information for Patients" subsection at the end of the package insert.
- c. Reiterate the proposed Pure red cell aplasia (PRCA) language under the "Information for Patients" subsection.
- d. DOSAGE AND ADMINISTRATION

- e. STORAGE SECTION

Revise statement "Store at....." to read _____

3. PATIENT PACKAGE INSERT LABELING

- a. Under Section B (page 9) of the subsection "How to prepare the dose of Aranesp", reverse _____

- b. DMETS recommends that the Patient Information Labeling be reviewed by the Division of Surveillance, Research, and Communication Support (DSRCS) to ensure comprehension level.

B. EPOGEN/PROCRIT

1. PACKAGE INSERT LABELING

- a. See Comment A(2)b.
- b. Reiterate the proposed PRCA language under the "Information for Patients" subsection.

c. _____

d. DOSAGE AND ADMINISTRATION

Under "PREPARATION AND ADMINISTRATION OF EPOGEN" subsection, revise statement "Store at..." to read "Store under refrigeration at 2 to 8C (36 to 46F)..."

e. STORAGE

Revise statement "Store at..." to read _____

2. PATIENT PACKAGE INSERT LABELING

- a. In accordance with 21 CFR 208.20(b)(7), create a section called "What are the possible or reasonably likely side effects of Epogen?" and list all the major side effects a patient should be aware of. Additionally, include the proposed PRCA language in this section. DMETS notes that Aranesp has a section titled, "What are the possible or reasonably likely side effects of Aranesp?" in Information for Patients, and the PRCA language is included in this section.
- b. DMETS recommends that the Patient Information Labeling be reviewed by the Division of Surveillance, Research, and Communication Support (DSRCS) to ensure comprehension level.

IV. DMETS RECOMMENDATIONS:

DMETS recommends implementation of the package insert and patient package insert labeling revisions outlined in Section III of this review in order to minimize potential user error. Additionally, DMETS has reviewed and made recommendations regarding the proposed Pure red cell aplasia (PRCA) language and the placement thereof in the package insert and patient package insert labeling (see Section III of this review).

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-827-1998.

Todd D. Bridges 10/3/05
Todd D. Bridges, R.Ph.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Linda Kim-Jung 10/3/05
Linda Kim-Jung, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

cc:

HFD-107: Patricia Keegan, Division Director

HFD-109: Monica Hughes, Project Manager

HFD-420: Todd Bridges, Safety Evaluator, DMETS

HFD-420: Linda Kim-Jung, Team Leader, DMETS

HFD-420: Diane Smith, Project Manager, DMETS

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (<http://www.fda.gov/cber/regsopp/8404.htm>). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see <http://www.fda.gov/cber/ich/ichguid.htm>).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CBER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 103234-5093 Product: Eprelnalfa Applicant: Amgen

Final Review Designation (circle one): Standard Priority

Submission Format (circle all that apply): Paper Electronic Combination

Submission organization (circle one): Traditional CTD

Filing Meeting: Date 7/24/05 Committee Recommendation (circle one): File RTF

RPM:

Mam
(signature/date)

Attachments:

- ☒ Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):

X Part A – RPM

Part B – Product/CMC/Facility Reviewer(s): _____

Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____

Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical)

Reviewers _____

- ☒ Memo of Filing Meeting _____

Part A. Regulatory Project Manager (RPM)

| CFR Module 1 Contents | Present? | If not, justification, action & status |
|---|--|--|
| Cover Letter | <input checked="" type="radio"/> Y <input type="radio"/> N | |
| Form 356h completed | <input checked="" type="radio"/> Y <input type="radio"/> N | |
| <input type="checkbox"/> including list of all establishment sites and their registration numbers | <input checked="" type="radio"/> Y <input type="radio"/> N | |
| <input type="checkbox"/> If foreign applicant, US Agent signature. | <input checked="" type="radio"/> Y <input type="radio"/> N | |
| Comprehensive Table of Contents | <input checked="" type="radio"/> Y <input type="radio"/> N | |
| Debarment Certification with correct wording (see * below) | Y <input checked="" type="radio"/> N | not needed |
| User Fee Cover Sheet | Y <input checked="" type="radio"/> N | not needed |
| User Fee payment received | Y <input checked="" type="radio"/> N | not needed |
| Financial certification &/or disclosure information | Y <input checked="" type="radio"/> N | not needed |
| Environment assessment or request for categorical exclusion (21 CFR Part 25) | Y <input checked="" type="radio"/> N | not needed |
| Pediatric rule: study, waiver, or deferral | Y <input checked="" type="radio"/> N | not needed |
| Labeling: | <input checked="" type="radio"/> Y <input type="radio"/> N | |
| <input type="checkbox"/> PI –non-annotated | <input checked="" type="radio"/> Y <input type="radio"/> N | |
| <input type="checkbox"/> PI –annotated | <input checked="" type="radio"/> Y <input type="radio"/> N | |
| <input type="checkbox"/> PI (electronic) | <input checked="" type="radio"/> Y <input type="radio"/> N | |
| <input type="checkbox"/> Medication Guide | Y <input checked="" type="radio"/> N | |
| <input type="checkbox"/> Patient Insert | <input checked="" type="radio"/> Y <input type="radio"/> N | |
| <input type="checkbox"/> package and container | Y <input checked="" type="radio"/> N | |
| <input type="checkbox"/> diluent | Y <input checked="" type="radio"/> N | |
| <input type="checkbox"/> other components | Y <input checked="" type="radio"/> N | |
| <input type="checkbox"/> established name (e.g. USAN) | Y <input checked="" type="radio"/> N | |
| <input type="checkbox"/> proprietary name (for review) | Y <input checked="" type="radio"/> N | |

* The Debarment Certification must have correct wording, e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge..."

| Examples of Filing Issues | Yes? | If not, justification, action & status |
|---|--|--|
| Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include: | <input checked="" type="radio"/> Y <input type="radio"/> N | |
| <input type="checkbox"/> legible | <input checked="" type="radio"/> Y <input type="radio"/> N | |
| <input type="checkbox"/> English (or translated into English) | <input checked="" type="radio"/> Y <input type="radio"/> N | |
| <input type="checkbox"/> compatible file formats | <input checked="" type="radio"/> Y <input type="radio"/> N | |
| <input type="checkbox"/> navigable hyper-links | <input checked="" type="radio"/> Y <input type="radio"/> N | |
| <input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays | <input checked="" type="radio"/> Y <input type="radio"/> N | |
| <input type="checkbox"/> summary reports reference the location of individual data and records | <input checked="" type="radio"/> Y <input type="radio"/> N | |

STN 103231-5043

Product

Epoetin alfa

Part A Page 2

| Examples of Filing Issues | Yes? | If not, justification, action & status |
|--|--|--|
| <input type="checkbox"/> protocols for clinical trials present <input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance) | Y <input checked="" type="radio"/> N | not needed |
| companion application received if a shared or divided manufacturing arrangement | Y <input checked="" type="radio"/> N | not needed |
| if CMC supplement: <input type="checkbox"/> description and results of studies performed to evaluate the change <input type="checkbox"/> relevant validation protocols <input type="checkbox"/> list of relevant SOPs | Y <input checked="" type="radio"/> Y <input checked="" type="radio"/> Y <input checked="" type="radio"/> | |
| if clinical supplement: <input type="checkbox"/> changes in labeling clearly highlighted <input type="checkbox"/> data to support all label changes <input type="checkbox"/> all required electronic components, including electronic datasets (e.g. SAS) | <input checked="" type="radio"/> N <input checked="" type="radio"/> N <input checked="" type="radio"/> N | |
| if electronic submission: <input type="checkbox"/> required paper documents (e.g. forms and certifications) submitted | <input checked="" type="radio"/> N | |

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Has orphan drug exclusivity been granted to another drug for the same indication?

If yes, review committee informed? N/A

Does this submission relate to an outstanding PMC? no

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period: N/A

• Name: _____

• Dates: _____

Recommendation (circle one): ☒ File ☐ RTF

RPM Signature: [Signature]

Branch Chief concurrence: [Signature]

7/25/05

103034, 5093

STN ~~103034, 5093~~Product EPHEDRINE

Part D Page 1

Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical) Reviewers

| CTD Module 2 Contents | Present? | | If not, justification, action & status |
|--|-------------------------------------|---|--|
| Overall CTD Table of Contents [2.1] | <input checked="" type="checkbox"/> | N | |
| Introduction to the summary documents (1 page) [2.2] | <input checked="" type="checkbox"/> | N | |
| Clinical overview [2.5] | <input checked="" type="checkbox"/> | N | |
| Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies) | <input checked="" type="checkbox"/> | N | |
| <input type="checkbox"/> Biopharmaceutics and associated analytical methods | Y | N | N/A ↓ |
| <input type="checkbox"/> Clinical pharmacology [includes immunogenicity] | Y | N | |
| <input type="checkbox"/> Clinical Efficacy [for each indication] | Y | N | |
| <input type="checkbox"/> Clinical Safety | <input checked="" type="checkbox"/> | N | |
| <input type="checkbox"/> Synopses of individual studies | Y | N | |

| CTD Module 5 Contents | Present? | | If not, justification, action & status |
|---|-------------------------------------|-------------------------------------|--|
| Module Table of Contents [5.1] | <input checked="" type="checkbox"/> | N | |
| Tabular Listing of all clinical studies [5.2] | <input checked="" type="checkbox"/> | N | |
| Study Reports and related information [5.3] | Y | N | |
| <input type="checkbox"/> Biopharmaceutic | Y | N | ↑ N/A ↓ |
| <input type="checkbox"/> Studies pertinent to Pharmacokinetics using Human Biomaterials | Y | N | |
| <input type="checkbox"/> Pharmacokinetics (PK) | Y | N | |
| <input type="checkbox"/> Pharmacodynamic (PD) | <input checked="" type="checkbox"/> | N | |
| <input type="checkbox"/> Efficacy and Safety | <input checked="" type="checkbox"/> | N | |
| <input type="checkbox"/> Postmarketing experience | <input checked="" type="checkbox"/> | N | |
| <input type="checkbox"/> Case report forms | <input checked="" type="checkbox"/> | N | |
| <input type="checkbox"/> Individual patient listings (indexed by study) | <input checked="" type="checkbox"/> | N | |
| o electronic datasets (e.g. SAS) | Y | N | N/A |
| Literature references and copies [5.4] | Y | <input checked="" type="checkbox"/> | |

| Examples of Filing Issues | Yes? | | If not, action & status |
|--|-------------------------------------|---|-------------------------|
| Content, presentation, and organization sufficient to permit substantive review? | <input checked="" type="checkbox"/> | N | |
| <input type="checkbox"/> legible | <input checked="" type="checkbox"/> | N | |
| <input type="checkbox"/> English (or certified translation into English) | <input checked="" type="checkbox"/> | N | |
| <input type="checkbox"/> compatible file formats | <input checked="" type="checkbox"/> | N | |
| <input type="checkbox"/> navigable hyper-links | <input checked="" type="checkbox"/> | N | |
| <input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays | <input checked="" type="checkbox"/> | N | |

STN

103234.5093

Product

EPOETIN ALFA

Part D Page 2

| Examples of Filing Issues | Yes? | If not, action & status |
|---|---|-------------------------|
| <input type="checkbox"/> summary reports reference the location of individual data and records | <input checked="" type="checkbox"/> Y N | |
| <input type="checkbox"/> protocols for clinical trials present | <input checked="" type="checkbox"/> Y N | |
| <input type="checkbox"/> all electronic submission components usable | <input checked="" type="checkbox"/> Y N | |
| statement for each clinical investigation: | | |
| <input type="checkbox"/> conducted in compliance with IRB requirements | Y N | N/A |
| <input type="checkbox"/> conducted in compliance with requirements for informed consent | Y N | |
| adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy) | Y N | N/A |
| adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication | Y N | N/A |
| study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim | Y N | N/A |
| study(ies) assess the contribution of each component of a combination product [21 CFR 610.17] | Y N | N/A |
| total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents) | Y N | N/A |
| adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy | Y N | N/A |
| drug interaction studies communicated as during IND review as necessary are included | Y N | N/A |
| assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review | Y N | N/A |
| comprehensive analysis of safety data from all current world-wide knowledge of product | Y N | N/A |

| Examples of Filing Issues | Yes? | If not, action & status |
|---|-------|-------------------------|
| data supporting the proposed dose and dose interval | Y N | N/A |
| appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data | Y N | N/A |
| adequate characterization of product specificity or mode of action | Y N | N/A |
| data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred | Y N | N/A |
| inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations | Y N | N/A |
| all information reasonably known to the applicant and relevant to the safety and efficacy described? | (Y) N | N/A |

| List of Clinical Studies (protocol number) | Final study report submitted? | | Financial disclosure or certification submitted? | | | SAS & other electronic datasets complete & usable? | | BiMo sites identified? | | |
|--|-------------------------------|---|--|---|----|--|---|------------------------|---|----|
| | Y | N | Y | N | NR | Y | N | Y | N | NR |
| | Y | N | Y | N | NR | Y | N | Y | N | NR |
| | Y | N | Y | N | NR | Y | N | Y | N | NR |
| | Y | N | Y | N | NR | Y | N | Y | N | NR |
| | Y | N | Y | N | NR | Y | N | Y | N | NR |
| | Y | N | Y | N | NR | Y | N | Y | N | NR |
| | Y | N | Y | N | NR | Y | N | Y | N | NR |
| | Y | N | Y | N | NR | Y | N | Y | N | NR |
| | Y | N | Y | N | NR | Y | N | Y | N | NR |
| | Y | N | Y | N | NR | Y | N | Y | N | NR |

Y= yes; N=no; NR=not required

STN 103234 5093

Product EPOLIN ALFA

Part D Page 4

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Is clinical site(s) inspection (BiMo) needed?

No

Is an Advisory Committee needed?

No

Recommendation (circle one): File RTF

Reviewer: Harry Hony m 9/15/03 Type (circle one): Clinical Clin/Pharm Statistical

(signature/ date)

Concurrence:

Branch Chief: _____
(signature/ date)

Division Director: _____
(signature/ date)

**BLA/NDA/PMA
Review Committee Assignment Memorandum**

STN: 103234-5093

☒ Initial Assignment
☐ Change

Applicant: Amgen

Product: Epoetin alfa

Addition of committee members

| Name | Reviewer Type* | Job Type | Assigned by | Date |
|-------------------|----------------------|-----------------------|-------------|---------|
| Monica Hughes | Reg. Project Manager | Admin/Regulatory | K. Jones | 6-30-05 |
| | Reviewer | Admin/Regulatory | | |
| | | Product* | | |
| | Reviewer | Product* | | |
| | Reviewer | Product | | |
| Harvey Luksenburg | Chairperson | Clinical | P. Keegan | 6-30-05 |
| | Reviewer | Clinical | | |
| | Reviewer | Clinical Pharmacology | | |
| | Reviewer | Pharm/Tox | | |
| | Reviewer | Biostatistics | | |
| | Reviewer | BiMo | | |
| Jennie Chang | Reviewer | Safety Evaluator | S. Lu | 6-30-05 |
| | Reviewer | CMC, Facility* | | |
| Catherine Gray | | Labeling | M. Keister | 6-30-05 |
| | | Other | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

*add inspector, if applicable

Deletion of Committee Member

| Name | Reviewer Type* | Job Type | Changed by | Date |
|------|----------------|----------|-------------|------|
| | | | | |
| | | | | |
| | | | | |
| | | | Chairperson | |
| | | | | |
| | | | | |
| | | | | |

*reviewer types: chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

Monica Hughes
Name Printed

[Signature]
Signature

7-12-05
Date

Memo entered in RMS by: [Signature]

Date: 7/25/05

QC by: LB

Date: 7/27/05

LICENSING ACTION RECOMMENDATION

Applicant: Amgen, Incorporated

STN: 103234/5093

Product:

Epoetin alfa

Indication / manufacturer's change:

to revise the Warnings section: Pure Red Cell Aplasia adverse reactions: Immunogenicity section
and Dosage and Administration: Chronic Renal Failure Section of the package insert

■ Approval:

- ☐ Summary Basis For Approval (SBA) included
☐ Memo of SBA equivalent reviews included

- ☐ Refusal to File: Memo included
☐ Denial of application / supplement: Memo included

RECOMMENDATION BASIS

■ Review of Documents listed on Licensed Action Recommendation Report

☐ Inspection of establishment

☐ Inspection report included

☐ BiMo inspections completed

☐ BiMo report included

☐ Review of protocols for lot no.(s) _____

☐ Test Results for lot no.(s) _____

☐ Review of Environmental Assessment

☐ FONSI included

☐ Categorical Exclusion

■ Review of labeling

Date completed 10/24/05

☐ None needed

CLEARANCE – PRODUCT RELEASE BRANCH

■ CBER Lot release not required

☐ Lot no.(s) in support – not for release _____

☐ Lot no.(s) for release _____

Director, Product Release Branch _____

CLEARANCE – REVIEW

Review Committee Chairperson: _____

Date: _____

Product Office's Responsible Division Director(s)*:

Pamela Keegan

Date: 10-26-2005

Date: _____

DMPQ Division Director* : _____

Date: _____

* If Product Office or DMPQ Review is conducted

CLEARANCE – APPLICATION DIVISION

☐ Compliance status checked

☐ Acceptable

☐ Hold

Date: _____

☐ Cleared from Hold

Date: _____

■ Compliance status check Not Required

Regulatory Project Manager (RPM) _____

Date: 10-24-05

Responsible Division Director _____

(where product is submitted, e.g., application division or DMPQ)

Date: _____