Aranesp®
(darbepoetin alfa)
For Injection

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 (IV) or subcutaneous (SC) administration.

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

Single-dose prefilled syringes are available containing 25, 40, 60, 100, 150, 200, 300, or 500 mcg of Aranesp®. To reduce the risk of accidental needlesticks to users, each prefilled syringe is equipped with a needle guard that covers the needle during disposal.

Single-dose vials and prefilled syringes 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: Dose Adjustment**). In patients with cancer receiving concomitant chemotherapy, the etiology of anemia is multifactorial.

Pharmacokinetics

The pharmacokinetics of Aranesp® were studied in patients with CRF and cancer patients receiving chemotherapy.

Over the therapeutic range of 0.45 to 4.5 mcg/kg, AUC) were linear with respect to dose, and no evid an expected < 2-fold increase in blood levels when c

Following SC administration, absorption is slow and patients, which reflected the rate of absorption, was IV administration to these patients, Aranesp® serum a distribution half-life of approximately 1.4 hours and SC administration in CRF patients' peak concentr hours), whereas cancer patients' peak concentration

When administered by IV administration, the termina longer than Epoetin alfa. The bioavailability of Aran administration is 37% (range: 30% to 50%).

CLINICAL STUDIES

Throughout this section of the package insert, the A nephrology and cancer clinical programs are designa

Chronic Renal Failure Patients

The safety and effectiveness of Aranesp® have b studies evaluated the safety and efficacy of Aran patients with CRF, and two studies assessed the concentrations in adult patients with CRF who erythropoietins.

De Novo Use of Aranesp®

In two open-label studies, Aranesp® or Epoetin a anemia in CRF patients who had not been erythropoietin. Study N1 evaluated CRF patients re not requiring dialysis (predialysis patients). In both 0.45 mcg/kg administered once weekly. The startin weekly in Study N1 and 50 U/kg twice weekly adjustments were instituted to maintain hemoglobi (Note: The recommended hemoglobin target is lowe **DOSAGE AND ADMINISTRATION: General** for re primary efficacy endpoint was the proportion of p increase in hemoglobin concentration to a level of 24 weeks (Study N2). The studies were designe Aranesp® but not to support conclusions regarding c

In Study N1, the hemoglobin target was achieved by treated with Aranesp® and 84% (95% CI: 66%, 95% The mean increase in hemoglobin over the initial 4 (95% CI: 0.82 g/dL, 1.37 g/dL).

In Study N2, the primary efficacy endpoint was a 129 patients treated with Aranesp® and 92% (95 with Epoetin alfa. The mean increase in hem 4 weeks of Aranesp® treatment was 1.38 g/dL (95

Conversion From Other Recombinant Erythropo

Two studies (N3 and N4) were conducted in adul other recombinant erythropoietins and compar

erythropoietins to maintain hemoglobin concentrations within a study target range of 9 to 13 g/dL. (Note: The recommended hemoglobin target is lower than the target range of these studies. See **DOSAGE AND ADMINISTRATION: General** 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. Study N3 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 N4 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 N3, a median weekly dose of 0.53 mcg/kg Aranesp® (25^{th}, 75^{th} percentiles: 0.30, 0.93 mcg/kg) was required to maintain hemoglobin in the study target range. In Study N4, a median weekly dose of 0.41 mcg/kg Aranesp® (25^{th}, 75^{th} percentiles: 0.26, 0.65 mcg/kg) was required to maintain hemoglobin in the study target range.

Cancer Patients Receiving Chemotherapy

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 six, 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.

Studies were conducted that evaluated doses of Aranesp® ranging from 0.5 mcg/kg to 8.0 mcg/kg administered weekly. Data from these studies indicate that there is a dose response relationship with respect to hemoglobin response. The minimally effective starting dose with respect to reducing transfusion requirements was 1.5 mcg/kg/week, with a plateau observed at 4.5 mcg/kg/week.

INDICATIONS AND USAGE

Aranesp® is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis, and for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.

CONTRAINDICATIONS

Aranesp® is contraindicated in patients with:

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

WARNINGS

Cardiovascular Events, Hemoglobin, and Rate of Rise of Hemoglobin

Aranesp® and other erythropoietic therapies may increase the risk of cardiovascular events, including death. The higher risk of cardiovascular events may be associated with higher hemoglobin and/or higher rates of rise of hemoglobin. The hemoglobin level should be managed carefully to avoid exceeding a target level of 12 g/dL.

In a clinical trial of Epoetin alfa (rHuEPO) treatment in hemodialysis patients with clinically evident cardiac disease, patients were randomized to a target hemoglobin of either 14 ± 1 g/dL or 10 ± 1 g/dL[2]. Higher mortality (35% versus 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.

In patients treated with Aranesp® or other recombinant erythropoietins in Aranesp® clinical trials, increases in hemoglobin greater than approximately 1.0 g/dL during any 2-week period were associated with increased incidence of cardiac arrest, neurologic events (including seizures and stroke), exacerbations of hypertension, congestive heart failure, vascular thrombosis/ischemia/infarction, acute myocardial infarction, and fluid overload/edema. It is recommended that the dose of Aranesp® be decreased if the hemoglobin increase exceeds 1.0 g/dL in any 2-week period, because of the association of excessive rate of rise of hemoglobin with these events.

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: Dose Adjustment**). 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 1.0 g/dL in any 2-week period.

Thrombotic Events and Increased Mortality

An increased incidence of thrombotic events has been observed in patients 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 4**).

In a randomized controlled study with another erythropoietic product 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 prevent anemia (maintain hemoglobin levels between 12 and 14 g/dL or hct 36 to 42%). Treatment with Epoetin alfa was associated with a higher rate of fatal thrombotic events (1.1% Epoetin alfa versus 0.2% placebo) in the first 4 months of the study. Mortality at one year, the primary endpoint of the study, was higher for the Epoetin alfa group (76% Epoetin alfa versus 70% placebo, p = 0.012); (see **PRECAUTIONS: Tumor Growth Factor Potential**). Until further information is available, the recommended target hemoglobin should not exceed 12 g/dL in men or women.

Pure Red Cell Aplasia

Pure red cell aplasia (PRCA), in association with neutralizing antibodies to native erythropoietin has been observed in patients treated with recombinant erythropoietins. This has been reported predominantly in patients with CRF. PRCA has been reported in a limited number of subjects exposed to other recombinant erythropoietin products prior to exposure to Aranesp®; therefore, the contribution of Aranesp® to the development of PRCA is unclear. Any patient with loss of response to Aranesp® should be evaluated for the etiology of loss of effect (see **PRECAUTIONS: General**). Aranesp® should be discontinued in any patient with evidence of PRCA and the patient evaluated for the presence of binding and neutralizing antibodies to Aranesp®, native erythropoietin, and any other recombinant erythropoietin administered to the patient. Amgen may be contacted to assist in this evaluation. In patients with PRCA secondary to neutralizing antibodies to erythropoietin, Aranesp® should not be administered.

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).

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 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 antibody to recombinant erythropoietins.

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 (12 g/dL) or rising too rapidly (greater than 1.0 g/dL in 2 weeks), the guidelines for dose and frequency of dose adjustments should be followed (see **WARNINGS** and **DOSAGE AND ADMINISTRATION: Dose Adjustment**).

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 predialysis patients generally receive less frequent monitoring of blood pressure and laboratory parameters than dialysis patients, predialysis patients 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.

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.

Tumor Growth Factor Potential

Aranesp® is a growth factor that primarily stimulates RBC production. Erythropoietin receptors are also found on the surfaces of normal, non-hematopoietic tissues and some malignant cell lines and tumor biopsy specimens. However, it is not known if these receptors are functional. The possibility that Aranesp® can act as a growth factor for any tumor type, particularly myeloid malignancies, has not been evaluated.

In a randomized, placebo-controlled study in 314 anemic subjects with advanced lung cancer randomized to either Aranesp® or placebo, statistically significant differences in time-to-progression (TTP) or overall survival (OS) were not observed; however, the study was not designed to detect or exclude clinically meaningful differences in either TTP or OS (see **CLINICAL STUDIES**).

Two additional studies explored the effect on survival and/or disease progression following administrations of two other erythropoietic products (ie, Epoetin alfa and Epoetin beta) with higher hemoglobin targets. The first study was a randomized controlled study in 939 women with metastatic breast cancer receiving chemotherapy where patients received either weekly Epoetin alfa or placebo for up to a year. This study was designed to prevent anemia (maintain hemoglobin levels between 12 and 14 g/dL or hct 36 to 42%). Mortality at 12 months was significantly higher in the Epoetin alfa arm (see **WARNINGS: Thrombotic Events and Increased Mortality**). This difference was observed primarily in the first 4 months of the study with more deaths attributed to breast cancer progression in the Epoetin alfa group (6% Epoetin

alfa versus 3% placebo). 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. The second 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 (median of 406 days Epoetin beta vs 745 days placebo, p = 0.04) in patients receiving Epoetin beta.

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

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

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 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.

It is recommended that Aranesp® should be administered by a healthcare professional. 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, including careful review of the accompanying "Information for Patients" insert. Patients and caregivers should also be cautioned against the reuse of needles, syringes, or drug product, and be thoroughly instructed in their proper disposal. A puncture-resistant container for the disposal of used syringes and needles should be made available to the patient.

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

The safety and efficacy of Aranesp® in pediatric patients have not been established. Pharmacokinetic data, obtained in 14 subjects, suggest that the pharmacokinetics in children between the ages of 5 and 18 years with nonhematologic malignancies were similar to those seen in adults with nonhematologic malignancies.

Geriatric Use

Of the 1598 CRF patients in clinical studies of Aranesp®, 42% were age 65 and over, while 15% were 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 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.

Chronic Renal Failure Patients

In all studies, the most frequently reported serious adverse reactions with Aranesp® were vascular access thrombosis, congestive heart failure, sepsis, and cardiac arrhythmia. The most commonly reported adverse reactions were infection, hypertension, hypotension, myalgia, headache, and diarrhea, (see **WARNINGS: Cardiovascular Events, Hemoglobin, and Rate of Rise of Hemoglobin, and Hypertension**). The most frequently reported adverse reactions 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 hypotension, hypertension, fever, myalgia, nausea, and chest pain.

The data described below reflect exposure to Aranesp® in 1598 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 = 775).

The rates of adverse events and association with Aranesp® are best assessed in the results from studies in which Aranesp® was used to stimulate erythropoiesis in patients anemic at study baseline (n = 348), and, in particular, the subset of these patients in randomized controlled trials (n = 276). Because there were no substantive differences in the rates of adverse reactions between these subpopulations, or between these subpopulations and the entire population of patients treated with Aranesp®, data from all 1598 patients were pooled.

The population encompassed an age range from 18 to 91 years. Fifty-seven percent of the patients were male. The percentages of Caucasian, Black, Asian, and Hispanic patients were 83%, 11%, 3%, and 1%, respectively. The median weekly dose of Aranesp® was 0.45 mcg/kg (25^{th}, 75^{th} percentiles: 0.29, 0.66 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 1 reflect those adverse events occurring in at least 5% of patients treated with Aranesp®.

Table 1. Adverse Events Occurring in ≥ 5% of CRF Patients

Event	Patients Treated With Aranesp® (n = 1598)
APPLICATION SITE	
Injection-site Pain	7%
BODY AS A WHOLE	
Peripheral Edema	11%
Fatigue	9%
Fever	9%
Death	7%
Chest Pain, Unspecified	6%
Fluid Overload	6%
Access Infection	6%
Influenza-like Symptoms	6%
Access Hemorrhage	6%
Asthenia	5%
CARDIOVASCULAR	
Hypertension	23%
Hypotension	22%
Cardiac Arrhythmias/Cardiac Arrest	10%
Angina Pectoris/Cardiac Chest Pain	8%
Thrombosis Vascular Access	8%
Congestive Heart Failure	6%
CNS/PNS	
Headache	16%
Dizziness	8%
GASTROINTESTINAL	
Diarrhea	16%
Vomiting	15%
Nausea	14%
Abdominal Pain	12%
Constipation	5%
MUSCULO-SKELETAL	
Myalgia	21%
Arthralgia	11%
Limb Pain	10%
Back Pain	8%

(Continued)

Table 1. Adverse Events Occurring in ≥ 5% of CRF Patients (Continued)

Event	Patients Treated With Aranesp® (n = 1598)
RESISTANCE MECHANISM	
Infection[a]	27%
RESPIRATORY	
Upper Respiratory Infection	14%
Dyspnea	12%
Cough	10%
Bronchitis	6%
SKIN AND APPENDAGES	
Pruritus	8%

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

386 The incidence rates for other clinically significant events are shown in Table 2.

Table 2. Percent Incidence of Other Clinically Significant Events in CRF Patients

Event	Patients Treated With Aranesp® (n = 1598)
Acute Myocardial Infarction	2%
Seizure	1%
Stroke	1%
Transient Ischemic Attack	1%

387 **Thrombotic Events**

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

393 ***Cancer Patients Receiving Chemotherapy***

394 The data described below reflect the exposure to Aranesp® in 873 cancer patients. Aranesp® was
395 evaluated in seven studies that were active-controlled and/or placebo-controlled studies of up to 6
396 months duration. The Aranesp®-treated patient demographics were as follows: median age of 63
397 years (range of 20 to 91 years); 40% male; 88% Caucasian, 5% Hispanic, 4% Black, and 3%
398 Asian. Over 90% of patients had locally advanced or metastatic cancer, with the remainder
399 having early stage disease. Patients with solid tumors (e.g., lung, breast, colon, ovarian
400 cancers), and lymphoproliferative malignancies (e.g., lymphoma, multiple myeloma) were
401 enrolled in the clinical studies. All of the 873 Aranesp®-treated subjects also received
402 concomitant cyclic chemotherapy.

403 The most frequently reported serious adverse events included death (10%), fever (4%),
404 pneumonia (3%), dehydration (3%), vomiting (2%), and dyspnea (2%). The most commonly
405 reported adverse events were fatigue, edema, nausea, vomiting, diarrhea, fever and dyspnea
406 (see **Table 3**). Except for those events listed in Tables 3 and 4, the incidence of adverse events

407 in clinical studies occurred at a similar rate compared with patients who received placebo and
408 were generally consistent with the underlying disease and its treatment with chemotherapy. The
409 most frequently reported reasons for discontinuation of Aranesp® were progressive disease,
410 death, discontinuation of the chemotherapy, asthenia, dyspnea, pneumonia, and gastrointestinal
411 hemorrhage. No important differences in adverse event rates between treatment groups were
412 observed in controlled studies in which patients received Aranesp® or other recombinant
413 erythropoietins.

414

415 **Table 3. 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 4. 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.

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 (21%) patients than in patients who received placebo (10%).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Aranesp® has not been adequately determined. Radioimmunoprecipitation assays were performed on sera from 1534 CRF and 833 cancer patients treated with Aranesp® in clinical studies. High-titer antibodies were not detected in patients with CRF, but assay sensitivity may be inadequate to reliably detect lower titers. Antibodies were detected by radioimmunoprecipitation in sera from three cancer patients; neutralizing activity, possibly related to antibodies, was detected in one of these three patients. There was no evidence of PRCA in that patient (see **WARNINGS: Pure Red Cell Aplasia**).

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Aranesp®, with the incidence of antibodies to other products may be misleading.

OVERDOSAGE

The maximum amount of Aranesp® that can be safely administered in single or multiple doses has not been determined. Doses over 3.0 mcg/kg/week for up to 28 weeks have been administered to CRF patients. Doses up to 8.0 mcg/kg every week and 15.0 mcg/kg every 3 weeks have been administered to cancer patients for up to 12-16 weeks. Excessive rise and rate of rise in hemoglobin concentration, however, have been associated with adverse events (see **WARNINGS** and **DOSAGE AND ADMINISTRATION: Dose Adjustment**). In the event of

polycythemia, Aranesp® should be temporarily withheld (see **DOSAGE AND ADMINISTRATION: Dose Adjustment**). If clinically indicated, phlebotomy may be performed.

DOSAGE AND ADMINISTRATION

General

IMPORTANT: Aranesp® dosing regimens are different for each of the indications described in this section of the package insert. Due to the longer serum half-life, Aranesp® should be administered less frequently than Epoetin alfa (for example, where Epoetin alfa is administered three times a week, Aranesp® should be administered weekly). Aranesp® should be administered under the supervision of a healthcare professional.

Aranesp® is supplied in either 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 needle sticks.

Chronic Renal Failure Patients

Aranesp® is administered either IV or SC as a single weekly injection. 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, other etiologies should be considered and evaluated (see **PRECAUTIONS: General** and **Laboratory Tests**). When Aranesp® therapy is initiated or adjusted, the hemoglobin should be followed weekly until stabilized and monitored at least monthly thereafter.

For patients who respond to Aranesp® with a rapid increase in hemoglobin (e.g., more than 1.0 g/dL in any 2-week period), the dose of Aranesp® should be reduced (see **DOSAGE AND ADMINISTRATION: Dose Adjustment**) because of the association of excessive rate of rise of hemoglobin with adverse events (see **WARNINGS: Cardiovascular Events, Hemoglobin,** and **Rate of Rise of Hemoglobin**).

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

Starting Dose

Correction of Anemia

The recommended starting dose of Aranesp® for the correction of anemia in CRF patients is 0.45 mcg/kg body weight, administered as a single IV or SC injection once weekly. Because of individual variability, doses should be titrated to not exceed a target hemoglobin concentration of 12 g/dL (see **DOSAGE AND ADMINISTRATION: Dose Adjustment**). For many patients, the appropriate maintenance dose will be lower than this starting dose. Predialysis patients, in particular, may require lower maintenance doses. Also, some patients have been treated successfully with a SC dose of Aranesp® administered once every 2 weeks.

Conversion From Epoetin alfa to Aranesp®

The starting weekly dose of Aranesp® should be estimated on the basis of the weekly Epoetin alfa dose at the time of substitution (see **Table 5**). Because of individual variability, doses should then be titrated to maintain the target hemoglobin. 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 (IV or SC) should be maintained.

Table 5. Estimated Aranesp® Starting Doses (mcg/week) Based on Previous Epoetin alfa Dose (Units/week)

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

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, 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 1.0 g/dL in a 2-week period, the dose should be decreased by approximately 25%.

If the increase in hemoglobin is less than 1.0 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.

Maintenance Dose

Aranesp® dosage should be adjusted to maintain a target hemoglobin not to exceed 12 g/dL. If the hemoglobin exceeds 12 g/dL, the dose may be adjusted as described above. Doses must be individualized to ensure that hemoglobin is maintained at an appropriate level for each patient.

Cancer Patients Receiving Chemotherapy

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

The dose should be adjusted for each patient to achieve and maintain a target hemoglobin. If there is less than a 1.0 g/dL increase in hemoglobin after 6 weeks of therapy, the dose of Aranesp® should be increased up to 4.5 mcg/kg. If hemoglobin increases by more than 1.0 g/dL in a 2-week period or if the hemoglobin exceeds 12 g/dL, the dose should be reduced by approximately 25%. If the hemoglobin exceeds 13 g/dL, doses should be temporarily withheld until the hemoglobin falls to 12 g/dL. At this point, therapy should be reinitiated at a dose approximately 25% below the previous dose.

Preparation and Administration of Aranesp®

Do not shake Aranesp® or leave vials or syringes exposed to bright light. After removing the vials or prefilled syringes from the cartons, keep them covered to protect from room light until

administration. Vigorous shaking or exposure to light may denature Aranesp® causing it to become biologically inactive. Always store vials or prefilled syringes 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 or prefilled syringes exhibiting particulate matter or discoloration.

Do not dilute Aranesp®.

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

Aranesp® is packaged in single-dose vials and prefilled syringes and contains no preservative. Discard any unused portion. <u>Do not pool unused portions from the vials or prefilled syringes. Do not use the vial or prefilled syringe more than one time.</u>

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 syringe should be disposed of by placing the entire prefilled syringe with guard activated into an approved puncture-proof container.

See the accompanying "Information for Patients" leaflet for complete instructions on the preparation and administration of Aranesp® for patients.

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® albumin solution is also available in single-dose prefilled syringes supplied with a 27 gauge, ½ inch needle. To reduce the risk of accidental needlesticks to users, each prefilled syringe is equipped with an UltraSafe® Needle Guard that covers the needle during disposal. 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)

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. 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.

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.

Manufactured by:

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