AMGEN®

Aranesp®
(darbepoetin alfa)

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(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, pharmacokinetic measures (Cmax, half-life, AUC) were linear with respect to dose, and no evidence of accumulation was observed beyond an expected < 2-fold increase in blood levels when compared to the initial dose.

Following SC administration, absorption is slow and rate limiting. The observed half-life in CRF patients, which reflected the rate of absorption, was 49 hours (range: 27 to 89 hours). Following IV administration to these patients, Aranesp® serum concentration-time profiles are biphasic, with a distribution half-life of approximately 1.4 hours and the mean terminal half-life of 21 hours. Post SC administration in CRF patients' peak concentrations occur at 34 hours (range: 24 to 72 hours), whereas cancer patients' peak concentrations are at 90 hours (range: 71 to 123 hours).

When administered by IV administration, the terminal half-life of Aranesp® is approximately 3-fold longer than Epoetin alfa. The bioavailability of Aranesp® as measured in CRF patients after SC administration is 37% (range: 30% to 50%).

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 multicenter studies. Two studies evaluated the safety and efficacy of Aranesp® for the correction of anemia in adult patients with CRF, and two studies assessed the ability of Aranesp® to maintain hemoglobin concentrations in adult patients with CRF who had been receiving other recombinant erythropoietins.

De Novo Use of Aranesp®

In two open-label studies, Aranesp® or Epoetin alfa were 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 (predialysis patients). In both studies, the starting dose of Aranesp® was 0.45 mcg/kg administered once weekly. The starting dose of Epoetin alfa was 50 U/kg 3 times weekly in Study N1 and 50 U/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: General** for recommended clinical hemoglobin target.) The primary efficacy endpoint was the proportion of patients who experienced at least a 1.0 g/dL increase in hemoglobin concentration to a level of at least 11.0 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 1.10 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).

Conversion From Other Recombinant Erythropoietins

Two studies (N3 and N4) were conducted in adult patients with CRF who had been receiving other recombinant erythropoietins and compared the abilities of Aranesp® and other 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® (25th, 75th 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® (25th, 75th 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. Based on Kaplan-Meier estimates, the proportion of subjects surviving at 12 months after randomization was lower in the Epoetin alfa group than in the placebo group (70% vs 76%), p = 0.012, log rank. However, due to insufficient monitoring and data collection, reliable comparisons cannot be made concerning the effect of Epoetin alfa on overall time to disease progression, progression-free survival, and overall survival. Until further information is available, the recommended target hemoglobin should not exceed 12 g/dL in men or women.

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).

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**).

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.

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
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 (25th, 75th 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%
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.

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%

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 data described below reflect the exposure to Aranesp® in 873 cancer patients. 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 3**). Except for those events listed in Tables 3 and 4, 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 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%).

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. 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. ***In patients on hemodialysis, the IV 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.

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. **Do not pool unused portions from the vials or prefilled syringes. Do not use the vial or prefilled syringe 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 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 Vial/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 Syringe/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 Syringe/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
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AMGEN®

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AMGEN®

Aranesp®
(darbepoetin alfa)

Information for Patients

This patient package insert contains information and directions for those patients whose doctor has determined may receive injections of Aranesp® at home, and their caregivers. This patient package insert does not include all information about Aranesp®. You should discuss any questions about treatment with Aranesp® with your doctor.

What is Aranesp®?

Aranesp® (Air-uh-nesp) is a man made protein that acts like the natural protein human erythropoietin (ee-rith-row-po-eh-tin). Erythropoietin is a hormone, produced primarily by healthy kidneys, which stimulates the bone marrow to make oxygen-carrying red blood cells.

What is Aranesp® used for?

Aranesp® is used to treat anemia (a lower than normal number of red blood cells) in patients with kidney disease who may or may not be on dialysis. Aranesp® is also used to treat anemia in cancer patients when the anemia is due to the effects of chemotherapy.

People with anemia may feel tired or lack energy. Some people may also have shortness of breath, chest pain, and feel cold much of the time.

How does Aranesp® work?

When kidneys are not working properly, they cannot produce enough erythropoietin, so the body cannot make enough red blood cells. Also, some forms of chemotherapy may prevent cancer patients from producing enough red blood cells.

Aranesp® works by stimulating your bone marrow to make more red blood cells. An increase in the number of red blood cells may relieve the symptoms of anemia.

Your doctor will know when Aranesp® is working because your blood tests will show an increase in the number of red blood cells. Your doctor may refer to the results of your blood tests as hemoglobin and/or hematocrit, and your doctor will be checking these tests while you are being treated with Aranesp®. The increase in the number of red blood cells is not immediate; it may take several weeks. The amount of time it takes to reach the red blood cell level that is right for you, and the dose of Aranesp® needed to make the red blood cell level rise, is different for each person. You may need Aranesp® dose adjustments before you reach your correct dose of Aranesp® and the correct dose may change over time.

Who <u>should not take</u> Aranesp®?

- People with uncontrolled high blood pressure should not take Aranesp®.
- People who are allergic to Aranesp®, other erythropoietins, medicines made using mammalian cells, or any of the ingredients (for example, albumin or polysorbate 80) in Aranesp® should not take Aranesp®.

Talk to your doctor if you have any questions about this information.

What are the possible or reasonably likely side effects of Aranesp®?

Your blood pressure may increase when the number of red blood cells rises, so your doctor or caregiver may monitor your blood pressure more frequently. Some people have also had infections, fevers, headaches, muscle aches or soreness, nausea, diarrhea, leg swelling, or chest pain. If you experience any of these symptoms, you should call your doctor.

If you are on hemodialysis, there is a risk of blood clots forming at your vascular access. Call your doctor if you think your access is blocked.

Patients with cancer may have an increased risk of blood clots in the veins (thrombophlebitis) or the lungs (pulmonary embolus). **Call your doctor if you experience pain and/or swelling in the legs or worsening in shortness of breath.**

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

Some people experience redness, swelling, or itching at the site of injection. This reaction may be an allergy to the ingredients in Aranesp®, or it may be a local irritation. If you notice any signs of redness, swelling, or itching at the site of injection, talk to your doctor.

Serious allergic reactions can also happen. These reactions can cause a rash over the whole body, shortness of breath, wheezing, a drop in blood pressure, swelling around the mouth or eyes, fast pulse, or sweating. If at any time a serious allergic reaction occurs, **stop using Aranesp® and call your doctor or emergency medical personnel immediately (for example, call 911).**

What about pregnancy or breastfeeding?

Aranesp® has not been studied in pregnant women and its effects on developing babies are not known. It is also not known if Aranesp® can get into human breast milk. If you are pregnant, plan to become pregnant, or think you may be pregnant, or are breastfeeding, you should talk to your doctor before using Aranesp®.

What important information do I need to know about taking Aranesp® at home?

In some rare cases, your doctor may decide that you will be able to use Aranesp® at home. If your doctor has determined that you can safely use Aranesp® at home, you and/or your caregiver will receive instructions on how much Aranesp® to use, how to inject it, how often it should be injected, and how to dispose of the unused portions of each vial or prefilled syringe. Your doctor will decide whether you use Aranesp® in vials or prefilled syringes. **You should always follow your doctor's instructions.**

Too much Aranesp® may cause your body to produce too many red blood cells too fast (lead to a hemoglobin that is too high). Producing too many red blood cells, or producing them too fast may cause serious problems. It is important that your blood pressure be monitored often and to report any changes outside of the guidelines that your doctor has given you, especially if you have heart disease. In addition, symptoms of temporary confusion or seizures should be reported to your doctor immediately. Certain laboratory tests, such as hemoglobin, hematocrit, or iron level measurements, may also need to be done more often and be reported to your doctor or dialysis center.

Over time, many kidney disease patients also need to take iron. Your doctor will know when or if you need an iron supplement from your laboratory test results.

Do not change the dose of Aranesp®. You should ask your doctor what to do if you miss a dose of Aranesp®.

Be sure to change the site for each injection to avoid soreness at any one site. Occasionally a problem may develop at the injection site. If there is a lump, swelling, or bruising at the injection site that does not go away, talk to your doctor.

If you have a hemodialysis vascular access, continue to check the access to make sure it is working. Call your doctor or dialysis center right away if you have any problems or questions.

Always call your doctor if you do not feel well while using Aranesp®.

What do you and/or your caregiver need to do to prepare and give an injection of Aranesp®?

When you receive your Aranesp®, always check to see that:

- The name Aranesp® appears on the package and vial or prefilled syringe label.
- The expiration date on the vial or prefilled syringe label has not passed. **You should not use a vial or prefilled syringe after the date on the label.**
- The strength of the Aranesp® vial or prefilled syringe (number of micrograms [mcg] in the colored square on the package and on the vial or prefilled syringe label) is the same as the doctor prescribed.
- The Aranesp® liquid in the vial or prefilled syringe is clear and colorless. Do not use Aranesp® if the liquid in the vial or prefilled syringe appears discolored or cloudy or if the liquid appears to contain lumps, flakes, or particles.
- The Aranesp® vial has a color cap on the top of the vial. Do not use a vial of Aranesp® if the color cap on the top of the vial has been removed or is missing.
- Do not use Aranesp® in a prefilled syringe if the grey cover on the needle is off, or the needle guard (yellow sleeve on the syringe) has been activated (pulled to extend over the needle). If you are using a vial of Aranesp®, only use the type of disposable syringe that your doctor prescribes.

The doctor or nurse will give you instructions on how to measure your dose of Aranesp®. This dose will be measured in milliliters. You should only use a syringe that is marked in tenths of milliliters, or mL (for example, 0.2 mL). The doctor or nurse may refer to an "mL" as a "cc" (1 mL = 1 cc). Using an unmarked syringe can lead to a mistake in the dose. If you do not use the correct syringe, you could inject too much or too little Aranesp®.

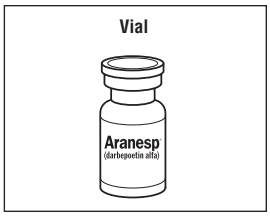
Only use disposable syringes and needles. Use the syringes and needles only once and dispose of them as instructed by your healthcare provider.

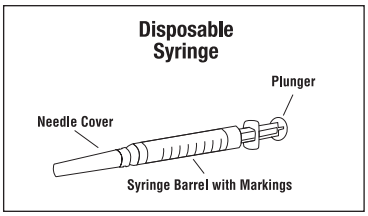
IMPORTANT: TO HELP AVOID POSSIBLE INFECTION, FOLLOW THESE INSTRUCTIONS.

<u>Setting up for an injection</u>

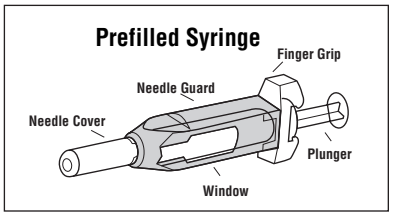
1. Find a clean, flat work surface such as a table.
2. If you are using a vial, remove a vial of Aranesp® from the refrigerator. If you are using a prefilled syringe, tear off one syringe (in wrapper) from the strip and place the others back in the refrigerator. Keep the syringe in its wrapper until you are ready to prepare your dose. Do not freeze Aranesp® or use a vial or prefilled syringe that has been frozen. Do not shake Aranesp® or leave vials or syringes exposed to bright light. Vigorous shaking or exposure to light may denature Aranesp® causing it to become biologically inactive.
3. Remove the vial or prefilled syringe of Aranesp® from its carton and place it on your flat work surface. Allow it to reach room temperature. This should take about 30 minutes. During this time, cover the vial or prefilled syringe to protect the solution from light.
4. You should use a vial or prefilled syringe only once. Do not put the needle through the rubber stopper more than once. DO NOT SHAKE THE VIAL OR PREFILLED SYRINGE. Shaking may damage the Aranesp®. If the Aranesp® vial or prefilled syringe has been shaken vigorously, the solution may appear foamy and it should not be used.

5. Assemble the supplies you will need for an injection:
   - Aranesp® vial and the correct disposable syringe and needle

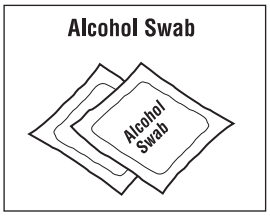


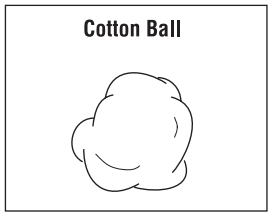


OR
- Aranesp® prefilled syringe with a transparent (clear) yellow plastic needle guard attached



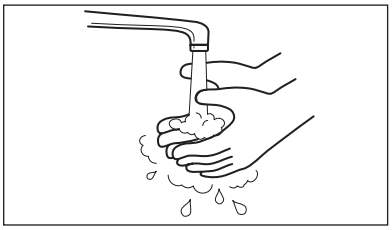
- Two alcohol swabs and one cotton ball or gauze. Open one alcohol wipe if you are using a prefilled syringe. Open two alcohol wipes if you are using a vial and disposable syringe.





- Puncture-proof disposal container

6. Wash your hands with soap and warm water.

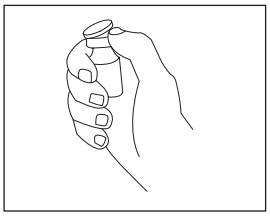


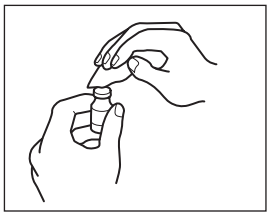
How to prepare the dose of Aranesp®

If you are using Aranesp® in a vial, follow the instructions in Section A. If you are using Aranesp® in a prefilled syringe, follow the instructions in Section B.

Section A. Preparing the dose of Aranesp® using a vial and disposable syringe

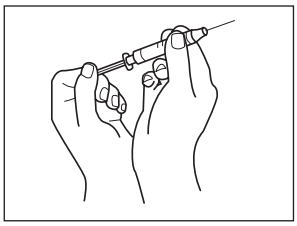
1. Take the color cap off the vial. Clean the rubber stopper with one alcohol swab.





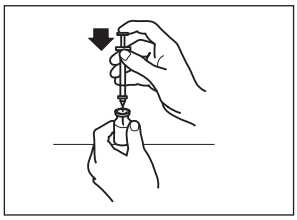
2. Check the package containing the syringe. If the package has been opened or damaged, do not use that syringe. You should dispose of that syringe in the puncture-proof disposal container. If the syringe package is undamaged, open the package and remove the syringe.

3. Pull the needle cover straight off the syringe. Then, pull back on the plunger to draw air into the syringe. The amount of air drawn into the syringe should be the same amount (mL or cc) as the dose of Aranesp® that your doctor prescribed.

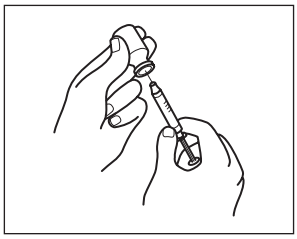


4. Keep the vial on your flat work surface and insert the needle straight down through the rubber stopper.

5. Push the plunger of the syringe down to inject the air from the syringe into the vial of Aranesp®.



6. Keeping the needle inside the vial, turn the vial upside down. Make sure that the tip of the needle is in the Aranesp® liquid.



7. Keeping the vial upside down, slowly pull back on the plunger to fill the syringe with Aranesp® liquid to the number (mL or cc) that matches the dose your doctor prescribed.
8. Keeping the needle in the vial, check for air bubbles in the syringe. If there are air bubbles, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe. Then slowly push the plunger up to force the air bubbles out of the syringe. Keep the tip of the needle in the liquid and once again pull the plunger back to the number on the syringe that matches your dose. Check again for air bubbles. The air in the syringe will not hurt you, but too large an air bubble can reduce your dose of Aranesp®. If there are still air bubbles, repeat the steps above to remove them.
9. Check again to make sure that you have the correct dose in the syringe. It is important that you use the exact dose prescribed by your doctor.
10. Lay the vial on its side with the needle still in it until after you have selected and prepared a site for injection. This will keep the needle from touching anything before you use it.

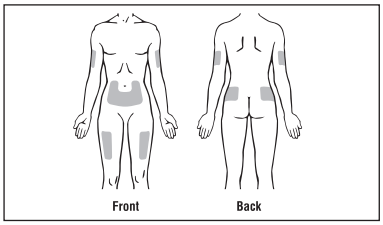
Go directly to the section "Selecting and preparing the injection site."

Section B. Preparing the dose of Aranesp® using a prefilled syringe

1. Open the package and remove the syringe from the tray. Check to see that the needle cover is on and the yellow needle guard is covering the barrel of the syringe. If the needle guard is covering the needle, then it has already been activated. DO NOT use that syringe. Dispose of that syringe in the puncture-proof disposal container. Use a new syringe. DO NOT slide the needle guard over the needle cover before injection. This will "activate" or lock the needle guard.
2. Hold the syringe with the needle pointing up to prevent the Aranesp® from leaking out of the needle. Carefully pull the needle cover straight off.
3. Still holding the syringe up, slowly push the plunger to the line on the syringe that matches the dose your doctor has prescribed.
4. Check the syringe for air bubbles. If there are air bubbles, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe. Slowly push the plunger up to force the air bubbles out of the syringe.
5. Check again to make sure that you have the correct dose in the syringe. It is important that you use the exact dose prescribed by your doctor.
6. When you put the syringe down on your working surface, be careful not to allow the needle to touch anything.

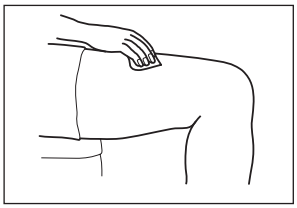
Selecting and preparing the injection site

1. Choose an injection site. Four recommended injection sites for Aranesp® include:
   - The outer area of the upper arms
   - The abdomen (except for the two-inch area around the navel)
   - The front of the middle thighs
   - The upper outer areas of the buttocks



Choose a new site each time you inject Aranesp®. Choosing a new site can help avoid soreness at any one site. Do not inject Aranesp® into an area that is tender, red, bruised, hard, or that has scars or stretch marks.

2. Clean the injection site with a new alcohol swab.

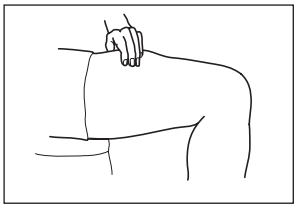


Injecting the dose of Aranesp® from a vial or prefilled syringe

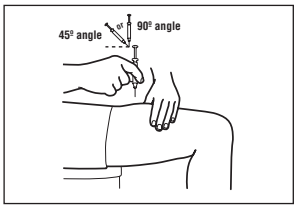
For patients not on hemodialysis:

1. Hold the syringe in the hand that you will use to inject Aranesp®. Use the other hand to pinch a fold of skin at the cleaned injection site.

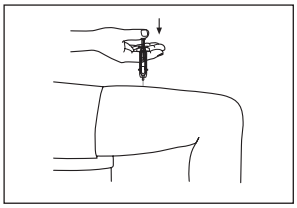
Note: If using a prefilled syringe with a needle guard, hold the syringe barrel through the two needle guard windows when giving the injection.



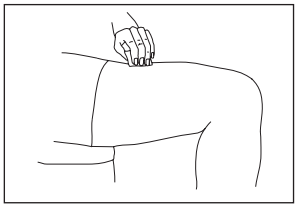
2. Holding the syringe like a pencil, use a quick "dart like" motion to insert the needle either straight up and down (90 degree angle) or at a slight angle (45 degrees) into the skin.



3. After the needle is inserted, let go of the skin. Pull the plunger back slightly. If no blood appears, slowly push the plunger all the way down, until all the Aranesp® is injected. If blood comes into the syringe, do not inject Aranesp® because the needle has entered a blood vessel. Withdraw the syringe and discard it in the puncture-proof disposal container. Repeat the steps to choose and clean a new injection site and prepare a new syringe. Remember to check again for blood before injecting Aranesp®.



4. When the syringe is empty, pull the needle out of the skin and place a cotton ball or gauze over the injection site and press for several seconds.



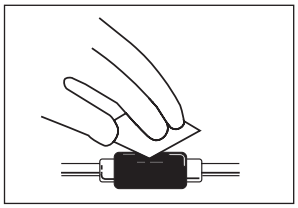
5. You should ONLY use a disposable syringe and Aranesp® vial or prefilled syringe once. You should discard the disposable syringe and vial or prefilled syringe with any remaining Aranesp®.

If a prefilled syringe was used, go directly to the section "Activation of the needle guard on used prefilled syringes."

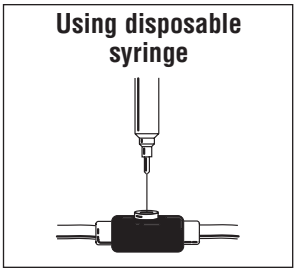
If a disposable syringe was used with a vial of Aranesp®, go directly to the section "Disposal of syringes and needles."

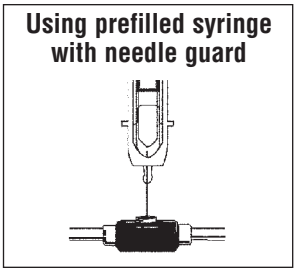
For patients on hemodialysis:

1. Clean the venous port of the hemodialysis tubing with a new alcohol swab.



2. Insert the needle of the syringe into the cleaned venous port and push the plunger all the way down to inject all the Aranesp®.



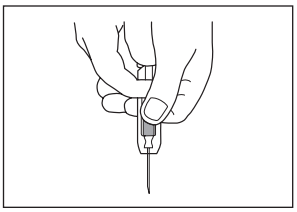


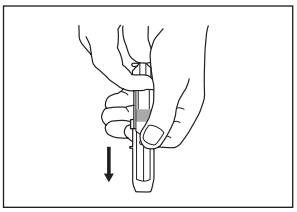
Remove the syringe from the venous port.

If a disposable syringe was used with a vial of Aranesp®, go directly to the section "Disposal of syringes and needles".

Activation of the needle guard on used prefilled syringes

1. After injecting Aranesp® from the prefilled syringe, do not recap the needle. Keep your hands behind the needle at all times. To activate the needle guard, hold the finger grip of the syringe with one hand and grasp the needle guard with your free hand, sliding it completely over the needle until the needle guard clicks into place. **NOTE: If an audible click is not heard, the needle guard may not be completely activated.**





Disposal of syringes and needles

Dispose of the syringe and needle or the syringe with activated needle guard as instructed by your healthcare provider, or by following these steps:

- Do not throw the needle or syringe in the household trash or recycle.
- DO NOT put the needle cover back on the needle. Place the used needle, needle cover, and syringe in a hard plastic disposal container with a screw-on cap or a metal container with a plastic lid, such as a coffee can, labeled "used syringes." If a metal container is used, cut a small hole in the plastic lid and tape the lid to the metal container. If a hard plastic container is used, always screw the cap on tightly after each use.
- Do not use glass or clear plastic containers.
- When the container is full, tape around the cap or lid to make sure the cap or lid does not come off.
- **Always** keep the container out of the reach of children.
- You should always check first with your healthcare provider for instructions on how to properly dispose of a filled disposal container. There may be special state and local laws for disposing of used needles and syringes. **Do not throw the disposal container in household trash. Do not recycle.**

How should Aranesp® be stored?

Aranesp® should be kept in its original carton to protect it from light, and stored in the refrigerator at 2° to 8°C (36° to 46°F). Do not place Aranesp® in the freezer. Do not use a vial or prefilled syringe of Aranesp® that has been frozen, left in light, or improperly refrigerated. It is important that Aranesp® be stored and used as stated in these instructions. Contact your healthcare provider with any questions about storage.

When traveling, transport Aranesp® in its original carton in an insulated container with a coolant such as blue ice. To avoid freezing, make sure the Aranesp® vial or prefilled syringe does not touch the coolant. Once you arrive, your Aranesp® should be placed in a refrigerator as soon as possible.

AMGEN®

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