CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

103234s5033

Trade Name: Epogen/Procrit

Generic Name: Epoetin Alfa

Sponsor: Amgen

Approval Date: May 21, 2004

Indications: To fulfill the commitment to evaluate the possible stimulatory effects of Epoetin Alfa treatment on solid tumor growth.

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APPLICATION NUMBER:

103234s5033

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103234/5033

MAY 21 2004

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

Dear Mr. Hunt:

Your request to supplement your biologics license application for Epoetin alfa to update the Clinical Experience, Cancer Patients on Chemotherapy subsection of the package insert, has been approved. In addition, the revisions to the Warnings section, and the revisions to the Precautions section of the package insert to include information regarding the observed effects of Epoetin alfa and other products in this class on response rate, time-to-progression and survival in patients with non-myeloid tumors, have been approved.

This fulfills your commitment to conduct and submit the results of a Phase 4 study (Protocol N93-004) to evaluate the possible stimulatory effects of Epoetin alfa treatment on solid tumor growth as stated in commitment number one of the April 1, 1993, approval letter for STN 103234/1015.

We acknowledge your written commitments to conduct a postmarketing study and to disseminate a Dear Health Care Professional Letter as described in your letter of May 18, 2004, as outlined below:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

1. To submit a draft "Dear Health Care Professional (Important Prescribing Information)" letter, draft envelope, and list of intended recipients by June 4, 2004, and reach agreement regarding the content of the letter with the Agency by June 18, 2004. Amgen will begin to disseminate the letter and the approved package insert to the oncology and hematology medical communities by July 2, 2004.

2. To conduct a study to establish the impact of Epogen/Procrit administration on overall survival, time-to-progression, and objective tumor response rates in the proposed study entitled, "A Double-Blind, Placebo-Controlled, Randomized Phase 4 Study of Epoetin alfa Versus Placebo in Subjects Receiving First Line Chemotherapy for Metastatic Breast Cancer". The draft protocol will be submitted to the FDA by August 31, 2004, and the final protocol will be submitted to the FDA by December 31, 2004.

Patient accrual will be completed by August 31, 2006, the study will be completed by December 31, 2007, and the final study report will be submitted to the FDA by June 30, 2008.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 103234. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA STN BL 103234. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- Postmarketing Study Protocol
- Postmarketing Study Final Report
- Postmarketing Study Correspondence
- Annual Report on Postmarketing Studies

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted), and
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the April 2001 Draft Guidance for Industry: Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cber/gdlns/post040401.htm) for further information.

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 as well as original paper copies (ten for circulars and five for other labels).

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cder/biologics/default.htm. Until further notice, however, all correspondence, except as provided elsewhere in this letter, should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

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

Sincerely,

Patricia Keegan

Patricia Keegan, M.D.
Director
Division of Therapeutic Biological Oncology Products
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103234s5033

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

Anemia in cancer patients may be related to the disease itself or the effect of concomitantly administered chemotherapeutic agents. EPOGEN® has been shown to increase hematocrit and decrease transfusion requirements after the first month of therapy (months 2 and 3), in anemic cancer patients undergoing chemotherapy.

A series of clinical trials enrolled 131 anemic cancer patients who were receiving cyclic cisplatin- or non cisplatin-containing chemotherapy. Endogenous baseline serum erythropoietin levels varied among patients in these trials with approximately 75% (n = 83/110) having endogenous serum erythropoietin levels ≤ 132 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

Intravenously administered EPOGEN® is eliminated at a rate consistent with first order kinetics with a circulating half-life ranging from approximately 4 to 13 hours in adult and pediatric patients with CRF.[14-16] Within the therapeutic dose range, detectable levels of plasma erythropoietin are maintained for at least 24 hours. After SC administration of EPOGEN® to patients with CRF, peak serum levels are achieved within 5 to 24 hours after administration and decline slowly thereafter. There is no apparent

difference in half-life between adult patients not on dialysis whose serum creatinine levels were greater than 3, and adult patients maintained on dialysis.

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

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

It has been demonstrated in normal volunteers that the 10,000 Units/mL citrate-buffered Epoetin alfa formulation and the 40,000 Units/mL phosphate-buffered Epoetin alfa formulation are bioequivalent after SC administration of single 750 Units/kg doses. The C_{max} and $t_{1/2}$ after administration of the phosphate buffered Epoetin alfa formulation were 1.8 ± 0.7 Units/mL and 19.0 ± 5.9 hours (mean ± SD), respectively. The corresponding mean ± SD values for the citrate-buffered Epoetin alfa formulation were 2 ± 0.9 Units/mL and 16.3 ± 3.0 hours. There was no notable accumulation in serum after two weekly 750 Units/kg SC doses of Epoetin alfa.

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

ndogenous 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	
	Points/Day	Points/2 Weeks
50 Units/kg	0.11	1.5
100 Units/kg	0.18	2.5
150 Units/kg	0.25	3.5

Over this dose range, approximately 95% of all patients responded with a clinically significant increase in hematocrit, and by the end of approximately 2 months of therapy virtually all patients were transfusion-independent. Changes in the quality of life of adult patients treated with EPOGEN® were assessed as part of a phase 3 clinical trial.[5,8] Once the target hematocrit (32% to 38%) was achieved, statistically significant improvements were demonstrated for most quality of life parameters measured, including energy and activity level, functional ability, sleep and eating behavior, health status, satisfaction with health, sex life, well-being, psychological effect, life satisfaction, and happiness. Patients also reported improvement in their disease symptoms. They showed a statistically significant increase in exercise capacity (VO_2 max), energy, and strength with a significant reduction in aching, dizziness, anxiety, shortness of breath, muscle weakness, and leg cramps.[8,21]

Adult Patients on Dialysis: Thirteen clinical studies were conducted, involving IV administration to a total of 1010 anemic patients on dialysis for 986 patient-years of EPOGEN® therapy. In the three largest of these clinical trials, the median maintenance dose necessary to maintain the hematocrit

between 30% to 36% was approximately 75 Units/kg TIW. In the US multicenter phase 3 study, approximately 65% of the patients required doses of 100 Units/kg TIW, or less, to maintain their hematocrit at approximately 35%. Almost 10% of patients required a dose of 25 Units/kg, or less, and approximately 10% required a dose of more than 200 Units/kg TIW to maintain their hematocrit at this level.

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

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

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

Patients With CRF Not Requiring Dialysis

Four clinical trials were conducted in patients with CRF not on dialysis involving 181 patients treated with EPOGEN® for approximately 67 patient-years of experience. These patients responded to EPOGEN® therapy in a manner similar to that observed in patients on dialysis. Patients with CRF not on dialysis demonstrated a dose-dependent and sustained increase in hematocrit when EPOGEN® was administered by either an IV or SC route, with similar rates of rise of hematocrit when EPOGEN® was administered by either route. Moreover, EPOGEN® doses of 75 to 150 Units/kg 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 ~~[Amgen]~~). 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

EPOGEN® 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 requiringed 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] ~~Intent-to-treat Population~~		~~Efficacy subset Data Confined to~~ During Months 2 and 3~~**~~[c]	
	EPOGEN®	Placebo	EPOGEN®	Placebo
Regimens without cisplatin	~~56% (19/34)~~ 44% (15/34)	~~50% (18/36)~~44% (16/36)	21% (6/29)	33% (11/33)
Regimens containing cisplatin	~~32% (9/28)~~ 50% (14/28)	~~53% (6/30)~~ 63% (19/30)	23% (5/22)~~*[d]~~	56% (14/25)
Combined	~~45% (28/62)~~ 47% (29/62)	~~52% (36/66)~~ 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.

Unadjusted 2-sided $p < 0.05$

** Limited to patients remaining on study beyond week 4 and includes only transfusions during weeks 5-12.

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.

Surgery Patients

EPOGEN® has been studied in a placebo-controlled, double-blind trial enrolling 316 patients scheduled for major, elective orthopedic hip or knee surgery who were expected to require ≥ 2 units of blood and who were not able or willing to participate in an autologous blood donation program. Based on previous studies which demonstrated that pretreatment hemoglobin is a predictor of risk of receiving transfusion,[20,28] patients were stratified into one of three groups based on their pretreatment hemoglobin [≤ 10 (n = 2), > 10 to ≤ 13 (n = 96), and > 13 to ≤ 15 g/dL (n = 218)] and then randomly assigned to receive 300 Units/kg EPOGEN®, 100 Units/kg EPOGEN® or placebo by SC injection for 10 days before surgery, on the day of surgery, and for 4 days after surgery.[18] All patients received oral iron and a low-dose post-operative warfarin regimen.[18]

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

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

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

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

CONTRAINDICATIONS

EPOGEN® is contraindicated in patients with:

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

WARNINGS

Pediatric Use

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

Thrombotic Events and Increased Mortality

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

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

In a randomized, prospective trial conducted with another Epoetin alfa product, in 939 women with metastatic carcinoma of the breast who were receiving chemotherapy, patients were assigned to receive either Epoetin alfa or placebo for up to a year, in a weekly schedule, with the primary goal of showing improved survival and improved quality of life in the Epoetin alfa treatment arm.[25] This study utilized a treatment strategy designed to maintain hemoglobin levels of 12- 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 ~~and overall survival yielded a p value of 0.012 based on log rank tests based on Kaplan Meier estimates; p = 0.0117).~~ 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.

ure Red Cell Aplasia

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

Albumin (Human)

EPOGEN® contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

Chronic Renal Failure Patients

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

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

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

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

In adult patients on dialysis, there was a higher incidence of seizures during the first 90 days of therapy (occurring in approximately 2.5% of patients) as compared with later timepoints.

Given the potential for an increased risk of seizures during the first 90 days of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely. Patients should be cautioned to avoid potentially hazardous activities such as driving or operating heavy machinery during this period.

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

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

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

Zidovudine-treated HIV-infected Patients

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

PRECAUTIONS

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

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

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

Hematology

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

In preclinical studies in dogs and rats, but not in monkeys, EPOGEN® therapy was associated with subclinical bone marrow fibrosis. Bone marrow fibrosis is a known complication of CRF in humans and may be related to secondary hyperparathyroidism or unknown factors. The incidence of bone marrow fibrosis was not increased in a study of adult patients on dialysis who were treated with EPOGEN® for 12 to 19 months, compared to the incidence of bone marrow fibrosis in a matched group of patients who had not been treated with EPOGEN®.

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

Lack or Loss of Response

If the patient fails to respond or to maintain a response to doses within the recommended dosing range, the following etiologies should be considered and evaluated:

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

Iron Evaluation

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

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

Drug Interaction

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

Pregnancy Category C

EPOGEN® has been shown to have adverse effects in rats when given in doses 5 times the human dose. There are no adequate and well-controlled studies in pregnant women. EPOGEN® should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

In studies in female rats, there were decreases in body weight gain, delays in appearance of abdominal hair, delayed eyelid opening, delayed ossification, and decreases in the number of caudal vertebrae in

e F1 fetuses of the 500 Units/kg group. In female rats treated IV, there was a trend for slightly increased fetal wastage at doses of 100 and 500 Units/kg. EPOGEN® has not shown any adverse effect at doses as high as 500 Units/kg in pregnant rabbits (from day 6 to 18 of gestation).

Nursing Mothers

Postnatal observations of the live offspring (F1 generation) of female rats treated with EPOGEN® during gestation and lactation revealed no effect of EPOGEN® at doses of up to 500 Units/kg. There were, however, decreases in body weight gain, delays in appearance of abdominal hair, eyelid opening, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 Units/kg group. There were no EPOGEN®-related effects on the F2 generation fetuses.

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

Pediatric Use

See WARNINGS: PEDIATRIC USE.

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

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

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

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

Chronic Renal Failure Patients

Patients with CRF Not Requiring Dialysis

Blood pressure and hemoglobin should be monitored no less frequently than for patients maintained on dialysis. Renal function and fluid and electrolyte balance should be closely monitored, as an improved sense of well-being may obscure the need to initiate dialysis in some patients.

Hematology

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of EPOGEN® before adjusting the dose. Because of the time required for erythropoiesis and the red cell half-life, an

erval 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 hematocrit should then be monitored at regular intervals.

A complete blood count with differential and platelet count should be performed regularly. During clinical trials, modest increases were seen in platelets and white blood cell counts. While these changes were statistically significant, they were not clinically significant and the values remained within normal ranges.

In patients with CRF, serum chemistry values (including blood urea nitrogen [BUN], uric acid, creatinine, phosphorus, and potassium) should be monitored regularly. During clinical trials in 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® and 2.9% (n = 2/68) of placebo-treated patients had seizures. Seizures in 1.6% (n = 1/63) of patients treated with EPOGEN® 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.

Thrombotic Events

In double-blind, placebo-controlled trials, 3.2% (n = 2/63) of patients treated with EPOGEN® 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).

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. ~~Time to treatment failure and survival were also assessed.~~ Patients were randomized to receive EPOGEN® 150 Units/kg or placebo subcutaneously TIW during chemotherapy~~; during study, mean hemoglobin levels in EPOGEN® treated patients ranged from 11.3 to 12.7 g/dL study drug doses were titrated to maintain a hemoglobin of 10 g/dL to 12 g/dL~~. 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 ~~not significantly different~~ similar in the EPOGEN® and placebo arms[25].

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

~~In a study of another Epoetin alfa product of 939 women with metastatic breast cancer, overall mortality, mortality attributed to disease progression, and incidence of thromboembolic events were all higher in patients receiving Epoetin alfa than in the placebo group (see WARNINGS; Thrombotic Events and Increased Mortality).~~

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

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

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

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

Surgery Patients

Thrombotic/Vascular Events

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

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

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

ADVERSE REACTIONS

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

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

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

	Percent of Patients Reporting Event	
Event	Patients Treated With EPOGEN® (n = 200)	Placebo-treated Patients (n = 135)
Hypertension	24%	19%
Headache	16%	12%
Arthralgias	11%	6%
Nausea	11%	9%
Edema	9%	10%
Fatigue	9%	14%
Diarrhea	9%	6%
Vomiting	8%	5%
Chest Pain	7%	9%
Skin Reaction (Administration Site)	7%	12%
Asthenia	7%	12%
Dizziness	7%	13%
Clotted Access	7%	2%

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

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

In the US EPOGEN® studies in adult patients on dialysis (over 567 patients), the incidence (number of events per patient-year) of the most frequently reported adverse events were: hypertension (0.75), headache (0.40), tachycardia (0.31), nausea/vomiting (0.26), clotted vascular access (0.25), shortness of breath (0.14), hyperkalemia (0.11), and diarrhea (0.11). Other reported events occurred at a rate of less than 0.10 events per patient per year.

Events reported to have occurred within several hours of administration of EPOGEN® were rare, mild, and transient, and included injection site stinging in dialysis patients and flu-like symptoms such as arthralgias and myalgias.

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

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

Hypertension: Increases in blood pressure have been reported in clinical trials, often during the first 90 days of therapy. On occasion, hypertensive encephalopathy and seizures have been observed in patients with CRF treated with EPOGEN®. When data from all patients in the US phase 3 multicenter trial were analyzed, there was an apparent trend of more reports of hypertensive adverse events in patients on dialysis with a faster rate of rise of hematocrit (greater than 4 hematocrit points in any 2-week period). However, in a double-blind, placebo-controlled trial, hypertensive adverse events were not reported at an increased rate in the group treated with EPOGEN® (150 Units/kg TIW) relative to the placebo group.

Seizures: There have been 47 seizures in 1010 patients on dialysis treated with EPOGEN® in clinical trials, with an exposure of 986 patient-years for a rate of approximately 0.048 events per patient-year. However, there appeared to be a higher rate of seizures during the first 90 days of therapy (occurring in approximately 2.5% of patients) when compared to subsequent 90-day periods. The baseline incidence of seizures in the untreated dialysis population is difficult to determine; it appears to be in the range of 5% to 10% per patient-year.[39-41]

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

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

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

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

dovudine-treated HIV-infected Patients

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

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

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

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

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

Seizures: In double-blind and open-label trials of EPOGEN® in zidovudine-treated HIV-infected patients, 10 patients have experienced seizures.[25] In general, these seizures appear to be related to underlying pathology such as meningitis or cerebral neoplasms, not EPOGEN® therapy.

Cancer Patients on Chemotherapy

Adverse experiences reported in clinical trials with EPOGEN® 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.

Surgery Patients

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

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

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

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

atients with pretreatment hemoglobin > 13 g/dL. However, the incidence of DVTs was within the range of that reported in the literature for orthopedic surgery patients.

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

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Chronic Renal Failure Patients

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

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

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

Starting Dose:	
Adults	50 to 100 Units/kg TIW; IV or SC
Pediatric Patients	50 Units/kg TIW; IV or SC
Reduce Dose When:	1. Hgb. approaches 12 g/dL or, 2. Hgb. increases > 1 g/dL in any 2-week period

Increase Dose If:	Hgb. does not increase by 2 g/dL after 8 weeks of therapy, and hgb. is below suggested target range
Maintenance Dose:	Individually titrate
Suggested Target Hgb. Range:	10 g/dL to 12 g/dL

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

Pretherapy Iron Evaluation: Prior to and during EPOGEN® therapy, the patient's iron stores, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, should be evaluated. Transferrin saturation should be at least 20%, and ferritin should be at least 100 ng/mL. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels that will adequately support erythropoiesis stimulated by EPOGEN®.

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

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

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

Maintenance Dose: The maintenance dose must be individualized for each patient on dialysis. In the US phase 3 multicenter trial in patients on hemodialysis, the median maintenance dose was 75 Units/kg TIW, with a range from 12.5 to 525 Units/kg TIW. Almost 10% of the patients required a dose of 25 Units/kg, or less, and approximately 10% of the patients required more than 200 Units/kg TIW to maintain their hematocrit in the suggested target range. In pediatric hemodialysis and peritoneal dialysis patients, the median maintenance dose was 167 Units/kg/week (49 to 447 Units/kg per week) and 76 Units/kg per week (24 to 323 Units/kg/week) administered in divided doses (TIW or BIW), respectively to achieve the target range of 30% to 36%.

If the hemoglobin remains below, or falls below, the suggested target range, iron stores should be re-evaluated. If the transferrin saturation is less than 20%, supplemental iron should be administered. If the transferrin saturation is greater than 20%, the dose of EPOGEN® may be increased. Such dose increases should not be made more frequently than once a month, unless clinically indicated, as the response time of the hemoglobin to a dose increase can be 2 to 6 weeks. Hemoglobin should be measured twice weekly for 2 to 6 weeks following dose increases. In adult patients with CRF not on dialysis, the maintenance dose must also be individualized. EPOGEN® doses of 75 to 150 Units/kg/week have been shown to maintain hematocrits of 36% to 38% for up to 6 months.

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

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

Zidovudine-treated HIV-infected Patients

Prior to beginning EPOGEN®, it is recommended that the endogenous serum erythropoietin level be determined (prior to transfusion). Available evidence suggests that patients receiving zidovudine with endogenous serum erythropoietin levels > 500 mUnits/mL are unlikely to respond to therapy with EPOGEN®.

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

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

Maintenance Dose: After attainment of the desired response (ie, reduced transfusion requirements or increased hemoglobin), the dose of EPOGEN® should be titrated to maintain the response based on factors such as variations in zidovudine dose and the presence of intercurrent infectious or inflammatory episodes. If the hemoglobin exceeds 13 g/dL, the dose should be discontinued until the hemoglobin drops to 12 g/dL. The dose should be reduced by 25% when treatment is resumed and then titrated to maintain the desired hemoglobin.

Cancer Patients on Chemotherapy

Although no specific serum erythropoietin level can be stipulated above which patients would be unlikely to respond to EPOGEN® therapy, treatment of patients with grossly elevated serum erythropoietin levels (eg, > 200 mUnits/mL) is not recommended. ~~are less likely to respond.~~ 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.

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 fall 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: ~~up~~ 10 g/dL to 12 g/dL

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

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.

OW 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.

EFERENCES

1. Egrie JC, Strickland TW, Lane J, et al. Characterization and Biological Effects of Recombinant Human Erythropoietin. *Immunobiol.* 1986;72:213-224.

2. Graber SE, Krantz SB. Erythropoietin and the Control of Red Cell Production. *Ann Rev Med.* 1978;29:51-66.

3. Eschbach JW, Adamson JW. Anemia of End-Stage Renal Disease (ESRD). *Kidney Intl.* 1985;28:1-5.

4. Eschbach JW, Egrie JC, Downing MR, et al. Correction of the Anemia of End-Stage Renal Disease with Recombinant Human Erythropoietin. *NEJM.* 1987;316:73-78.

5. Eschbach JW, Abdulhadi MH, Browne JK, et al. Recombinant Human Erythropoietin in Anemic Patients with End-Stage Renal Disease. *Ann Intern Med.* 1989;111:992-1000.

6. Eschbach JW, Egrie JC, Downing MR, et al. The Use of Recombinant Human Erythropoietin (r-HuEPO): Effect in End-Stage Renal Disease (ESRD). In: Friedman, Beyer, DeSanto, Giordano, eds. *Prevention of Chronic Uremia.* Philadelphia, PA: Field and Wood Inc; 1989:148-155.

7. Egrie JC, Eschbach JW, McGuire T, Adamson JW. Pharmacokinetics of Recombinant Human Erythropoietin (r-HuEPO) Administered to Hemodialysis (HD) Patients. *Kidney Intl.* 1988;33:262.

8. Evans RW, Rader B, Manninen DL, et al. The Quality of Life of Hemodialysis Recipients Treated with Recombinant Human Erythropoietin. *JAMA.* 1990;263:825-830.

9. Paganini E, Garcia J, Ellis P, et al. Clinical Sequelae of Correction of Anemia with Recombinant Human Erythropoietin (r-HuEPO); Urea Kinetics, Dialyzer Function and Reuse. *Am J Kid Dis.* 1988;11:16.

10. Delano BG, Lundin AP, Golansky R, et al. Dialyzer Urea and Creatinine Clearances Not Significantly Changed in r-HuEPO Treated Maintenance Hemodialysis (MD) Patients. *Kidney Intl.* 1988;33:219.

11. Stivelman J, Van Wyck D, Ogden D. Use of Recombinant Erythropoietin (r-HuEPO) with High Flux Dialysis (HFD) Does Not Worsen Azotemia or Shorten Access Survival. *Kidney Intl.* 1988;33:239.

12. Lim VS, DeGowin RL, Zavala D, et al. Recombinant Human Erythropoietin Treatment in Pre-Dialysis Patients: A Double-Blind Placebo Controlled Trial. *Ann Int Med.* 1989;110:108-114.

13. Stone WJ, Graber SE, Krantz SB, et al. Treatment of the Anemia of Pre-Dialysis Patients with Recombinant Human Erythropoietin: A Randomized, Placebo-Controlled Trial. *Am J Med Sci.* 1988;296:171-179.

14. Braun A, Ding R, Seidel C, Fies T, Kurtz A, Scharer K. Pharmacokinetics of recombinant human erythropoietin applied subcutaneously to children with chronic renal failure. *Pediatr Nephrol.* 1993;7:61-64.

15. Geva P, Sherwood JB. Pharmacokinetics of recombinant human erythropoietin (rHuEPO) in pediatric patients on chronic cycling peritoneal dialysis (CCPD). *Blood.* 1991;78 (Suppl 1):91a.

16. Jabs K, Grant JR, Harmon W, *et al.* Pharmacokinetics of Epoetin alfa (rHuEPO) in pediatric hemodialysis (HD) patients. *J Am Soc Nephrol.* 1991;2:380.

17. Kling PJ, Widness JA, Guillery EN, Veng-Pedersen P, Peters C, DeAlarcon PA. Pharmacokinetics and pharmacodynamics of erythropoietin during therapy in an infant with renal failure. *J Pediatr.* 1992;121:822-825.

18. deAndrade JR and Jove M. Baseline Hemoglobin as a Predictor of Risk of Transfusion and Response to Epoetin alfa in Orthoperdic Surgery Patients. *Am. J. of Orthoped.* 1996;25 (8):533-542.

19. Goldberg MA and McCutchen JW. A Safety and Efficacy Comparison Study of Two Dosing Regimens of Epoetin alfa in Patients Undergoing Major Orthopedic Surgery. *Am. J. of Orthoped.* 1996;25 (8):544-552.

20. Faris PM and Ritter MA. The Effects of Recombinant Human Erythropoietin on Perioperative Transfusion Requirements in Patients Having a Major Orthopedic Operation. *J. Bone and Joint surgery.* 1996;78-A:62-72.

21. Lundin AP, Akerman MJH, Chesler RM, et al. Exercise in Hemodialysis Patients after Treatment with Recombinant Human Erythropoietin. *Nephron.* 1991;58:315-319.

22. Amgen Inc., data on file.

23. Eschbach JW, Kelly MR, Haley NR, et al. Treatment of the Anemia of Progressive Renal Failure with Recombinant Human Erythropoietin. *NEJM.* 1989;321:158-163.

24. The US Recombinant Human Erythropoietin Predialysis Study Group. Double-Blind, Placebo-Controlled Study of the Therapeutic Use of Recombinant Human Erythropoietin for Anemia Associated with Chronic Renal Failure in Predialysis Patients. *Am J Kid Dis.* 1991;18:50-59.

25. Ortho Biologics, Inc., data on file.

26. Danna RP, Rudnick SA, Abels RI. Erythropoietin Therapy for the Anemia Associated with AIDS and AIDS Therapy and Cancer. In: MB Garnick, ed. *Erythropoietin in Clinical Applications - An International Perspective.* New York, NY: Marcel Dekker; 1990:301-324.

27. Fischl M, Galpin JE, Levine JD, et al. Recombinant Human Erythropoietin for Patients with AIDS Treated with Zidovudine. *NEJM.* 1990;322:1488-1493.

28. Laupacis A. Effectiveness of Perioperative Recombinant Human Eyrthropoietin in Elective Hip Replacement. *Lancet.* 1993;341:1228-1232.

29. Kerr DN. Chronic Renal Failure. In: Beeson PB, McDermott W, Wyngaarden JB, eds. *Cecil Textbook of Medicine.* Philadelphia, PA: W.B. Saunders; 1979:1351-1367.

30. Campos A, Garin EH. Therapy of renal anemia in children and adolescents with recombinant human erythropoietin (rHuEPO). *Clin Pediatr* (Phila). 1992;31:94-99.

31. Montini G, Zacchello G, Baraldi E, et al. Benefits and risks of anemia correction with recombinant human erythropoietin in children maintained by hemodialysis. *J Pediatr.* 1990;117:556-560.

32. Offner G, Hoyer PF, Latta K, Winkler L, Brodehl J, Scigalla P. One year's experience with recombinant erythropoietin in children undergoing continuous ambulatory or cycling peritoneal dialysis. *Pediatr Nephrol.* 1990;4:498-500.

33. Muller-Wiefel DE, Scigalla P. Specific problems of renal anemia in childhood. *Contrib Nephrol.* 1988;66:71-84.

34. Scharer K, Klare B, Dressel P, Gretz N. Treatment of renal anemia by subcutaneous erythropoietin in children with preterminal chronic renal failure. *Acta Paediatr.* 1993;82:953-958.

35. Mueller BU, Jacobsen RN, Jarosinski P, et al. Erythropoietin for zidovudine-associated anemia in children with HIV infection. *Pediatr AIDS and HIV Infect: Fetus to Adolesc.* 1994;5:169-173.

36. Zuccotti GV, Plebani A, Biasucci G, et al. Granulocyte-colony stimulating factor and erythropoietin therapy in children with human immunodeficiency virus infection. *J Int Med Res.* 1996;24:115-121.

37. Beck MN, Beck D. Recombinant erythropoietin in acute chemotherapy-induced anemia of children with cancer. *Med Pediatr Oncol.* 1995;25:17-21.

38. Bennetts G, Bertolone S, Bray G, Dinndorf P, Feusner J, Cairo M. Erythropoietin reduces volumes of red cell transfusions required in some subsets of children with acute lymphocytic leukemia. *Blood.* 1995;86:853a.

39. Raskin NH, Fishman RA. Neurologic Disorders in Renal Failure (First of Two Parts). *NEJM.* 1976;294:143-148.

40. Raskin NH and Fishman RA. Neurologic Disorders in Renal Failure (Second of Two Parts). *NEJM.* 1976;294:204-210.

41. Messing RO, Simon RP. Seizures as a Manifestation of Systemic Disease. *Neurologic Clinics.* 1986;4:563-584.

42. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *NEJM.* 1998;339:584-90.

43. Henke, M, Laszig, R, Rübe, C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomized, double-blind, placebo-controlled trial. *The Lancet.* 2003;362:1255-1260.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103234s5033

MEDICAL REVIEW

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

Memorandum

Date: September 29, 2005

From: Patricia Keegan, M.D., Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

To: BL STN 103234.5033

Subject: Medical Officer review

The following documents, prepared by Dr. Harvey Luksenburg, comprise the medical officer review materials for the labeling supplement (BL STN 103234.5033):

- The FDA briefing document prepared for the May 4, 2004 Oncologic Drugs Advisory Committee (ODAC) meeting;
- The memorandum dated May 1, 2004 containing an errata sheet to the ODAC briefing document; and
- The December 7, 2004 review of the clinical study report for EPO-INT-10.

Study EPO-INT-76

The Breast Cancer Erythropoietin Trial (BEST)

Harvey Luksenburg, M.D., Clinical Reviewer
CDER/ODVI/DTBOP

Claire Gnecco, Ph.D., Statistical Reviewer

December 7, 2004.

Table of Contents

I. Background

The Breast Cancer Erythropoietin Trial (BEST), designed by Johnson & Johnson, was conducted to extend and possibly confirm the results of an earlier trial (Study EPO-INT-10). EPO-INT-10[i] was a randomized, placebo-controlled trial that had enrolled 375 subjects. The patients had either solid or non-myeloid hematologic malignancies and hemoglobin levels of either ≤10.5 g/dl or between 10.5 and 12.0 g/dl after a hemoglobin decrease of at least 1.5 g/dl per cycle since starting chemotherapy. Patients received study drug for 12 to 24 weeks. No specific target hemoglobin was given, however, the dose of EPREX was to be held if the hemoglobin was greater than 15 g/dl, and restarted at 12 g/dl. The trial was not powered for survival, but there was a trend in overall survival favoring the EPREX arm (log rank test p=0.13; Cox regression analysis hazards ratio of 1.309 (p=0.052)). At 12 months, the Kaplan-Meier estimate of survival was 60% for the EPREX arm and 49% for the placebo arm. The median survival times were 17 months with EPREX and 11 months with placebo. An additional basis for initiation of EPO-INT-76 was the supposition that use of an erythropoietin to increase hemoglobin levels might improve survival given the literature suggesting a link between low hemoglobin levels (as a marker for tumor hypoxia), poorer response to treatment (both radiation and chemotherapy), and worsening survival.[ii]

Study EPO-INT-76 was designed to test the hypothesis that maintaining hemoglobin in the range of 12 to 14 g/dl via the administration of EPREX would improve survival and quality of life in patients with metastatic breast cancer receiving chemotherapy. The study was conducted at 139 sites in 20 countries (Western and Eastern Europe, Canada, Australia, South Africa). Eligible patients were women with breast cancer who were receiving first-line chemotherapy for metastatic disease. Randomization was stratified by the following three variables: disease restricted to the skeleton; extraskeletal measurable disease, extraskeletal nonmeasurable disease.

II. Study Design

Subjects were randomly assigned to receive either 40,000 IU EPREX or placebo subcutaneously QW. Study drug was administered once a week to maintain hemoglobin in the range of 12 to 14 g/dl for 12 months. The choice of chemotherapy or hormonal therapy was left to the discretion of the investigator. Study drug was to be initiated only when the hemoglobin was 13 g/dl or lower. The study drug was withheld if the hemoglobin rose above 14 g/dl.[iii] Hgb concentrations and reticulocyte counts were monitored weekly for the first 4 weeks to determine either when study drug administration was to begin or whether a dose adjustment was necessary. After the first 4 weeks of study drug administration, Hgb concentrations and reticulocyte counts were monitored every 3 to 4 weeks for the remainder of the double-blind treatment phase. The maximum dose of epoetin alfa was not to exceed 60,000 IU once a week.

Randomization was stratified by metastatic category (bon metastasis only versus other measurable metastatic lesions versus other nonmeasurable metastatic lesions).

Efficacy Endpoints

The primary efficacy endpoint for the double-blind phase of the study was the 12-month survival rate, defined as the proportion of subjects surviving at 12 months after randomization.

Secondary efficacy endpoints were change in Hgb concentration from baseline to individual study end, Hgb concentration over time, proportion of subjects receiving RBC transfusions from baseline to study end, standardized, cumulative RBC units transfused from baseline to study end, optimal tumor response to first-line chemotherapy, tumor response at end of first-line chemotherapy, tumor response at end of study, time to disease progression (TTP), and QOL measured by the Functional Assessment in Cancer Therapy—Anemia (FACT-An) and Cancer Linear Analogue Scale (CLAS) questionnaires.

Sample Size

The planned enrollment was 870 (435/treatment group). A total of 939 subjects (470 on placebo and 469 on epoetin alfa) were enrolled and analyzed in the intent-to-treat (all randomized) population. The sample size was based on the assumption of 70% survival in the placebo arm and 80% in the EPREX arm at the end of the 12-month double-blind treatment phase. This assumption took into consideration an estimate that 25% of the study population comprised subjects who had bone only metastases. The primary statistical objective was to detect a minimum absolute 10% improvement (i.e., 80% survival). A 100% follow-up was anticipated with respect to 12-month survival status. Based on these assumptions and a 2-sided significant level of 0.05, a planned total of 870 subjects (435/arm) yielded greater than 90% power for testing the null hypothesis of an equal 12-month survival rate between the two treatment arms.

Statistical Methods

Analysis of the primary efficacy endpoint was performed for the intent-to-treat and efficacy populations. Kaplan-Meier estimates were presented by treatment group and the estimated hazard ratio, with its 95% confidence interval were presented. Treatment comparisons were via the stratified (by metastatic disease category) logrank test. Two exploratory analyses were performed using stratified Cox PH regression models. The first model included treatment and prognostic factors thought likely to demonstrate significant heterogeneity in subject survival. The second Cox model included all of the factors from the first model plus all 2-way interactions. Survival results and subgroup analyses were also summarized for subject who died within 4 months of randomization. Hgb concentrations over time were analyzed longitudinally using linear mixed effects models and treatment comparisons were made with respect to the rate of change in Hgb from baseline to the last on-study value was via an ANOVA model that included terms of treatment and metastatic disease category. In addition, the proportion of Hgb levels maintained between 12 and 14 g/dl was analyzed via a logistic regression model for correlated variables. Hgb levels over time were summarized as a function of baseline anemia status and 12-month survival status, and the change from baseline to last value was summarized by baseline anemia status. Proportion receiving RBC

transfusions was analyzed via a logistic regression model including metastatic disease status and treatment group as explanatory variables; the estimated odds ratio and its associated 95% confidence interval were presented. Standardized (in 4-week intervals) cumulative RBC units transfused from randomization to study completion/withdrawal were analyzed via a Poisson regression model with over-dispersion parameter. Treatment differences in optimal tumor response rates to first-line chemotherapy and tumor response rates at double-blind phase end were analyzed via a stratified Cochran-Mantel-Haenszel test for ordinal response. In addition, a proportional odds model for ordinal data was used to model optimal tumor response data. Kaplan-Meier estimates for TTP were presence by treatment group using the stratified logrank test; the estimated hazard ratio and its associated 95% confidence interval were estimated using a stratified Cox PH model. An exploratory analysis of disease-free survival (DFS) was carried out using a similar approach. Quality of life data were analyzed using longitudinal methods. A mixed effects growth curve model analysis was used to estimate the area under the QOL curve from randomization to Month 12. Sensitivity analyses were carried out based on different assumptions concerning missing data. The association between change in Hgb concentration and QOL was examined via correlation techniques, which also controlled for multiple comparisons.

III. Study Results

A total of 939 subjects (470 on placebo and 469 on EPREX) were enrolled and analyzed in the intent-to-treat (all randomized) population.

The study was initiated in June 2000, and the last subject was enrolled in June 2001. In January 2002, an Independent Data Monitoring Committee was established at the request of the Ethics Committees of Germany and the United Kingdom. In April 2002, the IDMC reviewed the available data from 938 subjects. The Committee expressed concern over an unexpected excess mortality observed in the EPREX -treated arm. At the time of this interim analysis, there were 179 deaths, 101 in the EPREX- treated arm and 78 in the placebo arm. On April 24, 2002, the IDMC asked Johnson & Johnson to discontinue administration of the study drug to all participating subjects. J&J also commissioned an outside consulting firm to conduct a medical chart review, in which the primary documents were reviewed in a blinded manner in an attempt to "collect additional information concerning factors of prognostic significance for breast cancer and potentially fatal medical conditions". This latter review was conducted in August 2002. The results in the tables below contain data from the "Clinical Trial Database" which was derived from the Case Report Forms (CRFs) submitted by the investigators at each site; and the "Medical Chart Review Database" that was based on a chart review by an outside consulting firm.

IV. Materials Reviewed

Clinical Expert Report on INT-76, submitted by Johnson & Johnson Pharmaceutical Research and Development, April 23, 2003.

V. Summary of Key Findings

The results of the unplanned interim analysis of this study are as follows:

- The Kaplan-Meier estimates for 12-month survival in the intent-to-treat population was shorter in the EPREX arm (70%) compared with the placebo arm (76%). This difference was statistically significant (p=0.0117, relative risk=1.359).
- At 4 months after randomization, there was evidence of increased early mortality in patients randomized to EPREX; among 57 subjects who died within the first 4 months, 41 (72%) were in the EPREX arm and 16 (28%) were in the placebo arm.
- Twice as many patients in EPREX arm experienced disease progression as in the placebo arm: 28 (6%) versus 13 (3%).
- There was also an increased incidence to thrombotic vascular and cardiovascular adverse events: 2.3% in the EPREX arm versus 0.4% in the placebo arm.
- The overall response rate (complete and partial responses) was 46% in the placebo arm and 45% in the EPREX arm.
- Patients in the EPREX arm received study drug for an average of 30.4 weeks versus 36.9 weeks for the placebo arms.
- In the EPREX arm, 59% of hemoglobin determinations were within the target range (12-14 g/dl). In the placebo arm, this value was 45%.[iv] Of note, the median baseline hemoglobin was 12.8 g/dl in both arms.

VI. Detailed Study Results

A. Demographics and Baseline Characteristics

Study EPO- INT-76, Intent-to-treat Population

Characteristic	Placebo (N=470)	Epoetin alfa (N=469)	Total (N=939)
Age (years)			
N	470	469	939
Mean (SD)	55.1 (10.49)	55.8 (11.13)	55.5 (10.81)
Median	55.0	56.0	56.0
Range	30.0-84.0	24.0-83.0	24.0-84.0

Age Categories (years)			
≤ 35	10 (2)	14 (3)	24 (3)
36-45	65 (14)	66 (14)	131 (14)
46-55	149 (32)	133 (28)	282 (30)
56-65	156 (33)	145 (31)	301 (32)
66-75	75 (16)	86 (18)	161 (17)
≥ 76	15 (3)	25 (5)	40 (4)
Age at initial diagnosis (years)			
N	470	469	939
Mean (SD)	51.0 (10.78)	52.1 (11.00)	51.6 (10.90)
Median	51.0	52.0	51.0
Range	23.0-80.0	23.0-83.0	23.0-83.0
Age at initial diagnosis categories (years)			
≤ 35	33 (7)	28 (6)	61 (7)
36-45	118 (25)	108 (23)	226 (24)
46-55	165 (35)	157 (33)	322 (34)
56-65	108 (23)	119 (25)	227 (24)
66-75	42 (9)	51 (11)	93 (10)
≥ 76	4 (1)	6 (1)	10 (1)
Race, no. (%)			
White	465 (99%)	459 (98%)	924 (98%)
Black	0	4 (1)	4 (<1)
Asian	3 (1)	3 (1)	5 (1)
Other	2 (<1)	3 (1)	5 (1)
Body Mass Index (kg/m2)			
Mean (SD)	27.0 (4.90)	27.0 (5.08)	27.0 (4.99)
Median	26.4	26.6	26.5
Range	17.1-46.9	15.8-49.5	15.8-49.5
Body Mass Index categories (kg/m2)			
<18.5	9 (2)	11 (2)	20 (2)
18.5-24.9	169 (36)	176 (38)	345 (37)
24.9-29.9	168 (36)	160 (34)	328 (35)
≥ 30.0	123 (26)	121 (26)	244 (26)

Clinical Reviewer's Comment:

The two arms were well-balanced with regard to age distribution, age at initial diagnosis, race, and body mass index.

Baseline Laboratory Values

Hematology	Placebo (N=470)	Epoetin alfa (N=469)	Total (N=939)
Hemoglobin (g/dl)			
Mean (SD)	12.5 (1.69)	12.5 (1.82)	12.5 (1.76)
Median	12.8	12.8	12.8
Range	5.5-18.9	4.9-17.0	4.9-18.9
Hematocrit (%)			
Mean (SD)	38.3 (4.54)	38.0 (4.88)	38.2 (4.71)
Median	38.6	38.0	38.3
Range	22.8-57.0	21.6-51.0	21.6-57.0

Clinical Reviewer's Comment:

The two arms were well-balanced with regard to baseline hemoglobin values. The baseline values for white blood count, and platelet count (not shown) also showed no differences.

Baseline Tumor-Related Characteristics (Intent-to-treat Population)

Characteristic	Placebo (N=470)	Epoetin alfa (N=469)	Total (N=939)
Time since initial diagnosis (months)			
Mean (SD)	49.1 (53.33)	44.1 (46.11)	46.6 (49.89)
Median	35.1	32.4	33.9
Range	0.0-377.7	0.0-376.1	0.0-377.7
Time since metastatic diagnosis (months)			
Mean (SD)	6.3 (14.33)	6.6 (16.48)	6,4 (15.43)
Median	0.9	0.9	0.9
Range	0.0-113.4	0.0-123.5	0.0-123.5
Disease-free interval (months)			
Mean	42.8 (49.62)	37.6 (41.31)	40.2 (45.71)
Median	29.5	27.2	28.0
Range	0.0-362.8	0.0-336.4	0.0-362.8

Stage at initial diagnosis, no. (%)			
I	68 (14)	59 (13)	127 (14)
II	223 (47)	205 (44)	428 (46)
III	95 (20)	105 (22)	200 (21)
IV	81 (17)	96 (20)	177 (19)
Type of metastasis, no. (%)			
Only bone	73 (16)	66 (14)	139 (15)
Other	397 (84)	403 (86)	800 (85)
Estrogen receptor result, no. (%)			
Negative	131 (28)	126 (27)	257 (27)
Positive	232 (49)	226 (48)	458 (49)
Not determined	107 (23)	117 (25)	224 (24)
Postmenopausal, no. (%)			
No	110 (23)	109 (23)	219 (23)
Yes	359 (76)	360 (77)	719 (77)
Missing	1 (<1)	0	1 (<1)
Ascites, no. (%)			
No	453 (96%)	458 (98)	911 (97)
Yes	17 (4)	9 (2)	26 (3)
Pleural effusion, no. (%)			
No	396 (84)	389 (83)	785 (84)
Yes	74 (16)	78 (17)	152 (16)
ECOG Performance status, no. (%)			
0	222 (47)	198 (42)	420 (45)
1	199 (42)	216 (46)	415 (44)
2	49 (10)	55 (12)	104 (11)
1 or 2	248 (53)	271 (58)	519 (55)

Clinical Reviewer's Comment:

The two arms were well-balanced with respect to time since metastatic diagnosis, disease-free survival, stage at initial diagnosis, estrogen receptor status, menopausal status, distribution of metastatic disease, and performance status.

B. Prestudy Chemotherapy

Characterize	Placebo (N=470)	Epoetin alfa (N=469)	Total
Adjuvant chemotherapy, no. (%)			
No	237 (50%)	240 (51%)	477 (51)
Yes	233 (50%)	229 (49%)	462 (49)
Pre-study radiation therapy, no. (%)			
No	174 (37)	194 (41)	368 (39)
Yes	296 (63)	275 (59)	571 (61)
Adjuvant setting	256 (54)	238 (51)	494 (53)
Metastatic setting	105 (22)	81 (17)	186 (20)
Adjuvant chemo and radiation therapy, no. (%)			
No	300 (64)	312 (67)	612 (65)
Yes	170 (36)	157 (33)	327 (35)
Pre-study hormonal therapy, no. (%)			
No	203 (43)	182 (39)	385 (41)
Yes	267 (57)	287 (61)	554 (59)
Adjuvant setting	203 (43)	221 (47)	424 (45)
Metastatic setting	218 (46)	219 (47)	437 (47)
Time from end of adjuvant therapy to metastatic diagnosis (months)			
N	319	322	641
Mean (SD)	19.8 (35.92)	17.0 (28.00)	18.4 (32.19)

Median	**3.1**	**3.9**	**3.4**
Range	**0.0-285.1**	**0.0206.4**	**0.0-285.1**
Category of time from end adjuvant therapy to metastasis diagnosis, no. (%)			
=0 (Stage IV diagnosis date)	**132 (28)**	**118 (25)**	**250 (27)**
>0, ≤ 12 months	**70 (15)**	**84 (18)**	**154 (16)**
> 12 months	**117 (25)**	**120 (26)**	**237 (25)**
Missing	**151 (32)**	**147 (31)**	**298 (32)**

Clinical Reviewer's Comment:

The two arms were well balanced with respect to the percentages who received adjuvant chemotherapy, radiation therapy, hormonal therapy, and in the time intervals between the end of adjuvant therapy to the diagnosis of metastatic disease.

First-Line Chemotherapy

The most frequently used chemotherapeutic regimens were 5-FU/doxorubicin (Adriamycin)/cyclophosphamide (FAC): used in 22% placebo subjects and 24% of epoetin alfa subjects; CMF (13% and 12% respectively), and taxane (9% and 10%, respectively).

All other first-line chemotherapeutic regimens were used in fewer than 10% of subjects in either treatment group.

Clinical Reviewer's Comments:

The distribution of first-line chemotherapy regimens used in the study was similar between the two groups.

C. Interim Analysis of Primary Efficacy Endpoint

12 Month Survival

	Placebo	EPREX	Hazard ratio (95% CI) p value[a]
Intent-to-treat	N=470	N=469	1.37 (1.37,1.74) 0.0117
Died[b]	115 (24%)	148 (30%)	
Survived[b]	355 (76%)	321 (70%)	
Efficacy[c]	N=456	N=448	

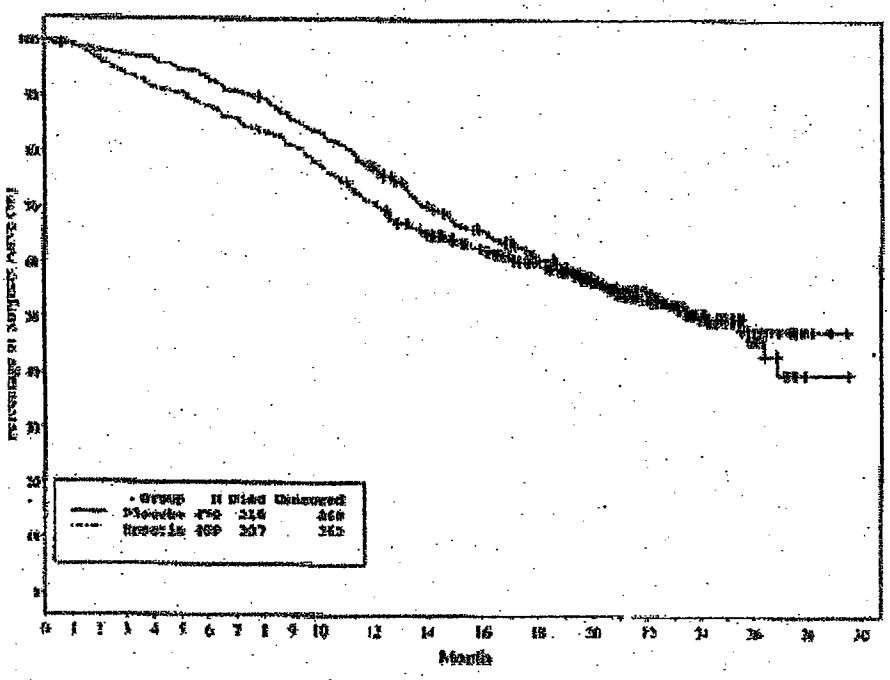
Died[b]	109(23%)	137 (29%)	1.35 (1.05,1.74)
Survived[b]	347 (77%)	sa311 (71%)	0.0189

[a] Based on Cox's model stratified by metastatic category

[b] Percentage of subjects who survived or died within 12 (+ 2 week window) of randomization are based on Kaplan-Meier estimates.

[c] Efficacy population comprised only of subject who receive study drug.

Kaplan-Meier Curves of Survival (August 2003[v])



Statistical Reviewer's Comments:

Kaplan-Meier probability estimates of the 12 month survival rate for the intent-to-treat population were lower in the EPREX group (70%) compared to the placebo group (76%), and this treatment group difference was statistically significant (p=0.0117; relative risk=1.359). The primary cause of death in both treatment groups was disease progression, accounting for 88% of all deaths within 12 months of randomization. After analyses adjusting for a large number of prognostic factors (i.e., 26), the EPREX group still had a significantly inferior survival (p=0.0182). In subgroup analysis, no single factor was identified as capable of accounting for this treatment group difference in the 12 months survival rate.

Clinical Reviewer's Comments:

In the intent-to-treat population, the survival was lower in the epoetin alfa arm (70%) than in the placebo arm (76%), based on Kaplan-Meier estimates. The analysis based on the logrank test stratified by metastatic category demonstrated that the difference between the treatment groups was statistically significant (p=0.0117).

The data concerning the cause of death at 12 months in the Clinical Trial Database is below:

	Placebo (N=470)	EPREX (N=469)	Total (N=939)
No. (%) died during 12 months	115 (24)	148 (32)	263 (28)
Cause of death during 12 months, no. (%)			
Chemotherapy toxicity	1 (1)	8 (5)	9 (3)
Disease progression	105 (91)	126 (85)	231 (88%)
Missing	0	2 (1)	2 (1)
Other	6 (5)	6 (4)	12 (5)
Thrombotic vascular event	3 (3)	6 (4)	9 (3)

Number of subjects who died at Four Mos/Number of Subjects Who Died at 12 Mos (Clinical Trial Database)

	Placebo	EPREX
TVE	1/3 (33%)	5/6 (83%)
Progressive disease	13/91 (14%)	28/126 (22%)

Clinical Reviewer's Comment:

The incidence of causes of death at 12 months was similar between the two arms. The incidence of death from disease progression (as a proportion of all deaths) was 91% in the placebo arm and 85% in the EPREX arm. The incidence of death from thrombotic vascular events (as a proportion of all deaths) was 3% in the placebo arm and 4% in the EPREX arm.

Of all subjects who died (at 12 months) a higher proportion of subjects died from both TVE and progressive disease at 4 months in the EPREX arm than in the placebo arm.

This data strongly suggests that the risk of death from TVE and progressive disease was increased at 4 months in the EPREX arm.

Increased Early Mortality at Four Months

Causes of Death Among Subjects Who Died Within the First 4 Months After Randomization (Study EPO-INT-76: Intent-to-treat Population)
Data Source: Clinical Trial Database[vi]

	Placebo (N=470)	EPREX (N=469)
No. (%) died within 4 months	16 (3)	41 (9)
No. (%) alive at 4 months	454 (97)	428 (91)
Cause of death within 4 months, no. (%)		
Chemotherapy toxicity	1 (0)	3 (1)
Disease progression	13 (3)	28 (6)
Missing	0	1 (0)[1]
Thrombotic vascular event	1 (0)	5 (1)
Other[2]	1 (0)	4 (1)

("Other" caused include: fatty embolism, ischemic colonic perforation, pulmonary edema, and unknown.)

Causes of Death in Subjects Dying During the 4 Months After Randomization
Data Source: Medical Chart Review Database

	Placebo (N=468)		Epoetin alfa (N=469)	
	N	%	N	%
Disease progression	10	2%	21	4%
Adverse event	1	<1%	10	2%
Other	5	1%	10	2%
Total	16	3%	41	9%

Statistical Reviewer's Comments:

Kaplan-Meier survival estimates indicated that the treatment difference was already evident at Month 4, and, at later time points, the survival curves for the two treatment groups were parallel. Of 57 subjects who died within the first 4 months, 16 were in the placebo group, and 41 were in the EPREX group. The Sponsor states that among subjects who died within 4 months of randomization, those assigned to the EPREX group tended to be older and sicker at study entry than those assigned to the placebo group. This was reflected in greater visceral involvement at study entry, a higher percentage of subjects who anemic at baseline (Hgb less than or equal to 10.5 g/dl), and fewer subjects whose tumors were estrogen receptor positive in the early death EPREX group compared to the placebo group. In the first 4 months after

[1] Cause of death was unknown. Subject died suddenly on Study Day 36.
[2]Other causes include: fatty embolism, ischemic colon perforation, pulmonary edema, unknown.

randomization, the incidence of fatal thrombotic/vascular events was higher in the EPREX group (5 of 469, or 1%) than in the placebo group (1 of 470, or 0%).

While a subgroup analysis of deaths within 4 months after showed a significant difference between treatment groups for a number of demographic and prognostic factors, none of these factors was able to account for most of the observed treatment group difference in 4 month mortality.

Clinical Reviewer's Comment:

The analysis of the Clinical Trial Database (compiled from the CRFs submitted by the investigators) demonstrated that, at 4 months, 9% of the subjects in the EPREX arm had died, compared with 3% in the placebo arm. When the causes of death at four months were tabulated, the risk of disease progression was more than twice as high in the EPREX arm (6% versus 3%). In addition, there were 5 subjects who died of a thrombotic vascular event.

Compared to the Clinical Trial Database, the Medical Chart Review Database, (compiled by an outside consultant, from patient charts) found a slightly decreased incidence of disease progression in the both arms, but there was still a higher incidence in the EPREX arm (4% versus 2%). It is not clear on what basis the consultant assigned causation for "adverse event" and "other", however, as seen below, he found a higher number of deaths from thrombotic/cardiovascular events in the EPREX arm at 4 months compared to that in the Clinical Trial Database.

Cardiovascular/Thrombotic/Vascular Deaths
(Study EPO-INT-76: All Randomized Subjects)
Data Source: Medical Chart Review Database

	Placebo (n=468)	EPREX (n=469)
	N (%)	N (%)
Cardiovascular/TVE death in the first 4 months after study randomization	2 (0.4%)	11 (2.3%)
Cardiovascular/TVE death more than 4 months after study randomized	7 (1.5%)	3 (0.6%)
Total	9 (1.9%)	14 (3.0%)

Further characterization of the cardiovascular/thrombotic/vascular deaths at 4 months in the Medical Chart Review:

Cardiovascular/Thrombotic/Vascular Deaths in Subjects Dying During the 4 Months After Randomization (All Randomized Subjects)
Data Source: Medical Chart Review Database

Subject number	TVE on-study	Type of TVE	Cause of death	Description	Baseline Hgb value	Last value of Hgb before TVE
Placebo						
3011	Confirmed	Pulmonary embolism	Death, other	Pulmonary embolism	11.2	11.6
3624	Confirmed	Myocardial ischemia	Death, other	Acute myocardial infarction/respiratory failure	13.1	12.80
EPREX						
1124	Suspected	Myocardial ischemia	Fatal adverse event	Sudden death	12.5	12.5
2026	Suspected	Pulmonary embolism	Fatal adverse event	Pulmonary embolism, cardiovascular	14.0	14.5
3003	No[1]	Not applicable	Death, other	Sudden death	12.9	12.0
3065	Suspected	Unknown	Fatal adverse event	Probable cardiac arrest due to severe anemia	5.90	5.90
3103	Confirmed	Myocardial ischemia	Fatal adverse event	Coronary artery disease/angina pectoris/cardiac failure	13.3	10.3
3192	Confirmed	Pulmonary embolism	Fatal adverse event	Pulmonary embolism	13.2	13.5
3207	No	Not applicable	Death, other	Left ventricular failure, pulmonary edema, neutropenic sepsis	12.0	12.0
3325	Suspected	Pulmonary embolism	fat adverse event	Pulmonary embolism	13.2	12.8
3385	Suspected	Pulmonary embolism	Death, other	Pulmonary embolism, catheter related sepsis.	13.0	11.6
3442	Suspected	Pulmonary	Fatal	Probable pulmonary	15.9	12.9

		embolism	adverse event	embolism, cardiac arrest, DIC		
3563	No[1]	Not applicable	Death, other	Sudden death	11.5	15.3

[1]Three subjects who were not reported in the CRF as having a TVE whilst on study were considered retrospectively to have died with suspicion of a cardiovascular cause due to a reported cause of death of either cardiac/sudden death.

Clinical Reviewer's Comment:

The outside consultant, reviewing the charts found 11 cases of death due to TVE in the EPREX arm at 4 months, as opposed to 5 cases of death due to TVE in the Clinical Trial Database. This gave an incidence of death from cardiovascular/thrombotic/vascular events during the first 4 months of 2.3% in the EPREX arm versus 0.4% in the placebo arm. The causes of death in the EPREX arm were pulmonary embolism (6), sudden death (3), and cardiac failure (2).

The risk of cardiovascular/thrombotic/vascular death after 4 months was slightly higher in the placebo group (placebo 1.5% versus EPREX 0.6%). The total (12 month) incidence of cardiovascular/thrombotic/vascular death was 3.0% in the EPREX arm versus 1.9% in the placebo arm.

Thus the highest risk of death occurred in the first 4 months. There is insufficient data as to whether the risk of death from cardiovascular/thrombotic vascular causes was due to the absolute value of the Hgb at the time of the fatal events.

Optimal Tumor Response to First-Line Chemotherapy

Tumor responses	Placebo (N=470)	Epoetin alfa (N=469)
Complete response	45 (10)	55 (12)
Partial response	170 (36)	154 (33)
No response (stable)	156 (33)	149 (32)
Progressive disease	84 (18)	87 (19)
New lesions		
No	19 (23)	25 (29)
Yes	56 (67)	43 (49)
Not specified	9 (11)	19 (22)
Unknown	15 (3)	24 (5)
p value	0.9303	

Time to Disease Progression

For the intent-to-treat population, time to disease progression was comparable for the 2 treatment groups (p=0.7059). Based on Kaplan-Meier estimates, 43% of subjects in the placebo group and 41% of those in the EPREX group had evidence of disease progression by Month 12.

Statistical Reviewer's Comments:

Although most of deaths within 12 months after randomization were due to disease progression, the difference in 12 months survival rate was not related to differences in disease progression between treatment and placebo group. Kaplan-Meier estimates of time to disease progression (TTP) and disease-free survival (DFS) for the intent-to-treat population did not differ between the two treatment groups (p=0.7059 and p=0.9843, respectively). The optimal tumor response rate to first-line chemotherapy was similar in the two treatment groups (214/470 (45.7%) versus 209/469 (44.6%), p=0.9303). Results of the proportional odds model further confirmed that the optimal tumor response profile was comparable for the two groups after controlling for the other main effects (odds ratio of 0.995; p=09676, intent-to-treat population). Tumor response at the end of first-line chemotherapy and tumor response at the end of study for the intent-to-treat group were also similar in both treatment arms.

Clinical Reviewer's Comment:

The proportion of subjects achieving CR + PR was 46% in the placebo and 45% in the EPREX arm. Overall, progressive disease was seen in 18% of the placebo and 19% of the EPREX arm. As mentioned in Item 6, even though the overall risk of dying of progressive disease was similar at 12 months, subjects in the EPREX arm had a greater risk of succumbing to progressive disease at 4 months than subjects in the placebo arm.

D. Extent of Exposure to Study Drug

Sponsor states:

"Subjects in the EPREX group received study drug for an average of 30.4 weeks, and received an average of 21.4 doses per subject. Subjects in the placebo group received study drug for an average of 36.9 weeks and received an average of 35.2 doses per subject."

Clinical Reviewer's Comment:

This result is to be expected, since placebo will not have an effect on the Hgb, and thus subjects who do not reach the target Hgb will continue to be dosed. Subjects who received EPREX will be more likely to attain the target Hgb, and the dose was to be withheld for a Hgb level > 14 g/dl.

E. Attainment of Target Hemoglobin and Transfusion Requirements

Sponsor states:

"The mean baseline Hgb was 12.5 g/dl for both arms. During the first 4 weeks, mean Hgb levels declined similarly in both treatment groups. In the placebo group, mean Hgb levels continued to decline through Week 20, after which time the degree of anemia improved. In

comparison, mean Hgb levels in the epoetin alfa [EPREX] group were increased after Week 4 and remained at or elevated above the baseline level for the remainder of the study."

"Maintenance of Hgb between target levels of 12 and 14 g/dl was analyzed for the number of weeks on study for subjects in the 2 treatment groups (i.e., for subject weeks). hemoglobin was maintained within the range of 12 to 14 g/dl for 6,324 of the 10,787 (59%) subject-weeks in the epoetin alfa [EPREX] group compared with 4,896 of the 10,861 (45%) subject-weeks in the placebo group; this difference was statistically significant ($p < 0.00001$)."

"Despite a low expected need for transfusions in this subject population, the proportion of subjects transfused from baseline to the end of the double-blind phase was lower in the epoetin alfa group (10%) than in the placebo group (14%) and that difference between the treatment groups almost reached statistical significance ($p=0.0595$)."

Statistical Reviewer's Comments:

The Sponsor states that the lower 12 months survival rate in the EPREX group was not the result of excessively elevated Hgb levels. Mean Hgb levels were unchanged at the end of the double-blind phase relative to baseline in the EPREX group (mean change of 0.1 g/dl; a mean reduction of 0.5 g/dl was seen in the placebo group [treatment comparison, p-0002, intent-to-treat]). Hgb levels in the EPREX were better maintained in the range of 12 to 14 g/dl compared to the placebo group, with 59% of all on-study Hgb measurements within target range in the EPREX group compared to 45% in the placebo group ($p < 0.0001$ for intent-to-treat). Overall, subjects who died within 12 months after randomization tended to have lower Hgb levels throughout the study and this was true in both treatment groups. There was a trend toward a statistically significant decrease in the proportion of subjects transfused in the EPREX group compared to placebo (10% versus 14% respectivel6, $p=0.0595$, intent-to-treat). No treatment difference was seen, however, in the mean cumulative number of RBC units transfused for the overall intent-to-treat population or the subset of subjects who were transfused.

VII. Analysis of Study Results of Principal Investigator

The results of this study have not been published. However, Dr. Leyland-Jones, the principal investigator of the study, did publish an article describing the results in Lancet Oncology[v]. He criticized the design and conduct of the study: "the study was not designed to prospectively collect data on many potential prognostic survival factors that might have affected the study outcome." "The study design suffered from a lack of standard assessment and documentation of important prognostic factors for survival including: definition of disease site; initial prognosis and specific assessment of tumor response at predefined intervals; and type duration and dose of chemotherapy". He stated "it is not currently possible to account for the observed difference in survival by referral to differences in prognostic indicators between treatment groups or to rule out the possibility of an adverse treatment effect"[vi].

However, he concluded, "the study findings do not support the use of erythropoietin as an adjunct to first-line chemotherapy for patients with metastatic breast cancer who have normal hemoglobin concentrations".

VIII. Analysis by FDA and Recommended Actions

The EPO-INT-76 trial is the largest clinical trial conducted to date in which the subjects receiving chemotherapy for a single tumor type were prospectively randomized to receive recombinant erythropoietin to a either a specific target Hgb or placebo. The hypothesis driving this trial was that survival would be enhanced in the arm that received erythropoietin directed to a specific target Hgb range. The results demonstrated the opposite—survival at 12 months, the primary efficacy endpoint, was significantly lower in the arm that received EPREX (76% for the placebo versus 70% for the EPREX arm.). In addition, in the EPREX arm, there was an unexpected increase in mortality at 4 months after randomization, which was found to be due largely to a greater risk of disease progression. There was also, at the 4 months timepoint, an increased mortality due to thrombotic/vascular events in the group that received EPREX.

Analysis of the demographic data, baseline tumor characteristics, baseline laboratory studies, and previously therapy demonstrated that all important known variables that may have been expected to predict a poor outcome were equally distributed between the two arms. The types of chemotherapy regimen that were administered during the study were also equally balanced. There was no difference in the percentages of complete or partial response between the two groups. The percentages of subjects who experienced disease progression at 12 months were also not statistically significant.

The only other prospective clinical trial in which subjects with a single type of malignancy were randomized to receive recombinant erythropoietin to a pre-specified target Hgb was that of Henke, et al[vii]. In this trial, subjects with squamous cell carcinoma of the head and neck, who were about to receive post-operative or primary definitive radiation treatment, were assigned to receive either epoetin beta or placebo. The group that received epoetin beta was dosed to a target Hgb of $\leq$ 14.0 g/dl. Three hundred and fifty one subjects were enrolled. The primary endpoint was locoregional progression-free survival, defined as the time to locoregional tumor progression or death, whichever came first. The results demonstrated a poorer locoregional progression-free survival for the group randomized to receive epoetin beta. The stage-adjusted and stratum-adjusted relative risk for locoregional progression-free survival was 1.62 for epoetin beta (95% confidence interval 1.22-2.14, p=0.0008). The corresponding Kaplan-Meier estimate showed a median locoregional progression-free survival of 745 days for placebo versus 406 days for epoetin beta (p=0.04).

In addition, three oncology studies sponsored by Johnson & Johnson that were designed to achieve target Hgb levels at normal or greater than normal levels were halted in September 2003 because of an excessive incidence of thrombotic vascular events in the arms receiving recombinant erythropoietin.

The implications of the results of these trials, that the administration of recombinant erythropoietin to subjects with malignancies could potentially lead to stimulation of tumor growth and an increased risk of thrombotic/cardiovascular events, led to the following actions by FDA:

IX. Oncology Drugs Advisory Committee on May 4, 2004

FDA proposed that future trials be conducted that are designed to prospectively examine the impact of recombinant erythropoietin on survival, tumor progression, and on the incidence of thrombotic/vascular events. FDA proposed that these trials incorporate the following key elements:

- Homogenous primary tumor.
- Homogenous chemotherapy and/or radiation regimens.
- Randomized, placebo-controlled.
- Data collection that will allow the systematic acquisition of information of tumor response, time to progression, and survival.
- Target hemoglobin values of no greater than 12.0 g/dl, with prespecified rules for dose adjustment.
- Prespecified definitions for cardiovascular and thrombovascular events.
- A Data Safety Monitoring Board with a charter that states criteria for halting the study in the event of a prespecified number of cardiovascular or thrombotic adverse events occurs.
- Collection of data regarding the erythropoietin receptor status of primary tumor sites.
- Studies on tumor populations with high, low, and intermediate quantities of erythropoietin receptors.

The Committee agreed that further studies to investigate survival and thrombotic/vascular events were warranted, and concurred with the incorporation of the above elements in such studies, with the exception of the last two bullets, i.e. the collection of data regarding erythropoietin receptor status, and studies of tumor populations with differing quantities of erythropoietin receptors. The Committee also was of the opinion that such studies, utilizing placebo controls, would be feasible and ethical if conducted in the United States.

X. Revised Product Information

FDA requested and approved revised labeling to incorporate the results of the BEST and the Henke studies for all recombinant erythropoietin products that are currently licensed in the United States. This new language is in WARNINGS: Thrombotic Events and Increased Mortality and PRECAUTIONS: Growth Factor Potential.

XI. Dear Health Care Provider Letter

FDA requested that the Sponsors (Amgen and J&JPRD) that market recombinant erythropoietins for the Oncology indication send Dear Health Care Provider Letters to be mailed to all practitioners with specialties pertaining to the care of patients with cancer.

[i] Littlewood TJ, et al. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: Results of a randomized, double-blind, placebo-controlled trial. *JCO* 19: 2865, 2001.

[ii] Albain, KS, et al. *JCO* 9:1618, 1991; Ohlhauser C, et al. Obermair A, et al. *Cancer* 83, 726, 1998. , Fein DA, et al. *JCO* 133:2077, 1995.

[iii] Clinical Expert Report on INT-76, submitted by Johnson & Johnson Pharmaceutical Research and Development, April 23, 2003, p. 11.

[iv] Ibid, p. 12.

[v] Leyland-Jones, B and the BEST Investigators and Study Group. *Lancet Oncology* 4:459, 2003.

[vi] Ibid, p. 104.

[vii] Henke et al. *Lancet* 362:1255, 2003.

72 Page(s) Removed.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103234s5033

BIOSTATISTICS REVIEW

Biostatistical Review

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s-BLA	**STN# 103234/5033** *Procrit Labeling Supplement* *Phase IV Commitment / Tumor Proliferation Issue* Submission received October 2002 Johnson & Johnson PRD, L.L.C. Raritan, NJ

Date:	May 17, 2004
Reviewer:	Clare Gnecco, Ph.D. Clare Gnecco
Through:	Aloka Chakravarty, Ph.D. Aloka Chakravarty Staff Director Biologic Therapeutics Statistical Staff
cc:	HFM-99/DCC: BLA #103234/5033 HFM-573/ Dr. Luksenburg HFM-570 / Dr. Keegan HFM-588/ Ms. Hughes HFD-700 / Dr. Chakravarty HFD-700/Chron – File: BLAPROCRIT.DOC

STATISTICAL REVIEW ISSUES / SUMMARY: The sponsor's major efficacy analyses were descriptive for Study #N93-004, the pivotal trial addressing the post-marketing commitment for possible tumor proliferation. These were investigated and descriptive statistical findings confirmed for this pivotal study. Also bearing on the issue of possible tumor proliferation with this product is Study #INT-76/EPO-CA-489, which utilized Eprex, a similar product. These two studies are the subject of this review.

The following summarizes the main statistical review findings for Study #N93-004: (1) The sponsor's claim of a non-negative impact on tumor proliferation is based on a 95%

CI for the difference in objective tumor response rates between Procrit and Placebo groups at the end of three chemotherapy cycles. This reviewer confirmed the calculation via both unadjusted and adjusted (by extent of disease) analyses. The pre-specified lower confidence limit was not breached. (2) The sponsor's claim of no difference between study agent and placebo arms in terms of changes in white blood count is based on a purely descriptive analysis of each group by chemotherapy treatment cycle. This analysis was confirmed. (3) The claim of chemotherapy dose intensity comparability, in terms of numbers of cycles and doses of etoposide and cisplatin administered, was confirmed. (4) The sponsor's survival findings were confirmed and this reviewer's stratified survival analysis (by stage of disease) was consistent with other findings.

The following summarizes the main statistical review findings for **Study #INT-76/EPO-CA-489**: (1) The sponsor's major efficacy analyses for survival, time to disease progression (TTP), and disease-free survival (DFS) were confirmed. (2) Also confirmed were the sponsor's exploratory analyses looking into why there were significantly more early deaths (within 4 months of randomization) in the epoetin alfa treatment group; these were consistent with the sponsor's explanation that these study drug arm patients appeared to have more extensive disease at study entry. (3) The sponsor provided the requested comprehensive survival analysis, which censored subjects at the time of crossover to new treatment. (4) The sponsor provided the requested treatment X baseline hemoglobin (Hgb) interaction analysis for the survival endpoint. The interaction between baseline Hgb and treatment was not significant ($p = 0.9856$), although the relative risk of the interaction term, 0.838, implied an upward trend in the relative risk between treatment groups among those subjects with higher baseline Hgb levels.

BACKGROUND:

Study #N93-004: This study, entitled *"The Effect of r-HuEPO in Patients with Small Cell Lung Cancer (SCLC): A Randomized, Double-Blind, Placebo-Controlled Trial,"* was undertaken as a Phase IV commitment for the approval of epoetin alfa for treating the anemia of cancer patients on chemotherapy in April 1993. The initiation date for this study was July 15, 1993. The study was prematurely terminated for poor recruitment on July 17, 2001.

Summary of Study #N93-004: This study was performed as part of a post-approval commitment to evaluate possible stimulatory effects of epoetin alfa on solid tumor growth. The **primary objective** was to determine the effect of epoetin alfa on tumor response in SCLC subjects receiving chemotherapy with VP-16 (etoposide) and cisplatin. The **secondary objectives** were to evaluate the effect of epoetin alfa on survival, erythroid parameters, and transfusion rate in SCLC subjects.

Design / Methodology: This was a phase IV, randomized, double-blind, parallel group, placebo-controlled trial conducted at 35 sites in the United States. At the time this study was initiated, the standard chemotherapy treatment regimen for SCLC was etoposide/cisplatin. Since that time, the standard of care for SCLC evolved such that it

now differs from what was specified in this study's protocol. As a result, recruitment was slow and the study was terminated early, with FDA agreement, after 224 subjects had been enrolled and completed the double-blind treatment phase.

There was a double-blind treatment phase with up to 12 cycles of chemotherapy followed by 3 years of double-blind follow-up for assessment of survival. Subjects with newly diagnosed SCLC were randomly assigned 1:1 to either epoetin alfa 150 IU/kg or placebo, administered s.c. 3 times per week, until approximately 3 weeks after completing the final chemotherapy cycle. Etoposide/cisplatin was to be administered every 3 weeks for at least 3 cycles. Approximately 3 weeks after Cycle 3 and after completion of the final cycle, the extent of measurable and evaluable disease was determined by appropriate imaging techniques. Disability ratings via ECOG scoring were assessed at baseline and at study completion/termination.

Sample Size: The planned accrual was 400 subjects. In fact, 224 subjects were enrolled and analyzed.

Efficacy Endpoints: The **primary efficacy endpoint** was the proportion of subjects in each treatment group who had a complete (CR) or partial response (PR) to chemotherapy after the third cycle of chemotherapy. **Secondary endpoints** included survival, proportion of subjects with a CR or PR after the final chemotherapy cycle, changes in hemoglobin (Hgb) levels over time, RBC transfusion rates on-study, and ECOG performance scores at baseline and the final visit.

Statistical Methods: Because the study was terminated prematurely for poor recruitment, analyses of efficacy endpoints consisted of descriptive summaries. The percent of subjects with an overall tumor response (CR + PR) at the end of Cycle 3 and after the final chemotherapy cycle, along with a 95% CI, were calculated by treatment and stage of disease at diagnosis. The observed difference in overall tumor response rates (epoetin alfa minus placebo) and its 95% CI were calculated. The **primary objective** was to show that overall tumor response rate in the epoetin alfa group was not 15% below that in the placebo group after 3 cycles of chemotherapy. Kaplan-Meier estimates of survival over the entire course of the study and follow-up were generated as a function of treatment and stage of disease at diagnosis. Kaplan-Meier estimates of on-study transfusion were also generated for each treatment group.

Sponsor's Efficacy Results for Pivotal Study #N93-004:

Baseline Balance: Patients were well balanced on baseline demographic and medical characteristics at study entry.

Primary Efficacy Endpoint: Evaluation of the primary efficacy endpoint indicated that the percentage of subjects exhibiting a CR or PR after 3 cycles of chemotherapy was numerically greater in the epoetin alfa treatment group (73%) than in the placebo group

(67%). The 95% CI for the difference in rates did not contain the pre-specified limit of –15%. The following sponsor's table summarizes these findings:

Sponsor's Table A: Overall Tumor Response Rate for Total Population and as a Function of Disease Stage at Diagnosis (After 3 Cycles of Chemotherapy)

ITT Population	Placebo	Epoetin Alfa
Objective Response (CR + PR)	77	79
N	115	109
Overall Response Rate (95% CI)	67% [58%, 76%]	72% [64%, 81%]
95% CI for Δ (Epoetin – Placebo)	6% [-6%, 18%]	
Extensive Stage SCLC		
N	68	72
Overall Response Rate (95% CI)	60% [49%, 72%]	74% [63%, 84%]
95% CI for Δ (Epoetin – Placebo)	13% [-2%, 29%]	
Limited Stage SCLC		
N	47	37
Overall Response Rate (95% CI)	77% [64%, 89%]	70% [56%, 85%]
95% CI for Δ (Epoetin – Placebo)	-6% [-25%, 13%]	

Objective tumor response rates after all chemotherapy cycles (a secondary endpoint) were similar for the epoetin alfa (60%) and placebo (56%) treatment groups. The observed difference is 4% with associated 95% CI of [-9%, 17%].

Reviewer's Comment: This reviewer confirmed both the unadjusted and adjusted (i.e., stratified by disease stage at diagnosis) primary endpoint analyses. The study met the pre-specified criterion of not exceeding –15% in the lower 95% confidence limit on the unadjusted analysis. For descriptive purposes, the p-value for the unadjusted comparison was p = 0.369 (two-sided) and the Cochran Mantel-Haenszel test p-value was p = 0.330 for the stratified analysis. Similarly, for the secondary endpoint of objective tumor response rate at the last chemotherapy cycle, the rates were similar for the epoetin alfa, 65/109 (60%), and placebo, 64/115 (56%), treatment groups. The observed Δ was 4% with an associated 95% CI of [-9%, 17%]. This reviewer's calculated p-value (for descriptive purposes) was 0.545.

Response duration was not calculated. No data were provided for date of tumor response.

Time to disease progression (TTP) could not be accurately calculated. In Protocol #N93-004 subjects were allowed to withdraw early for progressive disease. In these cases, the date of discontinuation was captured and not the actual date of progression. For the 25 subjects who were discontinued from the study for disease progression, the progression date was on or before the date of discontinuation.

Survival Analysis: This reviewer confirmed the sponsor's survival analysis, presented in Sponsor's Table 17 below:

Sponsor's Survival Table 17
ITT Analysis in Months*

	PLACEBO			EPOETIN ALFA		
	Estimate	95% CI		Estimate	95% CI	
Quartile		Lower	Upper		Lower	Upper
75%	5.9	3.5	7.7	6.6	4.3	7.6
Median	10.4	8.3	12.9	10.5	9.2	12.9
25%	23.3	15.3	27.3	17.1	14.0	20.1

* Note: To convert days to months, the sponsor used a divisor of 28 days rather than the more usual 30.437 days, which takes into account leap year.

A total of 201 out of 224 subjects enrolled in this study died at some time during the study treatment period or during the 3-year follow-up. As can be seen from Sponsor's Table A, a somewhat higher proportion of subjects assigned to the epoetin alfa arm had extensive stage disease at diagnosis (66%) compared to the placebo arm (59%). Since stage of disease (limited vs. extensive) was a randomization balancing factor, this reviewer examined the descriptive stratified Kaplan-Meier analysis provided by the sponsor. Kaplan-Meier survival plots were comparable in the epoetin alfa and placebo groups through Months 17 to 18 after study start. As for the overall ITT population, the variability after study completion along with the small number of subjects in the two extent of disease subgroups does not permit any conclusive statement to be made.

Chemotherapy Received: The sponsor's claim that exposure to chemotherapy was similar between the placebo and epoetin alfa treatment groups is based on descriptive analyses comprising the calculated frequency distribution of total chemotherapy cycles received, and dosing summary descriptive statistics by individual cycle (Cycles 1 through 12) for cisplatin and etoposide.
Reviewer's Comment: This reviewer confirmed the descriptive analyses.

White Blood Count: The sponsor's proposed labeling claim is as follows:

Reviewer's Comment: This statement is based on a descriptive analysis of change from baseline by study week for Weeks 1 through 34. This analysis was purely descriptive. Summary statistics (i.e., individual sample size for Week, mean, standard deviation, median, and range) were presented by study week for the placebo and epoetin alfa treatment groups separately. This reviewer confirmed this descriptive analysis.

Hemoglobin: Subjects in the placebo group experienced mean reductions in Hgb (from a mean value of 13.0 g/dL) of between –1.4 to –3.3 g/dL from Week 2 to Week 22.

During this period, mean values for placebo subjects averaged between 9.9 and 11.6 g/dL. By comparison, epoetin alfa subjects generally maintained their Hgb at or near baseline levels. Mean weekly Hgb for epoetin alfa patients ranged from 11.3 to 12.7 g/dL during the first 22 weeks, and mean changes were ≤ 1.1 g/dL. At the time of median exposure to study drug (94 days; 13 weeks), the mean change in baseline in Hgb was –2.9 g/dL for the placebo group and –0.2 g/dL for the epoetin alfa group. Sponsor's Table 18 presents mean Hgb summary statistics for both end of cycle 3 and end of study.

Sponsor's Table 18. Mean Hgb at End of Cycle 3 and End of Study (ITT)

	Placebo (N=115)			Epoetin Alfa (N=109)		
	Mean (SD)	Median	Range	Mean (SD)	Median	Range
Baseline	13.0 (1.50)	13.0	9.1 - 17.2	12.8 (1.53)	13.0	8.7 – 16.6
End of Cycle 3	10.6 (1.45)	10.5	6.4 - 14.2	12.5 (2.25)	12.6	6.2 – 17.1
End of Study	10.3 (1.61)	10.0	6.2 - 14.2	12.2 (2.26)	12.2	6.2 – 16.9

Reviewer's Comment: This reviewer examined the change in Hgb and the % change from Baseline to the end of Cycle 3. Descriptive findings are presented in the following Reviewer's Tables 1 and 2.

Reviewer's Table 1. Change in Hgb from Baseline to End of Cycle 3

Placebo (N=115)			Epoetin Alfa (N=109)		
Mean (SD)	Median	Range	Mean (SD)	Median	Range
-2.4 (1.87)	-2.4	-7.4 – 2.9	-0.2 (2.37)	0.0	-6.2 – 5.7

Reviewer's Table 2. % Change in Hgb from Baseline to End of Cycle 3

Placebo (N=115)			Epoetin Alfa (N=109)		
Mean (SD)	Median	Range	Mean (SD)	Median	Range
-17.4 (13.47)	-18.9	-51.2 – 25.7	-1.1 (18.9)	0.0	-42.2 – 51.8

This descriptive display indicates an improved profile for epoetin alfa patients for the first 3 chemotherapy cycles.

The sponsor provided the requested treatment X baseline hemoglobin (Hgb) interaction analysis for the survival endpoint. This was a stratified Cox's PH model including treatment, baseline Hgb (centered at 10.5g/DL), and the interaction term. Treatment effect was evaluated at a baseline Hgb of 10.5 g/dL. Under this model, the size of the treatment effect was dependent on baseline Hgb. When baseline Hgb was 10.5 g/dL, the

relative risk for 12-month mortality was estimated to be 1.306 (p = 0.0918, with epoetin alfa subjects at higher risk. The interaction between baseline Hgb and treatment was not significant (p = 0.9856), though the relative risk of the interaction term, 0.838, implied an upward trend of the relative risk between treatment groups among those subjects with higher baseline Hgb levels.

Transfusions: Across all chemotherapy cycles, fewer subjects in the epoetin alfa group required a RBC transfusion (26/109 or 24%) compared to the placebo group (42/115, 37%). The proportions transfused through Cycle 3 were comparable (around 18% each).

***Reviewer's Comment*:** Beginning with Cycle 4, dropouts in each treatment arm had increased substantially (46/115 or 40% on placebo and 44/109 or 40% on epoetin alfa). Excluding Cycle 1 and examining only Cycles 2 and 3 showed that twice as many placebo subjects were transfused during Cycles 2 and 3, 21 subjects on placebo and 11 patients on epoetin alfa.

Study #INT-76/EPO-INT-76/EPO-CA-489: This study, entitled *"A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Impact of Maintaining Hemoglobin Using Eprex (Epoetin Alfa; RWJJPRI-22512) in Metastatic Breast Carcinoma Subjects Receiving Chemotherapy,"* was included in this submission as it was a large recent trial utilizing a similar product, Eprex.

Summary of Study #INT-76/EPO-INT-76: This was a Phase 3, double-blind, randomized, placebo-controlled, multi-center trial to evaluate the impact of maintaining Hgb between 12 and g/dL using epoetin alfa in subjects with metastatic breast cancer who were receiving first-line chemotherapy (various regimens). Subjects were randomly assigned to receive either 40,000 IU epoetin alfa or placebo in a 1:1 ratio. Randomization was stratified by metastatic disease category (bone metastasis only vs. other measurable metastatic lesions vs. other non-measurable metastatic lesions) to ensure balance. However, for all statistical analyses, stratification was bone only versus other metastatic lesions. Study drug was administered once per week by s.c. injection to maintain Hgb in the range of 12 to 14 g/dL for 12 months. Subjects could have a RBC transfusion if clinically necessary during the study. After subjects had been on the study for 12 months, they completed the double-blind phase of the study and had the option of receiving 40,000 IU epoetin alfa once a week to maintain Hgb in the range of 12 to 14 g/dL in an open-label extension. An independent Data Monitoring Committee (IDMC) was established under Amendment 3 to review safety data. On April 42, 20002, the IDMC recommended that study medication be discontinued for all subjects. The IDMC recommendation was based on an excess mortality rate among subjects assigned to the epoetin alfa treatment group. At the time of the IDMC review, 179 deaths had been reported in the double-blind phase, specifically 101 in the epoetin alfa group; 78 in the placebo group. The IDMC further recommended that all subjects, including those who withdrew from the study, continue to have study evaluations performed. The sponsor notified investigators and health authorities on April 29, 2002 that study medication was to be discontinued for all subjects. Investigators were instructed to continue to perform

all study procedures described for the double-blind phase, with the exception of study drug administration. Subjects continued in the double-blind phase for its full 12-month duration.

Design/Methodology: This study was initiated on June 23, 2000 and completed on July 5, 2002. The study objective was to evaluate the impact on survival and QOL of maintaining Hgb in the range of 12 to 14 g/dL using epoetin alfa or placebo in subjects starting first-line chemotherapy (various regimens) for metastatic breast cancer. A total of 939 subjects were enrolled form 139 sites in 20 countries in Europe, Canada, South Africa, and Australia. Subjects who met the entry criteria were randomized and study drug was administered when Hgb was $\leq$ 13 g/dL. Hgb concentrations and reticulocyte counts were monitored weekly for the first 4 weeks to determine either when study drug administration was to begin or whether a dose adjustment was necessary. After the first 4 weeks of study drug administration, Hgb concentrations and reticulocyte counts were monitored every 3 to 4 weeks for the remainder of the double-blind treatment phase. The maximum dose of epoetin alfa was not to exceed 60,000 IU once a week.

Efficacy endpoints: The primary endpoint was survival during the first 12 months of treatment. Secondary endpoints included hematologic effects, tumor response rates, time to disease progression (TTP), RBC transfusions, and QOL.

Sample Size: The planned enrollment was 870 subjects (435/treatment group). A total of 939 subjects (470 on placebo and 469 on epoetin alfa) were enrolled and analyzed in the ITT (all randomized) population. The sample size was based on the assumption of 70% survival in the placebo group and 80% in the epoetin alfa group at the end of the 12-month double-blind treatment phase. This assumption took into account that 25% of the study population comprised subjects who had bone only metastases. The primary statistical objective was to detect a minimum absolute 10% improvement (i.e., 80% survival). A 100% follow-up was anticipated with respect to 12-month survival status. Based on these assumptions and a 2-sided significance level of 0.05, a planned total of 870 subjects (435/arm) yields power greater than 90% for testing the null hypothesis of an equal 12-month survival rate between the two treatment arms (using continuity-corrected Chi-square test). The modified safety population comprised all of those randomized subjects who received at least one dose of study drug.

Efficacy Endpoints: The **primary efficacy endpoint** for the double-blind phase of the study was the **12-month survival rate**, defined as the proportion of subjects surviving at 12 months after randomization. **Secondary efficacy endpoints** were change in Hgb concentration from baseline to individual study end, Hgb concentration over time, proportion of subjects receiving RBC transfusions from baseline to study end, standardized cumulative RBC units transfused from baseline to study end, optimal tumor response to first-line chemotherapy, tumor response at end of first-line chemotherapy, tumor response at end of study, time to disease progression (TTP), and QOL measured by the Functional Assessment in Cancer Therapy-Anemia (FACT-An) and Cancer Linear Analogue Scale (CLAS) questionnaires.

Statistical Methods: Analysis of the primary efficacy endpoint was performed for the ITT and efficacy populations. Kaplan-Meier estimates were presented by treatment group and the estimated hazard ratio, with its 95% CI, were presented. Treatment comparisons were via the stratified (by metastatic disease category) logrank test. Two

exploratory analyses were performed using stratified Cox PH regression models. The first model included treatment and prognostic factors thought likely to demonstrate significant heterogeneity in subject survival. The second Cox model included all of the factors from the first model plus all 2-way interactions. Survival results and subgroup analyses were also summarized for subjects who died within 4 months of randomization. Hgb concentrations over time were analyzed longitudinally using linear mixed effects models and treatment comparisons were made with respect to the rate of change in Hgb concentration over time. Treatment comparison of the mean change in Hgb from baseline to the last on-study value was via an ANOVA model that included terms for treatment and metastatic disease category. In addition, the proportion of Hgb levels maintained between 12 and 14 g/dL was analyzed via a logistic regression model for correlated variables. Hgb levels over time were summarized as a function of baseline anemia status and 12-month survival status, and the change from baseline to last value was summarized by baseline anemia status. Proportion receiving RBC transfusions was analyzed via a logistic regression model including metastatic disease status and treatment group as explanatory variables; the estimated odds ratio and it associated 95% CI were presented. Standardized (in 4-week intervals) cumulative RBC units transfused from randomization to study completion/withdrawal were analyzed via a Poisson regression model with over-dispersion parameter. Treatment differences in optimal tumor response rates to first-line chemotherapy and tumor response rates at double-blind phase end were analyzed via a stratified Cochran-Mantel-Haenszel test for ordinal responses. In addition, a proportional odds model for ordinal data was used to model optimal tumor response data. K-M estimates for TTP were presented by treatment group using the stratified logrank test; the estimated hazard ratio and its associated 95% CI were estimated using a stratified Cox PH model. An exploratory analysis of disease-free survival (DFS) was carried out using a similar approach. QOL data were analyzed using longitudinal methods. A mixed effects growth curve model analysis was used to estimate the area under the QOL curve (AUC_{QOL}) from randomization to Month 12. Sensitivity analyses were carried out based on different assumptions concerning missing data. The association between change in Hgb concentration and QOL was examined via correlation techniques, which also controlled for multiple comparisons.

Sponsor's Efficacy Results for Study #INT-76/EPO-INT-76: Kaplan-Meier (K-M) probability estimates of the 12-month survival rate for the ITT population were lower in the epoetin alfa group (70%) compared to the placebo group (76%), and this treatment group difference was statistically significant ($p = 0.0117$; relative risk = 1.359). The primary cause of death in both treatment groups was disease progression, accounting for 88% of all deaths within 12 months of randomization. After analyses adjusting for a large number of prognostic factors (i.e., 26), the epoetin alfa group still had a significantly inferior survival ($p=0.0182$). In subgroup analyses, no single factor was identified as capable of accounting for this treatment group difference in the 12-month survival rate.

K-M survival estimates indicated that the treatment difference was already evident at Month 4, and, at later time points, the survival curves for the two treatment groups were parallel. Of 57 subjects who died within the first 4 months, 16 were in the placebo group and 41 were in the epoetin alfa group. The sponsor states that among subjects who died

within 4 months of randomization, those assigned to the epoetin alfa group tended to be older and sicker at study entry than those assigned to the placebo group. This was reflected in greater visceral involvement at study entry, a higher percentage of subjects who were anemia at baseline (Hgb less than or equal to 10.5 g/dL), and fewer subjects whose tumors were estrogen receptor positive in the early death epoetin alfa group compared to the placebo group. In the first 4 months after randomization, the incidence of fatal thrombotic/vascular events was higher in the epoetin alfa group (5 of 469 or 1%) than in the placebo group (1 of 470 or 0%). While a subgroup analysis of deaths within 4 months after randomization showed a significant difference between treatment groups for a number of demographic and prognostic factors, none of these factors was able to account for most of the observed treatment group difference in 4-month mortality rate.

Secondary Efficacy Endpoints: Although most deaths within 12 months after randomization were due to disease progression, the difference in 12-months survival rate was not related to difference in disease progression between treatment and placebo group. K-M estimates of time to disease progression (TTP) and disease-free survival (DFS) for the ITT population did not differ between the two treatment groups ($p = 0.7059$ and $p = 0.9843$, respectively). The optimal tumor response rate to first-line chemotherapy was similar in the two treatment groups (215/470 (45.7%) vs. 209/469 (44.6%), $p = 0.9303$). Results of the proportional odds model further confirmed that the optimal tumor response profile was comparable for the two groups after controlling for the other main effects (odds ratio of 0.995; $p = 0.9676$, ITT population). Tumor response at the end of first-line chemotherapy and tumor response at the end of study for the ITT group were also similar in both treatment arms.

The sponsor states that the lower 12-month survival rate in the epoetin alfa group was not the result of excessively elevated Hgb levels. Mean Hgb levels were unchanged at the end of the double-blind phase relative to baseline in the epoetin alfa group (mean change of 0.1 g/dL; a mean reduction of 0.5 g/dL was seen in the placebo group (treatment comparison, $p= 0.0001$, ITT). Hgb levels in the epoetin alfa group were better maintained in the range of 12 to 14 g/dL compared to the placebo group, with 59% of all on-study Hgb measurements within target range in the epoetin alfa group compared to 45% in the placebo group ($p < 0.0001$ for ITT). Overall, subjects who died within 12 months after randomization tended to have lower Hgb levels throughout the study and this was true in both treatment groups. There was a trend toward a statistically significant decrease in the proportion of subjects transfused in the epoetin alfa group compared to placebo (10% vs. 14%, respectively; $p = 0.0595$, ITT). No treatment difference was seen, however, in the mean cumulative number of RBC units transfused for the overall ITT population or the subset of subjects who were transfused. No significant difference between treatment groups was found for health-related QOL measures as reflected in the FACT-An or CLAS questionnaires.

Safety Findings: Overall, treatment with epoetin alfa did not result in AE's that were unexpected for this population of subjects with metastatic cancer undergoing first-line chemotherapy. The incidence of treatment-emergent AE's was similar between the placebo (91%) and epoetin alfa (94%) groups. The incidence of treatment-emergent SAE's was 42% in the epoetin alfa group and 34% in the placebo group. Most SAE's were reported with an incidence rate of 1% or less for both treatment groups. The majority of the treatment-emergent AE's and SAE's were judged by the investigator to be

not related or of doubtful relationship to study drug therapy. The incidence of discontinuations due to AE's was similar between the placebo (5%) and epoetin alfa (4%) groups. Many of the AE's leading to discontinuation were disease related. The overall incidence of treatment-emergent thrombotic/vascular events was similar between the two treatment groups (14% in placebo vs. 16% in epoetin alfa). The incidence of SAE's involving platelet, bleeding, and clotting disorders was higher in the epoetin alfa group (5%) than in the placebo group (3%), as well as the incidence of SAE's involving vascular (extracardiac) disorders (epoetin alfa: 3%; placebo: 1%). The incidence of drug-related serious thrombotic/vascular events was higher in the epoetin alfa group (2%) than in the placebo group (1%). There were no apparent differences between the two treatment groups in mean values over the course of the study for laboratory parameters or vital sign measurements.

Reviewer's Comment: This reviewer confirmed all of the sponsor's major efficacy findings for the Eprex study.

OVERALL SUMMARY AND CONCLUSIONS:

This reviewer's analyses of the major efficacy endpoints for the pivotal study, #N93-004, and the Eprex Study, #INT-76/EPO-CA-489, based on the electronic databases provided, confirm the sponsor's reported statistical findings.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103234s5033

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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

Memorandum

Memo Date: May 14, 2004

From: Monica Hughes, CDER/OND/ODE VI/DRMP, HFM-588

To: sBLA 103234/5033 file
Amgen Incorporated
Epoetin alfa

Subject: Review of Amgen Incorporated Request for Categorical Exclusion under 21 CFR Part 25.31(c)

I have reviewed the October 16, 2002, submission to the Amgen Incorporated BLA supplement, STN 103234/5033 that contains a request for categorical exclusion. Erythropoietin is a glycoprotein that stimulates red blood cell production. Epoetin alfa, a 165 amino acid glycoprotein manufactured by recombinant DNA technology, has the same biological effects as endogenous erythropoietin. Epoetin alfa 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.

Epoetin alfa 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. The product, Epoetin alfa, is available in either single-dose preservative-free vials, or multi-dose preserved vials. Both are composed entirely of naturally occurring amino acids and is thus expected to react *in vivo* and in the environment as a naturally occurring protein. There are no extraordinary circumstances that would significantly affect the environment. Therefore, I find that the request for categorical exclusion from an environmental assessment is justified under 21CFR Part 25.31(c).

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103234/5033

MAR 0 4 2004

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

Dear Mr. Hunt:

This letter is in regard to the supplement to your biologics license application for Epoetin alfa to update the safety data in the package insert, and to include statements regarding the stimulatory effects of Epoetin alfa on solid tumor growth submitted under section 351 of the Public Health Service Act. Reference is also made to your December 9, 2003 resubmission, received on December 11, 2003, containing revised labeling that you submitted in response to our August 15, 2003 complete response letter. We consider this a complete, class 1 response to our action letter.

We have completed the review of your supplement, including all amendments received through January 23, 2004. Our review finds that the information and data submitted are inadequate for final approval action at this time based on the deficiencies outlined below.

1. Your proposed labeling is not acceptable. Revisions are required in the following sections of the package insert: Indications and Usage, Clinical Experience, Warnings, Precautions, Adverse Reactions, Overdosage and Dosage and Administration. Please revise the labeling as indicated in the enclosed draft package insert that was previously sent to you by facsimile on February 23, 2004.

2. Several issues pertinent to clarifying the safety and effectiveness of Epoetin alfa require additional information that may be obtained from postmarketing studies. We request that you propose studies to address the following issues:

   a. the impact of Epoetin alfa on response rates and time to progression, obtained in randomized, controlled studies conducted in patients with a single tumor type receiving a uniform anti-cancer treatment regimen.

   b. the impact of Epoetin alfa on vascular events (e.g., thromboembolic, myocardial infarction, stroke), obtained in randomized, controlled studies conducted in patients with a single tumor type receiving a uniform anti-cancer treatment regimen.

c. the impact of Epoetin alfa on survival, obtained in randomized, controlled studies conducted in patients with a single tumor type receiving a uniform anti-cancer treatment regimen.

Please describe your plans to address the above issues in sufficient detail to permit our evaluation of the adequacy of the proposals. We request that your response include:

- A detailed protocol or, at a minimum, a detailed outline describing all design features of the study including sample size and justification, eligibility criteria with rationale, dosing regimens and duration, clinical assessments to be performed and their timing, and endpoints to be analyzed.

- Proposed schedule for conducting the study, including all major milestones for the study, e.g. submission of finalized protocol to the FDA, initiation of an animal study, completion of patient accrual, completion of the study, and submission of the final study report, SAS datasets and applicable revised labeling to the FDA.

Please be advised that submission of complete protocols for review and comment should be made to your IND and may be cross-referenced in your response to this letter.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cder/biologics/default.htm. Until further notice, however, all correspondence should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

If you have any questions, please contact the Regulatory Project Manager, Michael Harlow at (301) 827-5101.

Sincerely,

Patricia Keegan

Patricia Keegan, M.D.
Director
Division of Therapeutic Biological Oncology Products
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: Package Insert