FDA COMPLETE RESPONSE AND SAFETY LABELING CHANGE ORDER: JULY 30, 2008

Aranesp®
(darbepoetin alfa)
For Injection

WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR and THROMBOEMBOLIC EVENTS, and INCREASED RISK OF TUMOR PROGRESSION OR RECURRENCE

Renal failure: **Patients experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemoglobin levels (13.5 vs. 11.3 g/dL; 14 vs. 10 g/dL) in two clinical studies. Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL.**

Cancer:

- **ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers (see WARNINGS: Table 1).**
- **To decrease these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusion.**
- **Use ESAs only for treatment of anemia due to concomitant myelosuppressive chemotherapy.**
- **ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure. ~~When the anticipated outcome of myelosuppressive chemotherapy is cure, ESAs are only indicated for treatment of anemia when red blood cell transfusion is not a treatment option.~~**
- **Discontinue following the completion of a chemotherapy course.**

(See WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events, WARNINGS: Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence, INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION.)

DESCRIPTION

Aranesp® is an erythropoiesis stimulating protein, closely related to erythropoietin, that is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Aranesp® is a 165-amino acid protein that differs from recombinant human erythropoietin in containing 5 N-linked oligosaccharide chains, whereas recombinant human erythropoietin contains 3 chains.[1] The two additional N-glycosylation sites result from amino acid substitutions in the erythropoietin peptide backbone. The additional carbohydrate chains increase the approximate molecular weight of the glycoprotein from 30,000 to 37,000 daltons. Aranesp® is formulated as a sterile, colorless, preservative-free protein solution for intravenous or subcutaneous administration.

Single-dose vials are available containing 25, 40, 60, 100, 150, 200, 300, or 500 mcg of Aranesp®.

Single-dose prefilled syringes and prefilled SureClick™ autoinjectors are available containing 25, 40, 60, 100, 150, 200, 300, or 500 mcg of Aranesp®. Each prefilled syringe is equipped with a needle guard that covers the needle during disposal.

Single-dose vials, prefilled syringes and autoinjectors are available in two formulations that contain excipients as follows:

Polysorbate solution Each 1 mL contains 0.05 mg polysorbate 80, and is formulated at pH 6.2 ± 0.2 with 2.12 mg sodium phosphate monobasic monohydrate, 0.66 mg sodium phosphate dibasic anhydrous, and 8.18 mg sodium chloride in Water for Injection, USP (to 1 mL).

Albumin solution Each 1 mL contains 2.5 mg albumin (human), and is formulated at pH 6.0 ± 0.3 with 2.23 mg sodium phosphate monobasic monohydrate, 0.53 mg sodium phosphate dibasic anhydrous, and 8.18 mg sodium chloride in Water for Injection, USP (to 1 mL).

CLINICAL PHARMACOLOGY

Mechanism of Action

Aranesp® stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. A primary growth factor for erythroid development, erythropoietin is produced in the kidney and released into the bloodstream in response to hypoxia. In responding to hypoxia, erythropoietin interacts with progenitor stem cells to increase red blood cell (RBC) production. Production of endogenous erythropoietin is impaired in patients with chronic renal failure (CRF), and erythropoietin deficiency is the primary cause of their anemia. Increased hemoglobin levels are not generally observed until 2 to 6 weeks after initiating treatment with Aranesp® (see **DOSAGE AND ADMINISTRATION**). In patients with cancer receiving concomitant chemotherapy, the etiology of anemia is multifactorial.

Pharmacokinetics

Adult Patients

The pharmacokinetics of Aranesp® were studied in patients with CRF receiving or not receiving dialysis and cancer patients receiving chemotherapy.

Following intravenous administration in CRF patients receiving dialysis, Aranesp® serum concentration-time profiles were biphasic, with a distribution half-life of approximately 1.4 hours and a mean terminal half-life of 21 hours. The terminal half-life of Aranesp® was approximately 3-fold longer than that of Epoetin alfa when administered intravenously.

Following subcutaneous administration of Aranesp® to CRF patients (receiving or not receiving dialysis), absorption was slow and peak concentrations occurred at 48 hours (range: 12 to 72 hours). In CRF patients receiving dialysis, the average half-life was 46 hours (range: 12 to 89 hours), and in CRF patients not receiving dialysis, the average half-life was 70 hours (range: 35 to 139 hours). Aranesp® apparent clearance was approximately 1.4 times faster on average in patients receiving dialysis compared to patients not receiving dialysis. The bioavailability of Aranesp® in CRF patients receiving dialysis after subcutaneous administration was 37% (range: 30% to 50%).

Following the first subcutaneous dose of 6.75 mcg/kg (equivalent to 500 mcg for a 74-kg patient) in patients with cancer, the mean terminal half-life was 74 hours (range: 24 to 144 hours). Peak concentrations were observed at 90 hours (range: 71 to 123 hours) after a dose of 2.25 mcg/kg, and 71 hours (range: 28 to 120 hours) after a dose of 6.75 mcg/kg. When administered on a once every 3 week schedule, 48-hour post-dose Aranesp® levels after the fourth dose were similar to those after the first dose.

Over the dose range of 0.45 to 4.5 mcg/kg Aranesp® administered intravenously or subcutaneously on a once weekly schedule and 4.5 to 15 mcg/kg administered subcutaneously on a once every 3 week schedule, systemic exposure was approximately proportional to dose. No evidence of accumulation was observed beyond an expected < 2-fold increase in blood levels when compared to the initial dose.

Pediatric Patients

Aranesp® pharmacokinetics were studied in 12 pediatric CRF patients (age 3-16 years) receiving or not receiving dialysis. Following a single intravenous or subcutaneous Aranesp® dose, Cmax and half-life were similar to those obtained in adult CRF patients on dialysis. Following a single subcutaneous dose, the average bioavailability was 54% (range: 32% to 70%), which was higher than that obtained in adult CRF patients on dialysis.

CLINICAL STUDIES

Throughout this section of the package insert, the Aranesp® study numbers associated with the nephrology and cancer clinical programs are designated with the letters "N" and "C", respectively.

Chronic Renal Failure Patients

The safety and effectiveness of Aranesp® have been assessed in a number of multicenter studies. Two studies evaluated the safety and efficacy of Aranesp® for the correction of anemia in adult patients with CRF, and three studies (2 in adults and 1 in pediatric patients) assessed the ability of Aranesp® to maintain hemoglobin concentrations in patients with CRF who had been receiving other recombinant erythropoietins.

De Novo Use of Aranesp®

Once Weekly Aranesp® Starting Dose

In two open-label studies, Aranesp® or Epoetin alfa was administered for the correction of anemia in CRF patients who had not been receiving prior treatment with exogenous erythropoietin. Study N1 evaluated CRF patients receiving dialysis; Study N2 evaluated patients not requiring dialysis. In both studies, the starting dose of Aranesp® was 0.45 mcg/kg administered once weekly. The starting dose of Epoetin alfa was 50 Units/kg 3 times weekly in Study N1 and 50 Units/kg twice weekly in Study N2. When necessary, dosage adjustments were instituted to maintain hemoglobin in the study target range of 11 to 13 g/dL. (Note: The recommended hemoglobin target is lower than the target range of these studies. See **DOSAGE AND ADMINISTRATION** for recommended clinical hemoglobin target.) The primary efficacy endpoint was the proportion of patients who experienced at least a 1 g/dL increase in hemoglobin concentration to a level of at least 11 g/dL by 20 weeks (Study N1) or 24 weeks (Study N2). The studies were designed to assess the safety and effectiveness of Aranesp® but not to support conclusions regarding comparisons between the two products.

In Study N1, the hemoglobin target was achieved by 72% (95% CI: 62%, 81%) of the 90 patients treated with Aranesp® and 84% (95% CI: 66%, 95%) of the 31 patients treated with Epoetin alfa. The mean increase in hemoglobin over the initial 4 weeks of Aranesp® treatment was 1.1 g/dL (95% CI: 0.82 g/dL, 1.37 g/dL).

In Study N2, the primary efficacy endpoint was achieved by 93% (95% CI: 87%, 97%) of the 129 patients treated with Aranesp® and 92% (95% CI: 78%, 98%) of the 37 patients treated with Epoetin alfa. The mean increase in hemoglobin from baseline through the initial 4 weeks of Aranesp® treatment was 1.38 g/dL (95% CI: 1.21 g/dL, 1.55 g/dL).

Once Every 2 Week Aranesp® Starting Dose

In two single arm studies (N3 and N4), Aranesp® was administered for the correction of anemia in CRF patients not receiving dialysis. In both studies, the starting dose of Aranesp® was 0.75 mcg/kg administered once every 2 weeks.

In Study N3 (study duration of 18 weeks), the hemoglobin goal (hemoglobin concentration $\geq$ 11 g/dL) was achieved by 92% (95% CI: 86%, 96%) of the 128 patients treated with Aranesp®.

In Study N4 (study duration of 24 weeks), the hemoglobin goal (hemoglobin concentration of 11-13 g/dL) was achieved by 85% (95% CI: 77%, 93%) of the 75 patients treated with Aranesp®.

Conversion From Other Recombinant Erythropoietins

Two adult studies (N5 and N6) and one pediatric study (N7) were conducted in patients with CRF who had been receiving other recombinant erythropoietins. The studies compared the abilities of Aranesp® and other erythropoietins to maintain hemoglobin concentrations within a study target range of 9 to 13 g/dL in adults and 10 to 12.5 g/dL in pediatric patients. (Note: The recommended hemoglobin target is lower than the target range of these studies. See **DOSAGE AND ADMINISTRATION** for recommended clinical hemoglobin target.) CRF patients who had been receiving stable doses of other recombinant erythropoietins were randomized to Aranesp®, or to continue with their prior erythropoietin at the previous dose and schedule. For patients randomized to Aranesp®, the initial weekly dose was determined on the basis of the previous total weekly dose of recombinant erythropoietin.

Adult Patients

Study N5 was a double-blind study conducted in North America, in which 169 hemodialysis patients were randomized to treatment with Aranesp® and 338 patients continued on Epoetin alfa. Study N6 was an open-label study conducted in Europe and Australia in which 347 patients were randomized to treatment with Aranesp® and 175 patients were randomized to continue on Epoetin alfa or Epoetin beta. Of the 347 patients randomized to Aranesp®, 92% were receiving hemodialysis and 8% were receiving peritoneal dialysis.

In Study N5, a median weekly dose of 0.53 mcg/kg Aranesp® (25th, 75th percentiles: 0.30, 0.93 mcg/kg) was required to maintain hemoglobin in the study target range. In Study N6, a median weekly dose of 0.41 mcg/kg Aranesp® (25th, 75th percentiles: 0.26, 0.65 mcg/kg) was required to maintain hemoglobin in the study target range.

Pediatric Patients

Study N7 was an open-label, randomized study, conducted in the United States in pediatric patients from 1 to 18 years of age with CRF receiving or not receiving dialysis. Patients that were stable on Epoetin alfa were randomized to receive either darbepoetin alfa (n = 82) administered once weekly (subcutaneously or intravenously) or to continue receiving Epoetin alfa (n = 42) at the current dose, schedule, and route of administration. A median weekly dose of 0.41 mcg/kg Aranesp® (25th, 75th percentiles: 0.25, 0.82 mcg/kg) was required to maintain hemoglobin in the study target range.

Cancer Patients Receiving Chemotherapy

Efficacy in patients with anemia due to concomitant chemotherapy was demonstrated based on reduction in the requirement for RBC transfusions.

Once Weekly Dosing

The safety and effectiveness of Aranesp® in reducing the requirement for RBC transfusions in patients undergoing chemotherapy was assessed in a randomized, placebo-controlled, double-blind, multinational study (C1). This study was conducted in anemic (Hgb ≤ 11 g/dL) patients with advanced, small cell or non-small cell lung cancer, who received a platinum-containing chemotherapy regimen. Patients were randomized to receive Aranesp® 2.25 mcg/kg (n = 156) or placebo (n = 158) administered as a single weekly SC injection for up to 12 weeks. The dose was escalated to 4.5 mcg/kg/week at week 6, in subjects with an inadequate response to treatment, defined as less than 1 g/dL hemoglobin increase. There were 67 patients in the Aranesp® arm who had their dose increased from 2.25 to 4.5 mcg/kg/week, at any time during the treatment period.

Efficacy was determined by a reduction in the proportion of patients who were transfused over the 12-week treatment period. A significantly lower proportion of patients in the Aranesp® arm, 26% (95% CI: 20%, 33%) required transfusion compared to 60% (95% CI: 52%, 68%) in the placebo arm (Kaplan-Meier estimate of proportion; $p < 0.001$ by Cochran–Mantel-Haenszel test). Of the 67 patients who received a dose increase, 28% had a 2 g/dL increase in hemoglobin over baseline, generally occurring between weeks 8 to 13. Of the 89 patients who did not receive a dose increase, 69% had a 2 g/dL increase in

hemoglobin over baseline, generally occurring between weeks 6 to 13. On-study deaths occurred in 14% (22/156) of patients treated with Aranesp® and 12% (19/158) of the placebo-treated patients.

Once Every 3 Week Dosing

The safety and effectiveness of once every 3 week Aranesp® therapy in reducing the requirement for red blood cell (RBC) transfusions in patients undergoing chemotherapy was assessed in a randomized, double-blind, multinational study (C2). This study was conducted in anemic (Hgb < 11 g/dL) patients with non-myeloid malignancies receiving multicycle chemotherapy. Patients were randomized to receive Aranesp® at 500 mcg once every 3 weeks (n = 353) or 2.25 mcg/kg (n = 352) administered weekly as a subcutaneous injection for up to 15 weeks. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 mcg in the once every 3 week group and 1.35 mcg/kg in the once weekly group) if hemoglobin increased by more than 1 g/dL in a 14-day period. Study drug was withheld if hemoglobin exceeded 13 g/dL. In the once every 3 week group, 254 patients (72%) required dose reductions (median time to first reduction at 6 weeks). In the once weekly group, 263 patients (75%) required dose reductions (median time to first reduction at 5 weeks).

Efficacy was determined by a comparison of the Kaplan-Meier estimates of the proportion of patients who received at least one RBC transfusion between day 29 and the end of treatment. Three hundred thirty-five patients in the once every 3 week group and 337 patients in the once weekly group remained on study through or beyond day 29 and were evaluated for efficacy. Twenty-seven percent (95% CI: 22%, 32%) of patients in the once every 3 week group and 34% (95% CI: 29%, 39%) in the weekly group required a RBC transfusion. The observed difference in the transfusion rates (once every 3 week-once weekly) was -6.7% (95% CI: -13.8%, 0.4%).

INDICATIONS AND USAGE

Anemia With Chronic Renal Failure

Aranesp® is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis.

Anemia With Non-Myeloid Malignancies Due to Chemotherapy

Aranesp® is indicated for the treatment of anemia due to the effect of concomitantly administered chemotherapy based on studies that have shown a reduction in the need for RBC transfusions in patients with metastatic, non-myeloid malignancies. Studies to determine whether Aranesp® increases mortality or decreases progression-free/recurrence-free survival are ongoing.

- Aranesp® is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy.
- Aranesp® is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure. ~~When the anticipated outcome of myelosuppressive chemotherapy is cure (e.g., receiving neo-adjuvant or adjuvant chemotherapy), Aranesp® is only indicated for treatment of anemia when red blood cell transfusion is not a treatment option~~ due to the absence of studies that adequately characterize the impact of Aranesp® on progression-free and overall survival (see **WARNINGS: Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence**).
- Aranesp® use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.

CONTRAINDICATIONS

Aranesp® is contraindicated in patients with:

- uncontrolled hypertension
- known hypersensitivity to the active substance or any of the excipients

WARNINGS

Increased Mortality, Serious Cardiovascular and Thromboembolic Events

Patients with chronic renal failure experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemoglobin levels (13.5 vs. 11.3 g/dL; 14 vs. 10 g/dL) in two clinical studies. Patients with chronic renal failure and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular events and mortality than other patients. Aranesp® and other ESAs increased the risks for death and serious cardiovascular events in controlled clinical trials of patients with cancer. These events included myocardial infarction, stroke, congestive heart failure, and hemodialysis vascular access thrombosis. A rate of hemoglobin rise of > 1 g/dL over 2 weeks may contribute to these risks.

In a randomized prospective trial, 1432 anemic chronic renal failure patients who were not undergoing dialysis were assigned to Epoetin alfa (rHuEPO) treatment targeting a maintenance hemoglobin concentration of 13.5 g/dL or 11.3 g/dL. A major cardiovascular event (death, myocardial infarction, stroke, or hospitalization for congestive heart failure) occurred among 125 (18%) of the 715 patients in the higher hemoglobin group compared to 97 (14%) among the 717 patients in the lower hemoglobin group [Hazard Ratio (HR) 1.3, 95% CI: 1.0, 1.7, p = 0.03].[2]

Increased risk for serious cardiovascular events was also reported from a randomized, prospective trial of 1265 hemodialysis patients with clinically evident cardiac disease (ischemic heart disease or congestive heart failure). In this trial, patients were assigned to Epoetin alfa treatment targeted to a maintenance hemoglobin of either 14 ± 1 g/dL or 10 ± 1 g/dL.[3] Higher mortality (35% vs. 29%) was observed in the 634 patients randomized to a target hemoglobin of 14 g/dL than in the 631 patients assigned a target hemoglobin of 10 g/dL. The reason for the increased mortality observed in this study is unknown; however, the incidence of nonfatal myocardial infarction, vascular access thrombosis, and other thrombotic events was also higher in the group randomized to a target hemoglobin of 14 g/dL.

An increased incidence of thrombotic events has also been observed in patients with cancer treated with erythropoietic agents. In patients with cancer who received Aranesp®, pulmonary emboli, thrombophlebitis, and thrombosis occurred more frequently than in placebo controls (see **ADVERSE REACTIONS: *Cancer Patients Receiving Chemotherapy*, Table 5**).

In a randomized controlled study (referred to as Cancer Study 1 - the 'BEST' study) with another ESA in 939 women with metastatic breast cancer receiving chemotherapy, patients received either weekly Epoetin alfa or placebo for up to a year. This study was designed to show that survival was superior when an ESA was administered to prevent anemia (maintain hemoglobin levels between 12 and 14 g/dL or hematocrit between 36% and 42%). The study was terminated prematurely when interim results demonstrated that a higher mortality at 4 months (8.7% vs. 3.4%) and a higher rate of fatal thrombotic events (1.1% vs. 0.2%) in the first 4 months of the study were observed among patients treated with Epoetin alfa. Based on Kaplan-Meier estimates, at the time of study termination, the 12-month survival was lower in the Epoetin alfa group than in the placebo group (70% vs. 76%; HR 1.37, 95% CI: 1.07, 1.75, p = 0.012).[4]

A systematic review of 57 randomized controlled trials (including Cancer Studies 1 and 5 - the 'BEST' and 'ENHANCE' studies) evaluating 9353 patients with cancer compared ESAs plus RBC transfusion with RBC transfusion alone for prophylaxis or treatment of anemia in cancer patients with or without concurrent antineoplastic therapy. An increased relative risk (RR) of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06; 35 trials and 6769 patients) was observed in ESA-treated patients. An overall survival hazard ratio of 1.08 (95% CI: 0.99, 1.18; 42 trials and 8167 patients) was observed in ESA-treated patients.[5]

An increased incidence of deep vein thrombosis (DVT) in patients receiving Epoetin alfa undergoing surgical orthopedic procedures has been observed. In a randomized controlled study (referred to as the 'SPINE' study), 681 adult patients, not receiving prophylactic anticoagulation and undergoing spinal surgery, received Epoetin alfa and standard of care (SOC) treatment, or SOC treatment alone.

Preliminary analysis showed a higher incidence of DVT, determined by either Color Flow Duplex Imaging or by clinical symptoms, in the Epoetin alfa group [16 patients (4.7%)] compared to the SOC group [7 patients (2.1%)]. In addition, 12 patients in the Epoetin alfa group and 7 patients in the SOC group had other thrombotic vascular events.

Increased mortality was observed in a randomized placebo-controlled study of Epoetin alfa in adult patients who were undergoing coronary artery bypass surgery (7 deaths in 126 patients randomized to Epoetin alfa 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.

Aranesp® is not approved for reduction in allogeneic RBC transfusions in patients scheduled for surgical procedures.

Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence

Erythropoiesis-stimulating agents resulted in decreased locoregional control/progression-free survival and/or overall survival (see Table 1). These findings were observed in studies of patients with advanced head and neck cancer receiving radiation therapy (Cancer Studies 5 and 6), in patients receiving chemotherapy for metastatic breast cancer (Cancer Study 1) or lymphoid malignancy (Cancer Study 2), and in patients with non-small cell lung cancer or various malignancies who were not receiving chemotherapy or radiotherapy (Cancer Studies 7 and 8).

Table 1: Randomized, Controlled Trials with Decreased Survival and/or Decreased Locoregional Control

Study / Tumor / (n)	Hemoglobin Target	Achieved Hemoglobin (Median Q1,Q3)	Primary Endpoint	Adverse Outcome for ESA-containing Arm
Chemotherapy				
Cancer Study 1 Metastatic breast cancer (n=939)	12-14 g/dL	12.9 g/dL 12.2, 13.3 g/dL	12-month overall survival	Decreased 12-month survival
Cancer Study 2 Lymphoid malignancy (n=344)	13-15 g/dL (M) 13-14 g/dL (F)	11.0 g/dL 9.8, 12.1 g/dL	Proportion of patients achieving a hemoglobin response	Decreased overall survival
Cancer Study 3 Early breast cancer (n=733)	12.5-13 g/dL	13.1 g/dL 12.5, 13.7 g/dL	Relapse-free and overall survival	Decreased 3 yr. relapse-free and overall survival
Cancer Study 4 Cervical Cancer (n=114)	12-14 g/dL	12.7 g/dL 12.1, 13.3 g/dL	Progression-free and overall survival and locoregional control	Decreased 3 yr. progression-free and overall survival and locoregional control
Radiotherapy Alone				
Cancer Study 5 Head and neck cancer (n=351)	≥15 g/dL (M) ≥14 g/dL (F)	Not available	Locoregional progression-free survival	Decreased 5-year locoregional progression-free survival Decreased overall survival

Cancer Study 6 Head and neck cancer (n=522)	14-15.5 g/dL	Not available	Locoregional disease control	Decreased locoregional disease control
No Chemotherapy or Radiotherapy				
Cancer Study 7 Non-small cell lung cancer (n=70)	12-14 g/dL	Not available	Quality of life	Decreased overall survival
Cancer Study 8 Non-myeloid malignancy (n=989)	12-13 g/dL	10.6 g/dL 9.4, 11.8 g/dL	RBC transfusions	Decreased overall survival

Decreased overall survival:

Cancer Study 1 (the 'BEST' study) was previously described (see **WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events**). Mortality at 4 months (8.7% vs. 3.4%) was significantly higher in the Epoetin alfa arm. The most common investigator-attributed cause of death within the first 4 months was disease progression; 28 of 41 deaths in the Epoetin alfa arm and 13 of 16 deaths in the placebo arm were attributed to disease progression. Investigator assessed time to tumor progression was not different between the two groups. Survival at 12 months was significantly lower in the Epoetin alfa arm (70% vs. 76%, HR 1.37, 95% CI: 1.07, 1.75; p = 0.012).[4]

Cancer Study 2 was a Phase 3, double-blind, randomized (Aranesp® vs. placebo) study conducted in 344 anemic patients with lymphoid malignancy receiving chemotherapy. With a median follow-up of 29 months, overall mortality rates were significantly higher among patients randomized to Aranesp® as compared to placebo (HR 1.36, 95% CI: 1.02, 1.82).

Cancer Study 7 was a Phase 3, multicenter, randomized (Epoetin alfa vs. placebo), double-blind study, in which patients with advanced non-small cell lung cancer receiving only palliative radiotherapy or no active therapy were treated with Epoetin alfa to achieve and maintain hemoglobin levels between 12 and 14 g/dL. Following an interim analysis of 70 of 300 patients planned, a significant difference in survival in favor of the patients on the placebo arm of the trial was observed (median survival 63 vs. 129 days; HR 1.84; p = 0.04).

Cancer Study 8 was a Phase 3, double-blind, randomized (Aranesp® vs. placebo), 16-week study in 989 anemic patients with active malignant disease, neither receiving nor planning to receive chemotherapy or radiation therapy. There was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions. The median survival was shorter in the Aranesp® treatment group (8 months) compared with the placebo group (10.8 months); HR 1.30, 95% CI: 1.07, 1.57.

Decreased progression-free survival and overall survival:

Cancer Study 3 (the 'PREPARE' study) was a randomized controlled study in which Aranesp® was administered to prevent anemia conducted in 733 women receiving neo-adjuvant breast cancer treatment. After a median follow-up of approximately 3 years the survival rate (86% vs. 90%, HR 1.42, 95% CI: 0.93, 2.18) and relapse-free survival rate were lower (72% vs. 78%, HR 1.33, 95% CI: 0.99, 1.79) in the Aranesp®-treated arm compared to the control arm.

Cancer Study 4 (protocol GOG 191) was a randomized controlled study that enrolled 114 of a planned 460 cervical cancer patients receiving chemotherapy and radiotherapy. Patients were randomized to receive Epoetin alfa to maintain hemoglobin between 12 and 14 g/dL or to transfusion support as needed. The study was terminated prematurely due to an increase in thromboembolic events in Epoetin alfa-treated patients compared to control (19% vs. 9%). Both local recurrence (21% vs. 20%) and distant recurrence (12% vs. 7%) were more frequent in Epoetin alfa-treated patients compared to control. Progression-free survival at 3 years was lower in the Epoetin alfa-treated group compared to control (59% vs. 62%, HR 1.06, 95% CI: 0.58, 1.91). Overall survival at 3 years was lower in the Epoetin alfa-treated group compared to control (61% vs. 71%, HR 1.28, 95% CI: 0.68, 2.42).

Cancer Study 5 (the 'ENHANCE' study) was a randomized controlled study in 351 head and neck cancer patients where Epoetin beta or placebo was administered to achieve target hemoglobins of 14 and 15 g/dL for women and men, respectively. Locoregional progression-free survival was significantly shorter in patients receiving Epoetin beta (HR 1.62, 95% CI: 1.22, 2.14, p = 0.0008) with a median of 406 days Epoetin beta vs. 745 days placebo. Overall survival was significantly shorter in patients receiving Epoetin beta (HR 1.39, 95% CI: 1.05, 1.84; p = 0.02).

Decreased locoregional control:

Cancer Study 6 (DAHANCA 10) was conducted in 522 patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy randomized to Aranesp® with radiotherapy or radiotherapy alone. An interim analysis on 484 patients demonstrated that locoregional control at 5 years was significantly shorter in patients receiving Aranesp® (RR 1.44, 95% CI: 1.06, 1.96; p = 0.02). Overall survival was shorter in patients receiving Aranesp® (RR 1.28, 95% CI: 0.98, 1.68; p = 0.08).

Hypertension

Patients with uncontrolled hypertension should not be treated with Aranesp®; blood pressure should be controlled adequately before initiation of therapy. Blood pressure may rise during treatment of anemia with Aranesp® or Epoetin alfa. In Aranesp® clinical trials, approximately 40% of patients with CRF required initiation or intensification of antihypertensive therapy during the early phase of treatment when the hemoglobin was increasing. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with Aranesp® or Epoetin alfa.

Special care should be taken to closely monitor and control blood pressure in patients treated with Aranesp®. During Aranesp® therapy, patients should be advised of the importance of compliance with antihypertensive therapy and dietary restrictions. If blood pressure is difficult to control by pharmacologic or dietary measures, the dose of Aranesp® should be reduced or withheld (see **DOSAGE AND ADMINISTRATION**). A clinically significant decrease in hemoglobin may not be observed for several weeks.

Seizures

Seizures have occurred in patients with CRF participating in clinical trials of Aranesp® and Epoetin alfa. During the first several months of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely. While the relationship between seizures and the rate of rise of hemoglobin is uncertain, it is recommended that the dose of Aranesp® be decreased if the hemoglobin increase exceeds 1 g/dL in any 2-week period.

Pure Red Cell Aplasia

Cases of pure red cell aplasia (PRCA) and of severe anemia, with or without other cytopenias, associated with neutralizing antibodies to erythropoietin have been reported in patients treated with Aranesp®. This has been reported predominantly in patients with CRF receiving Aranesp® by subcutaneous administration. Any patient who develops a sudden loss of response to Aranesp®, accompanied by severe anemia and low reticulocyte count, should be evaluated for the etiology of loss of effect, including the presence of neutralizing antibodies to erythropoietin (see **PRECAUTIONS: Lack or Loss of Response to Aranesp®**). If anti-erythropoietin antibody-associated anemia is suspected, withhold Aranesp® and other erythropoietic proteins. Contact Amgen (1-800-77AMGEN) to perform assays for binding and neutralizing antibodies. Aranesp® should be permanently discontinued in patients with

antibody-mediated anemia. Patients should not be switched to other erythropoietic proteins as antibodies may cross-react (see **ADVERSE REACTIONS: Immunogenicity**).

Albumin (Human)

Aranesp® is supplied in two formulations with different excipients, one containing polysorbate 80 and another containing albumin (human), a derivative of human blood (see **DESCRIPTION**). Based on effective donor screening and product manufacturing processes, Aranesp® formulated with albumin 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.

PRECAUTIONS

General

The safety and efficacy of Aranesp® therapy have not been established in patients with underlying hematologic diseases (e.g., hemolytic anemia, sickle cell anemia, thalassemia, porphyria).

The needle cover of the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Lack or Loss of Response to Aranesp®

A lack of response or failure to maintain a hemoglobin response with Aranesp® doses within the recommended dosing range should prompt a search for causative factors. Deficiencies of folic acid, iron, or vitamin B_{12} should be excluded or corrected. Depending on the clinical setting, intercurrent infections, inflammatory or malignant processes, osteofibrosis cystica, occult blood loss, hemolysis, severe aluminum toxicity, and bone marrow fibrosis may compromise an erythropoietic response. In the absence of another etiology, the patient should be evaluated for evidence of PRCA and sera should be tested for the presence of antibodies to erythropoietin (see **WARNINGS: Pure Red Cell Aplasia**). See **DOSAGE AND ADMINISTRATION: *Chronic Renal Failure Patients*, Dose Adjustment** for management of patients with an insufficient hemoglobin response to Aranesp® therapy.

Hematology

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of Aranesp® before adjusting the dose. Because of the time required for erythropoiesis and the RBC half-life, an interval of 2 to 6 weeks may occur between the time of a dose adjustment (initiation, increase, decrease, or discontinuation) and a significant change in hemoglobin.

In order to prevent the hemoglobin from exceeding the recommended target range (10 to 12 g/dL) or rising too rapidly (greater than 1 g/dL in 2 weeks), the guidelines for dose and frequency of dose adjustments should be followed (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

Allergic Reactions

There have been rare reports of potentially serious allergic reactions, including skin rash and urticaria, associated with Aranesp®. Symptoms have recurred with rechallenge, suggesting a causal relationship exists in some instances. If a serious allergic or anaphylactic reaction occurs, Aranesp® should be immediately and permanently discontinued and appropriate therapy should be administered.

Patients with CRF Not Requiring Dialysis

Patients with CRF not yet requiring dialysis may require lower maintenance doses of Aranesp® than patients receiving dialysis. Though CRF patients not on dialysis generally receive less frequent monitoring of blood pressure and laboratory parameters than dialysis patients, CRF patients not on dialysis may be more responsive to the effects of Aranesp®, and require judicious monitoring of blood pressure and hemoglobin. Renal function and fluid and electrolyte balance should also be closely monitored.

Patients Transitioning to Dialysis

During the transition period onto dialysis, hemoglobin and blood pressure should be monitored carefully and patients may need to have their maintenance doses adjusted to maintain hemoglobin levels within the range of 10 to 12 g/dL (see **DOSAGE AND ADMINISTRATION: Maintenance Dose**).

Dialysis Management

Therapy with Aranesp® results in an increase in RBCs and a decrease in plasma volume, which could reduce dialysis efficiency; patients who are marginally dialyzed may require adjustments in their dialysis prescription.

Laboratory Tests

After initiation of Aranesp® therapy, the hemoglobin should be determined weekly until it has stabilized and the maintenance dose has been established (see **DOSAGE AND ADMINISTRATION**). After a dose adjustment, the hemoglobin should be determined weekly for at least 4 weeks, until it has been determined that the hemoglobin has stabilized in response to the dose change. The hemoglobin should then be monitored at regular intervals.

In order to ensure effective erythropoiesis, iron status should be evaluated for all patients before and during treatment, as the majority of patients will eventually require supplemental iron therapy. Supplemental iron therapy is recommended for all patients whose serum ferritin is below 100 mcg/L or whose serum transferrin saturation is below 20%.

Information for Patients

Patients should be informed of the increased risks of mortality, serious cardiovascular events, thromboembolic events, and increased risk of tumor progression or recurrence (see **WARNINGS**). Patients should be informed of the possible side effects of Aranesp® and be instructed to report them to the prescribing physician. Patients should be informed of the signs and symptoms of allergic drug reactions and be advised of appropriate actions. Patients should be counseled on the importance of compliance with their Aranesp® treatment, dietary and dialysis prescriptions, and the importance of judicious monitoring of blood pressure and hemoglobin concentration should be stressed.

In those rare cases where it is determined that a patient can safely and effectively administer Aranesp® at home, appropriate instruction on the proper use of Aranesp® should be provided for patients and their caregivers. Patients should be instructed to read the Aranesp® Medication Guide and Patient Instructions for Use and should be informed that the Medication Guide is not a disclosure of all possible side effects. Patients and caregivers should also be cautioned against the reuse of needles, syringes, prefilled SureClick™ autoinjectors, or drug product, and be thoroughly instructed in their proper disposal. A puncture-resistant container for the disposal of used syringes, autoinjectors, and needles should be made available to the patient. Patients should be informed that the needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex), which should not be handled by persons sensitive to latex.

Drug Interactions

No formal drug interaction studies of Aranesp® have been performed.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenicity: The carcinogenic potential of Aranesp® has not been evaluated in long-term animal studies. Aranesp® did not alter the proliferative response of non-hematological cells in vitro or in vivo. In toxicity studies of approximately 6 months duration in rats and dogs, no tumorigenic or unexpected mitogenic responses were observed in any tissue type. Using a panel of human tissues, the in vitro tissue binding profile of Aranesp® was identical to Epoetin alfa. Neither molecule bound to human tissues other than those expressing the erythropoietin receptor.

Mutagenicity: Aranesp® was negative in the in vitro bacterial and CHO cell assays to detect mutagenicity and in the in vivo mouse micronucleus assay to detect clastogenicity.

Impairment of Fertility: When administered intravenously to male and female rats prior to and during mating, reproductive performance, fertility, and sperm assessment parameters were not affected at any doses evaluated (up to 10 mcg/kg/dose, administered 3 times weekly). An increase in post implantation fetal loss was seen at doses equal to or greater than 0.5 mcg/kg/dose, administered 3 times weekly.

Pregnancy Category C

When Aranesp® was administered intravenously to rats and rabbits during gestation, no evidence of a direct embryotoxic, fetotoxic, or teratogenic outcome was observed at doses up to 20 mcg/kg/day. The only adverse effect observed was a slight reduction in fetal weight, which occurred at doses causing exaggerated pharmacological effects in the dams (1 mcg/kg/day and higher). No deleterious effects on uterine implantation were seen in either species. No significant placental transfer of Aranesp® was observed in rats. An increase in post implantation fetal loss was observed in studies assessing fertility (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility: Impairment of Fertility**).

Intravenous injection of Aranesp® to female rats every other day from day 6 of gestation through day 23 of lactation at doses of 2.5 mcg/kg/dose and higher resulted in offspring (F1 generation) with decreased body weights, which correlated with a low incidence of deaths, as well as delayed eye opening and delayed preputial separation. No adverse effects were seen in the F2 offspring.

There are no adequate and well-controlled studies in pregnant women. Aranesp® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

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

Pediatric Use

Pediatric CRF Patients

A study of the conversion from Epoetin alfa to Aranesp® among pediatric CRF patients over 1 year of age showed similar safety and efficacy to the findings from adult conversion studies (see **CLINICAL PHARMACOLOGY** and **CLINICAL STUDIES**). Safety and efficacy in the initial treatment of anemic pediatric CRF patients or in the conversion from another erythropoietin to Aranesp® in pediatric CRF patients less than 1 year of age have not been established.

Pediatric Cancer Patients

The safety and efficacy of Aranesp® in pediatric cancer patients have not been established.

Geriatric Use

Of the 1801 CRF patients in clinical studies of Aranesp®, 44% were age 65 and over, while 17% were age 75 and over. Of the 873 cancer patients in clinical studies receiving Aranesp® and concomitant chemotherapy, 45% were age 65 and over, while 14% were age 75 and over. No overall differences in safety or efficacy were observed between older and younger patients.

ADVERSE REACTIONS

General

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of Aranesp® cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.

Immunogenicity

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

In clinical studies, the percentage of patients with antibodies to Aranesp® was examined using the BIAcore assay. Sera from 1501 CRF patients and 1159 cancer patients were tested. At baseline, prior to Aranesp® treatment, binding antibodies were detected in 59 (4%) of CRF patients and 36 (3%) of cancer patients. While receiving Aranesp® therapy (range 22-177 weeks), a follow-up sample was taken. One additional CRF patient and eight additional cancer patients developed antibodies capable of binding Aranesp®. None of the patients had antibodies capable of neutralizing the activity of Aranesp® or endogenous erythropoietin at baseline or at end of study. No clinical sequelae consistent with PRCA were associated with the presence of these antibodies.

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

Chronic Renal Failure Patients

Adult Patients

In all studies, the most frequently reported serious adverse events with Aranesp® were infection, congestive heart failure, angina pectoris/cardiac chest pain, thrombosis vascular access, and cardiac arrhythmia/cardiac arrest. The most frequently reported adverse events resulting in clinical intervention (e.g., discontinuation of Aranesp®, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were infection, hypertension, hypotension, and muscle spasm. See **WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events** and **Hypertension**.

The data described below reflect exposure to Aranesp® in 1801 CRF patients, including 675 exposed for at least 6 months, of whom 185 were exposed for greater than 1 year. Aranesp® was evaluated in active-controlled (n = 823) and uncontrolled studies (n = 978). These data include a pooled analysis of CRF patients not on dialysis and dialysis patients who were studied for the correction of anemia and maintenance of hemoglobin.

The population encompassed an age range from 18 to 94 years. Fifty-five percent of the patients were male. The percentages of Caucasian, Black, Asian, and Hispanic patients were 80%, 13%, 3%, and 2%, respectively. The median weekly dose of Aranesp® for patients who received either once weekly or once every 2 week administration was 0.44 mcg/kg (25th, 75th percentiles: 0.30, 0.64 mcg/kg).

Some of the adverse events reported are typically associated with CRF, or recognized complications of dialysis, and may not necessarily be attributable to Aranesp® therapy. No important differences in adverse event rates between treatment groups were observed in controlled studies in which patients received Aranesp® or other recombinant erythropoietins.

The data in Table 2 reflect those adverse events occurring in at least 5% of patients treated with Aranesp®.

Table 2. Adverse Events Occurring in ≥ 5% of CRF Patients

Event	Patients Treated with Aranesp® (n = 1801)
APPLICATION SITE	
Injection Site Pain	6%
BODY AS A WHOLE	
Peripheral Edema	10%
Fatigue	9%
Fever	7%
Death	6%
Chest Pain, Unspecified	7%
Fluid Overload	6%
Access Infection	6%
Influenza-like Symptoms	6%
Access Hemorrhage	7%
Asthenia	5%
CARDIOVASCULAR	
Hypertension	20%
Hypotension	20%
Cardiac Arrhythmias/Cardiac Arrest	8%
Angina Pectoris/Cardiac Chest Pain	8%
Thrombosis Vascular Access	6%
Congestive Heart Failure	5%
CNS/PNS	
Headache	15%
Dizziness	7%
GASTROINTESTINAL	
Diarrhea	14%
Vomiting	14%
Nausea	11%
Abdominal Pain	10%
Constipation	5%
MUSCULO-SKELETAL	
Muscle Spasm	17%
Arthralgia	9%
Limb Pain	8%
Back Pain	7%

(Continued)

Table 2. Adverse Events Occurring in ≥ 5% of CRF Patients (Continued)

Event	Patients Treated with Aranesp® (n = 1801)
RESISTANCE MECHANISM	
Infection[a]	24%
RESPIRATORY	
Upper Respiratory Infection	15%
Dyspnea	10%
Cough	9%
Bronchitis	5%
SKIN AND APPENDAGES	
Pruritus	6%

[a] Infection includes sepsis, bacteremia, pneumonia, peritonitis, and abscess.

The incidence rates for other clinically significant events are shown in Table 3.

Table 3. Percent Incidence of Other Clinically Significant Events in CRF Patients

Event	Patients Treated with Aranesp® (n = 1801)
Acute Myocardial Infarction	2%
Stroke	2%
Seizure	1%
Transient Ischemic Attack	≤1%

Pediatric Patients

In Study N7, Aranesp® was administered to 81 pediatric CRF patients who had stable hemoglobin concentrations while previously receiving Epoetin alfa (see **CLINICAL STUDIES**). In this study, the most frequently reported serious adverse events with Aranesp® were catheter sepsis, fever, catheter related infection, chronic renal failure, and vascular access complication. The most commonly reported adverse events were fever, headache, nasopharyngitis, hypertension, hypotension, injection site pain, cough, peritonitis, and vomiting. Aranesp® administration was discontinued because of injection site pain in two patients and moderate hypertension in a third patient.

Studies have not evaluated the effects of Aranesp® when administered to pediatric patients as the initial treatment for the anemia associated with CRF.

Thrombotic Events

Vascular access thrombosis in hemodialysis patients occurred in clinical trials at an annualized rate of 0.22 events per patient year of Aranesp® therapy. Rates of thrombotic events (e.g., vascular access thrombosis, venous thrombosis, and pulmonary emboli) with Aranesp® therapy were similar to those observed with other recombinant erythropoietins in these trials; the median duration of exposure was 12 weeks.

Cancer Patients Receiving Chemotherapy

The incidence data described below reflect the exposure to Aranesp® in 873 cancer patients including patients exposed to Aranesp® once weekly (547, 63%), once every 2 weeks (128, 16%), and once every 3 weeks (198, 23%). Aranesp® was evaluated in seven studies that were active-controlled and/or placebo-controlled studies of up to 6 months duration. The Aranesp®-treated patient demographics were as follows: median age of 63 years (range of 20 to 91 years); 40% male; 88% Caucasian, 5% Hispanic,

4% Black, and 3% Asian. Over 90% of patients had locally advanced or metastatic cancer, with the remainder having early stage disease. Patients with solid tumors (e.g., lung, breast, colon, ovarian cancers) and lymphoproliferative malignancies (e.g., lymphoma, multiple myeloma) were enrolled in the clinical studies. All of the 873 Aranesp®-treated subjects also received concomitant cyclic chemotherapy.

The most frequently reported serious adverse events included death (10%), fever (4%), pneumonia (3%), dehydration (3%), vomiting (2%), and dyspnea (2%). The most commonly reported adverse events were fatigue, edema, nausea, vomiting, diarrhea, fever, and dyspnea (see **Table 4**). Except for those events listed in Tables 4 and 5, the incidence of adverse events in clinical studies occurred at a similar rate compared with patients who received placebo and were generally consistent with the underlying disease and its treatment with chemotherapy. The most frequently reported reasons for discontinuation of Aranesp® were progressive disease, death, discontinuation of the chemotherapy, asthenia, dyspnea, pneumonia, and gastrointestinal hemorrhage. No important differences in adverse event rates between treatment groups were observed in controlled studies in which patients received Aranesp® or other recombinant erythropoietins.

Table 4. Adverse Events Occurring in ≥ 5% of Patients Receiving Chemotherapy

Event	Aranesp® (n = 873)	Placebo (n = 221)
BODY AS A WHOLE		
Fatigue	33%	30%
Edema	21%	10%
Fever	19%	16%
CNS/PNS		
Dizziness	14%	8%
Headache	12%	9%
GASTROINTESTINAL		
Diarrhea	22%	12%
Constipation	18%	17%
METABOLIC/NUTRITION		
Dehydration	5%	3%
MUSCULO-SKELETAL		
Arthralgia	13%	6%
Myalgia	8%	5%
SKIN AND APPENDAGES		
Rash	7%	3%

Table 5. Incidence of Other Clinically Significant Adverse Events in Patients Receiving Chemotherapy

Event	All Aranesp® (n = 873)	Placebo (n = 221)
Hypertension	3.7%	3.2%
Seizures/Convulsions[a]	0.6%	0.5%
Thrombotic Events	6.2%	4.1%
Pulmonary Embolism	1.3%	0.0%
Thrombosis[b]	5.6%	4.1%

[a] Seizures/Convulsions include the preferred terms: Convulsions, Convulsions Grand Mal, and Convulsions Local.

[b] Thrombosis includes: Thrombophlebitis, Thrombophlebitis Deep, Thrombosis Venous, Thrombosis Venous Deep, Thromboembolism, and Thrombosis.

In a randomized controlled trial of Aranesp® 500 mcg once every 3 weeks (n = 353) and Aranesp® 2.25 mcg/kg once weekly (n = 352), the incidences of all adverse events and of serious adverse events were similar between the two groups.

Thrombotic and Cardiovascular Events

Overall, the incidence of thrombotic events was 6.2% for Aranesp® and 4.1% for placebo. However, the following events were reported more frequently in Aranesp®-treated patients than in placebo controls: pulmonary embolism, thromboembolism, thrombosis, and thrombophlebitis (deep and/or superficial). In addition, edema of any type was more frequently reported in Aranesp®-treated patients (21%) than in patients who received placebo (10%).

OVERDOSAGE

The expected manifestations of Aranesp® overdosage include signs and symptoms associated with an excessive and/or rapid increase in hemoglobin concentration, including any of the cardiovascular events described in **WARNINGS** and listed in **ADVERSE REACTIONS**. Patients receiving an overdosage of Aranesp® should be monitored closely for cardiovascular events and hematologic abnormalities. Polycythemia should be managed acutely with phlebotomy, as clinically indicated. Following resolution of the effects due to Aranesp® overdosage, reintroduction of Aranesp® therapy should be accompanied by close monitoring for evidence of rapid increases in hemoglobin concentration (> 1 g/dL in any 2-week period). In patients with an excessive hematopoietic response, reduce the Aranesp® dose in accordance with the recommendations described in **DOSAGE AND ADMINISTRATION**.

DOSAGE AND ADMINISTRATION

IMPORTANT: See BOXED WARNINGS and WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events.

Aranesp® is supplied in vials or in prefilled syringes with UltraSafe® Needle Guards*. Following administration of Aranesp® from the prefilled syringe, the UltraSafe® Needle Guard should be activated to prevent accidental needlesticks.

Aranesp® is also supplied in prefilled SureClick™ autoinjectors containing the same dosage strengths as the prefilled syringes. Because the autoinjectors are designed to deliver the full content, autoinjectors should only be used for patients who need the full dose. If the required dose is not available in an autoinjector, prefilled syringes, or vials should be used to administer the required dose. Autoinjectors are for subcutaneous administration only.

Chronic Renal Failure Patients

Aranesp® may be administered either intravenously or subcutaneously as a single weekly injection. ***In patients on hemodialysis, the intravenous route is recommended*.** The dose should be started and slowly adjusted as described below based on hemoglobin levels. If a patient fails to respond or maintain a response, this should be evaluated (see **WARNINGS: Pure Red Cell Aplasia, PRECAUTIONS: Lack or Loss of Response to Aranesp®** and **PRECAUTIONS: Laboratory Tests**). When Aranesp® therapy is initiated or adjusted, the hemoglobin should be followed weekly until stabilized and monitored at least monthly thereafter. During therapy, hematological parameters should be monitored regularly. Doses must be individualized to ensure that hemoglobin is maintained at an appropriate level for each patient.

For patients who respond to Aranesp® with a rapid increase in hemoglobin (e.g., more than 1 g/dL in any 2-week period), the dose of Aranesp® should be reduced.

Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL.

Starting Dose

Correction of Anemia

The initial dose by subcutaneous or intravenous administration is 0.45 mcg/kg body weight, as a single injection once weekly. Alternatively, in patients not receiving dialysis, an initial dose of 0.75 mcg/kg may be administered subcutaneously as a single injection once every 2 weeks. If hemoglobin excursions outside the recommended range occur, the Aranesp® dose should be adjusted as described below.

The use of Aranesp® in pediatric CRF patients as the initial treatment to correct anemia has not been studied.

Maintenance Dose

The dose should be individualized to maintain hemoglobin levels within the range of 10 to 12 g/dL (see **Dose Adjustment**). If hemoglobin excursions outside the recommended range occur, the Aranesp® dose should be adjusted as described below. For many patients, the appropriate maintenance dose will be lower than the starting dose. CRF patients not on dialysis, in particular, may require lower maintenance doses. In the maintenance phase, Aranesp® may continue to be administered as a single injection once weekly or once every 2 weeks.

Dose Adjustment

The dose should be adjusted for each patient to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL. If hemoglobin excursions outside the recommended range occur, the Aranesp® dose should be adjusted as described below. 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, doses 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 hemoglobin is less than 1 g/dL over 4 weeks and iron stores are adequate (see **PRECAUTIONS: Laboratory Tests**), the dose of Aranesp® 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.

For patients whose hemoglobin does not attain a level within the range of 10 to 12 g/dL despite the use of appropriate Aranesp® dose titrations over a 12-week period:

- do not administer higher Aranesp® doses and use the lowest dose that will maintain a hemoglobin level sufficient to avoid the need for recurrent RBC transfusions,
- evaluate and treat for other causes of anemia (see **PRECAUTIONS: Lack or Loss of Response to Aranesp®**), and

- thereafter, hemoglobin should continue to be monitored and if responsiveness improves, Aranesp® dose adjustments should be made as described above; discontinue Aranesp® if responsiveness does not improve and the patient needs recurrent RBC transfusions.

Conversion From Epoetin alfa to Aranesp®

The starting weekly dose of Aranesp® for adults and pediatric patients should be estimated on the basis of the weekly Epoetin alfa dose at the time of substitution (see **Table 6**). For pediatric patients receiving a weekly Epoetin alfa dose of < 1,500 units/week, the available data are insufficient to determine an Aranesp® conversion dose. Because of variability, doses should be titrated to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL. Due to the longer serum half-life, Aranesp® should be administered less frequently than Epoetin alfa. Aranesp® should be administered once a week if a patient was receiving Epoetin alfa 2 to 3 times weekly. Aranesp® should be administered once every 2 weeks if a patient was receiving Epoetin alfa once per week. The route of administration (intravenous or subcutaneous) should be maintained.

Table 6. Estimated Aranesp® Starting Doses (mcg/week) for Patients Based on Previous Epoetin alfa Dose (Units/week)

Previous Weekly Epoetin alfa Dose (Units/week)	Weekly Aranesp® Dose (mcg/week)	
	Adult	Pediatric
< 1,500	6.25	See text*
1,500 to 2,499	6.25	6.25
2,500 to 4,999	12.5	10
5,000 to 10,999	25	20
11,000 to 17,999	40	40
18,000 to 33,999	60	60
34,000 to 89,999	100	100
≥ 90,000	200	200

*For pediatric patients receiving a weekly Epoetin alfa dose of < 1,500 units/week, the available data are insufficient to determine an Aranesp® conversion dose.

Cancer Patients Receiving Chemotherapy

For pediatric patients, see **PRECAUTIONS: Pediatric Use**.

The recommended starting dose for Aranesp® administered weekly is 2.25 mcg/kg as a subcutaneous injection.

The recommended starting dose for Aranesp® administered once every 3 weeks is 500 mcg as a subcutaneous injection.

Therapy should not be initiated at hemoglobin levels ≥ 10 g/dL, ~~except where the patient is unable to tolerate this degree of anemia due to co-morbid conditions.~~ For both dosing schedules, the dose should be adjusted for each patient to maintain the lowest hemoglobin level sufficient to avoid RBC transfusion. If the rate of hemoglobin increase is more than 1 g/dL per 2-week period or when the hemoglobin reaches a level needed to avoid transfusion, the dose should be reduced by 40% of the previous dose. If the hemoglobin exceeds a level needed to avoid transfusion ~~or exceeds 12 g/dL~~, Aranesp® should be

temporarily withheld until the hemoglobin approaches a level where transfusions may be required. At this point, therapy should be reinitiated at a dose 40% below the previous dose.

For patients receiving weekly administration, if there is less than a 1 g/dL increase in hemoglobin after 6 weeks of therapy, the dose of Aranesp® should be increased up to 4.5 mcg/kg.

Discontinue Aranesp® if after 8 weeks of therapy there is no response as measured by hemoglobin levels or if transfusions are still required.

Discontinue Aranesp® following the completion of a chemotherapy course (see **BOXED WARNINGS: *Cancer***).

Preparation and Administration of Aranesp®

Do not shake Aranesp® or leave vials, syringes, or prefilled SureClick™ autoinjectors exposed to light. After removing the vials, prefilled syringes, or autoinjectors from the refrigerator, protect from room light until administration. Vigorous shaking or exposure to light may denature Aranesp®, causing it to become biologically inactive. Always store vials, prefilled syringes, or autoinjectors of Aranesp® in their carton until use.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials, prefilled syringes, or autoinjectors exhibiting particulate matter or discoloration.

Do not dilute Aranesp®.

Do not administer Aranesp® in conjunction with other drug solutions.

Aranesp® contains no preservatives. Discard any unused portion. **Do not pool unused portions from the vials or prefilled syringes. Do not use the vial, prefilled syringe, or autoinjector more than one time.**

Following administration of Aranesp® from the prefilled syringe, activate the UltraSafe® Needle Guard. Place your hands behind the needle, grasp the guard with one hand, and slide the guard forward until the needle is completely covered and the guard clicks into place. NOTE: If an audible click is not heard, the needle guard may not be completely activated.

The prefilled SureClick™ autoinjector is designed to deliver the full dose. The completion of the injection is signaled by an audible click. Removal of the autoinjector from the injection site automatically extends a needle cover.

The autoinjectors, the syringes used with vials, and the entire prefilled syringe with activated needle guard should be disposed of in a puncture-proof container.

See the accompanying "Patient Instructions for Use" insert for complete instructions on the preparation and administration of Aranesp® for patients, including injection site selection.

HOW SUPPLIED

Aranesp® is available in single-dose vials in two solutions, an albumin solution and a polysorbate solution. The words "Albumin Free" appear on the polysorbate container labels and the package main panels as well as other panels as space permits. Aranesp® single-dose prefilled syringes and prefilled SureClick™ autoinjectors are available in albumin and polysorbate solutions. Both prefilled syringes and autoinjectors are supplied with a 27-gauge, ½-inch needle.

Each prefilled syringe is equipped with an UltraSafe® Needle Guard that is manually activated to cover the needle during disposal. The needle cover of the prefilled syringe contains dry natural rubber (a derivative of latex). The autoinjector has a needle cover that automatically extends as the autoinjector is removed from the injection site after completion of the injection.

Aranesp® is available in the following packages:

Single-dose Vial, Polysorbate Solution

1 Vial/Pack, 4 Packs/Case	**4 Vials/Pack, 4 Packs/Case**	**4 Vials/Pack, 10 Packs/Case**
200 mcg/1 mL (NDC 55513-006-01)	200 mcg/1 mL (NDC 55513-006-04)	25 mcg/1 mL (NDC 55513-002-04)
300 mcg/1 mL (NDC 55513-110-01)	300 mcg/1 mL (NDC 55513-110-04)	40 mcg/1 mL (NDC 55513-003-04)
500 mcg/1 mL (NDC 55513-008-01)		60 mcg/1 mL (NDC 55513-004-04)
		100 mcg/1 mL (NDC 55513-005-04)
		150 mcg/0.75 mL (NDC 55513-053-04)

Single-dose Vial, Albumin Solution

1 Vial/Pack, 4 Packs/Case	**4 Vials/Pack, 4 Packs/Case**	**4 Vials/Pack, 10 Packs/Case**
200 mcg/1 mL (NDC 55513-014-01)	200 mcg/1 mL (NDC 55513-014-04)	25 mcg/1 mL (NDC 55513-010-04)
300 mcg/1 mL (NDC 55513-015-01)	300 mcg/1 mL (NDC 55513-015-04)	40 mcg/1 mL (NDC 55513-011-04)
500 mcg/1 mL (NDC 55513-016-01)		60 mcg/1 mL (NDC 55513-012-04)
		100 mcg/1 mL (NDC 55513-013-04)
		150 mcg/0.75 mL (NDC 55513-054-04)

Single-dose Prefilled Syringe (SingleJect®) with a 27-gauge, ½-inch needle with an UltraSafe® Needle Guard, Polysorbate Solution

1 Syringe/Pack, 4 Packs/Case	**4 Syringes/Pack, 4 Packs/Case**	**4 Syringes/Pack, 10 Packs/Case**

200 mcg/0.4 mL (NDC 55513-028-01)	200 mcg/0.4 mL (NDC 55513-028-04)	25 mcg/0.42 mL (NDC 55513-057-04)
300 mcg/0.6 mL (NDC 55513-111-01)	300 mcg/0.6 mL (NDC 55513-111-04)	40 mcg/0.4 mL (NDC 55513-021-04)
500 mcg/1 mL (NDC 55513-032-01)		60 mcg/0.3 mL (NDC 55513-023-04)
		100 mcg/0.5 mL (NDC 55513-025-04)
		150 mcg/0.3 mL (NDC 55513-027-04)

Single-dose Prefilled Syringe (SingleJect®) with a 27-gauge, ½-inch needle with an UltraSafe® Needle Guard, Albumin Solution

1 Syringe/Pack, 4 Packs/Case	**4 Syringes/Pack, 4 Packs/Case**	**4 Syringes/Pack, 10 Packs/Case**
200 mcg/0.4 mL (NDC 55513-044-01)	200 mcg/0.4 mL (NDC 55513-044-04)	25 mcg/0.42 mL (NDC 55513-058-04)
300 mcg/0.6 mL (NDC 55513-046-01)	300 mcg/0.6 mL (NDC 55513-046-04)	40 mcg/0.4 mL (NDC 55513-037-04)
500 mcg/1 mL (NDC 55513-048-01)		60 mcg/0.3 mL (NDC 55513-039-04)
		100 mcg/0.5 mL (NDC 55513-041-04)
		150 mcg/0.3 mL (NDC 55513-043-04)

Single-dose Prefilled SureClick™ Autoinjector with a 27-gauge, ½-inch needle, Polysorbate Solution

1 Autoinjector/Pack

25 mcg/0.42 mL
(NDC 55513-090-01)

40 mcg/0.4 mL
(NDC 55513-091-01)

60 mcg/0.3 mL

(NDC 55513-092-01)

100 mcg/0.5 mL
(NDC 55513-093-01)

150 mcg/0.3 mL
(NDC 55513-094-01)

200 mcg/0.4 mL
(NDC 55513-095-01)

300 mcg/0.6 mL
(NDC 55513-096-01)

500 mcg/1 mL
(NDC 55513-097-01)

Single-dose Prefilled SureClick™ Autoinjector with a 27-gauge, ½-inch needle, Albumin Solution

1 Autoinjector/Pack

25 mcg/0.42 mL
(NDC 55513-080-01)

40 mcg/0.4 mL
(NDC 55513-081-01)

60 mcg/0.3 mL
(NDC 55513-082-01)

100 mcg/0.5 mL
(NDC 55513-083-01)

150 mcg/0.3 mL
(NDC 55513-084-01)

200 mcg/0.4 mL
(NDC 55513-085-01)

300 mcg/0.6 mL
(NDC 55513-086-01)

500 mcg/1 mL
(NDC 55513-087-01)

Storage

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

REFERENCES

1. Egrie JC, Browne JK. Development and characterization of novel erythropoiesis stimulating protein (NESP). *Br J Cancer*. 2001; 84 (suppl 1): 3-10.
2. Singh AK, Szczech L, Tang KL, et al. Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease. *N Engl J Med.* 2006; 355: 2085-98.
3. 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. *N Engl J Med*. 1998; 339: 584-590.
4. Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining Normal Hemoglobin Levels With Epoetin Alfa in Mainly Nonanemic Patients With Metastatic Breast Cancer Receiving First-Line Chemotherapy: A Survival Study. *JCO.* 2005; 23(25): 1-13.
5. Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant Human Erythropoietins and Cancer Patients: Updated Meta-Analysis of 57 Studies Including 9353 Patients. *J Natl Cancer Inst.* 2006; 98: 708-14.

Rx only

This product, or its use, may be covered by one or more US Patents, including US Patent No. 5,618,698, in addition to others including patents pending.

AMGEN®

Manufactured by:

Amgen Manufacturing, Limited, a subsidiary of Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

©2001-2008 Amgen Inc. All rights reserved.
* UltraSafe® is a registered trademark of Safety Syringes, Inc.

3xxxxxx – v
Revised: