

Pediatric Patients

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

CLINICAL STUDIES

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

Chronic Renal Failure Patients

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

De Novo Use of Aranesp[®]

In two open-label studies, Aranesp[®] or Epoetin alfa was administered for the correction of anemia in CRF patients who had not been receiving prior treatment with exogenous erythropoietin. Study N1 evaluated CRF patients receiving dialysis; Study N2 evaluated patients not requiring dialysis (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** 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 adult studies (N3 and N4) and one pediatric study (N5) were conducted in patients with CRF who had been receiving other recombinant erythropoietins. The studies compared the abilities of Aranesp[®] and other erythropoietins to maintain hemoglobin concentrations within a study target range of 9 to 13 g/dL in adults and 10 to 12.5 g/dL in pediatric patients. (Note: The recommended hemoglobin target is lower than the target range of these studies. See **DOSAGE AND ADMINISTRATION** for recommended clinical hemoglobin target.) CRF patients who had been receiving stable doses of other recombinant erythropoietins were randomized to Aranesp[®], or to continue with their prior erythropoietin at the previous dose and schedule. For patients randomized to Aranesp[®], the initial weekly dose was determined on the basis of the previous total weekly dose of recombinant erythropoietin.

FDA APPROVED: 12-17-07

Aranesp[®]
(darbepoetin alfa)
For Injection

WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR and THROMBOEMBOLIC EVENTS, and TUMOR PROGRESSION

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

Cancer:

- ESAs shortened overall survival and/or time-to-tumor progression in clinical studies in patients with advanced breast, head and neck, lymphoid, and non-small cell lung malignancies when dosed to target a hemoglobin of ≥ 12 g/dL.
- The risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to target a hemoglobin of < 12 g/dL.
- To minimize these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusions.
- Use only for treatment of anemia due to concomitant myelosuppressive chemotherapy.
- Discontinue following the completion of a chemotherapy course.

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

DESCRIPTION

Aranesp[®] is an erythropoiesis stimulating protein, closely related to erythropoietin, that is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Aranesp[®] is a 165-amino acid protein that differs from recombinant human erythropoietin in containing 5 N-linked oligosaccharide chains, whereas recombinant human erythropoietin contains 3 chains.¹ The two additional N-glycosylation sites result from amino acid substitutions in the erythropoietin peptide backbone. The additional carbohydrate chains increase the approximate molecular weight of the glycoprotein from 30,000 to 37,000 daltons. Aranesp[®] is formulated as a sterile, colorless, preservative-free protein solution for intravenous (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 and prefilled SureClick[™] autoinjectors are available containing 25, 40, 60, 100, 150, 200, 300, or 500 mcg of Aranesp[®]. Each prefilled syringe is equipped with a needle guard that covers the needle during disposal.

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

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

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

CLINICAL PHARMACOLOGY

Mechanism of Action

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

Pharmacokinetics

Adult Patients

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

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

Following subcutaneous (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). Peak concentrations occurred at 34 hours (range: 24 to 72 hours). The bioavailability of Aranesp[®] as measured in CRF patients after SC administration was 37% (range: 30% to 50%).

Following the first SC dose of 6.75 mcg/kg (equivalent to 500 mcg for a 74-kg patient) in patients with cancer, the mean terminal half-life was 74 hours (range: 24 to 144 hours). Peak concentrations were observed at 90 hours (range: 71 to 123 hours) after a dose of 2.25 mcg/kg, and 71 hours (range: 28 to 120 hours) after a dose of 6.75 mcg/kg. When administered on a once-every-3-week (Q3W) schedule, 48-hour post-dose Aranesp[®] levels after the fourth dose were similar to those after the first dose.

Over the dose range of 0.45 to 4.5 mcg/kg Aranesp[®] administered IV or SC on a once-weekly (QW) schedule and 4.5 to 15 mcg/kg administered SC on a Q3W schedule, systemic exposure was approximately proportional to dose. No evidence of accumulation was observed beyond an expected < 2-fold increase in blood levels when compared to the initial dose.

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Adult Patients

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.

Pediatric Patients

Study N5 was an open-label, randomized study, conducted in the United States in pediatric patients from 1 to 18 years of age with CRF receiving or not receiving dialysis. Patients that were stable on Epoetin alfa were randomized to receive either darbepoetin alfa (n = 82) administered once weekly (SC or IV) or to continue receiving Epoetin alfa (n = 42) at the current dose, schedule, and route of administration. A median weekly dose of 0.41 mcg/kg Aranesp® (25th, 75th percentiles: 0.25, 0.82 mcg/kg) was required to maintain hemoglobin in the study target range.

Cancer Patients Receiving Chemotherapy

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

Once-Weekly (QW) Dosing

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

Efficacy was determined by a reduction in the proportion of patients who were transfused over the 12-week treatment period. A significantly lower proportion of patients in the Aranesp® arm, 26% (95% CI: 20%, 33%) required transfusion compared to 60% (95% CI: 52%, 68%) in the placebo arm (Kaplan-Meier estimate of proportion; p < 0.001 by Cochran-Mantel-Haenszel test). Of the 67 patients who received a dose increase, 28% had a 2 g/dL increase in hemoglobin over baseline, generally occurring between weeks 8 to 13. Of the 89 patients who did not receive a dose increase, 69% had a 2 g/dL increase in hemoglobin over baseline, generally occurring between weeks 6 to 13. On-study deaths occurred in 14% (22/156) of patients treated with Aranesp® and 12% (19/158) of the placebo-treated patients.

Once-Every-3-Week (Q3W) Dosing

The safety and effectiveness of Q3W Aranesp[®] therapy in reducing the requirement for red blood cell (RBC) transfusions in patients undergoing chemotherapy was assessed in a randomized, double-blind, multinational study (C2). This study was conducted in anemic (Hgb < 11 g/dL) patients with non-myeloid malignancies receiving multicycle chemotherapy. Patients were randomized to receive Aranesp[®] at 500 mcg Q3W (n = 353) or 2.25 mcg/kg (n = 352) administered weekly as a SC injection for up to 15 weeks. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 mcg in the Q3W group and 1.35 mcg/kg in the QW group) if hemoglobin increased by more than 1 g/dL in a 14-day period. Study drug was withheld if hemoglobin exceeded 13 g/dL. In the Q3W group, 254 patients (72%) required dose reductions (median time to first reduction at 6 weeks). In the QW group, 263 patients (75%) required dose reductions (median time to first reduction at 5 weeks).

Efficacy was determined by a comparison of the Kaplan-Meier estimates of the proportion of patients who received at least one RBC transfusion between day 29 and the end of treatment. Three hundred thirty-five patients in the Q3W group and 337 patients in the QW group remained on study through or beyond day 29 and were evaluated for efficacy. Twenty-seven percent (95% CI: 22%, 32%) of patients in the Q3W group and 34% (95% CI: 29%, 39%) in the weekly group required a RBC transfusion. The observed difference in the transfusion rates (Q3W-QW) was -6.7% (95% CI: -13.8%, 0.4%).

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.
- in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. Aranesp[®] use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being. Aranesp[®] is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy.

CONTRAINDICATIONS

Aranesp[®] is contraindicated in patients with:

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

WARNINGS

Increased Mortality, Serious Cardiovascular and Thromboembolic Events

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

In a randomized prospective trial, 1432 anemic chronic renal failure patients who were not undergoing dialysis were assigned to Epoetin alfa (rHuEPO) treatment targeting a maintenance hemoglobin concentration of 13.5 g/dL or 11.3 g/dL. A major cardiovascular event (death, myocardial infarction, stroke, or hospitalization for congestive heart failure) occurred among 125 (18%) of the 715 patients in

the higher hemoglobin group compared to 97 (14%) among the 717 patients in the lower hemoglobin group [Hazard Ratio (HR) 1.3, 95% CI: 1.0, 1.7, p = 0.03].²

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

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

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

A systematic review of 57 randomized controlled trials (including Cancer Studies 1 and 3 - the 'BEST' and 'ENHANCE' studies) evaluating 9353 patients with cancer compared ESAs plus RBC transfusion with RBC transfusion alone for prophylaxis or treatment of anemia in cancer patients with or without concurrent antineoplastic therapy. An increased relative risk (RR) of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06; 35 trials and 6769 patients) was observed in ESA-treated patients. An overall survival hazard ratio of 1.08 (95% CI: 0.99, 1.18; 42 trials and 8167 patients) was observed in ESA-treated patients.⁵

An increased incidence of deep vein thrombosis (DVT) in patients receiving Epoetin alfa undergoing surgical orthopedic procedures has been observed. In a randomized controlled study (referred to as the 'SPINE' study), 681 adult patients, not receiving prophylactic anticoagulation and undergoing spinal surgery, received Epoetin alfa and standard of care (SOC) treatment, or SOC treatment alone. Preliminary analysis showed a higher incidence of DVT, determined by either Color Flow Duplex Imaging or by clinical symptoms, in the Epoetin alfa group [16 patients (4.7%)] compared to the SOC group [7 patients (2.1%)]. In addition, 12 patients in the Epoetin alfa group and 7 patients in the SOC group had other thrombotic vascular events.

Increased mortality was observed in a randomized placebo-controlled study of Epoetin alfa in adult patients who were undergoing coronary artery bypass surgery (7 deaths in 126 patients randomized to Epoetin alfa versus no deaths among 56 patients receiving placebo). Four of these deaths occurred during the period of study drug administration and all four deaths were associated with thrombotic events.

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

Increased Mortality and/or Tumor Progression

Erythropoiesis-stimulating agents, when administered to target a hemoglobin of > 12 g/dL, shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy [Cancer Studies 3 and 4 (DAHANCA 10) in Table 1]. ESAs also shortened survival in patients with metastatic breast cancer (Cancer Study 1) and in patients with lymphoid malignancy (Cancer Study 2) receiving chemotherapy when administered to target a hemoglobin of \geq 12 g/dL. In addition, ESAs shortened survival in patients with non-small cell lung cancer and in a study enrolling patients with various malignancies who were not receiving chemotherapy or radiotherapy; in these two studies, ESAs were administered to target a hemoglobin of \geq 12 g/dL (Cancer Studies 5 and 6 in Table 1). Although studies evaluated hemoglobin targets of \geq 12 g/dL in these tumor types, the risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to target a hemoglobin of < 12 g/dL.

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

Study / Tumor / (n)	Hemoglobin Target	Achieved Hemoglobin (Median Q1,Q3)	Primary Endpoint	Adverse Outcome for ESA-containing Arm
Chemotherapy				
Cancer Study 1 Metastatic breast cancer (n=939)	12-14 g/dL	12.9 g/dL 12.2, 13.3 g/dL	12-month overall survival	Decreased 12-month survival
Cancer Study 2 Lymphoid malignancy (n=344)	13-15 g/dL (M) 13-14 g/dL (F)	11.0 g/dL 9.8, 12.1 g/dL	Proportion of patients achieving a hemoglobin response	Decreased overall survival
Radiotherapy Alone				
Cancer Study 3 Head and neck cancer (n=351)	\geq 15 g/dL (M) \geq 14 g/dL (F)	Not available	Locoregional progression-free survival	Decreased 5-year locoregional progression-free survival Decreased overall survival
Cancer Study 4 Head and neck cancer (n=522)	14-15.5 g/dL	Not available	Locoregional disease control	Decreased locoregional disease control
No Chemotherapy or Radiotherapy				
Cancer Study 5 Non-small cell lung cancer (n=70)	12-14 g/dL	Not available	Quality of life	Decreased overall survival
Cancer Study 6 Non-myeloid malignancy (n=989)	12-13 g/dL	10.6 g/dL 9.4, 11.8 g/dL	RBC transfusions	Decreased overall survival

Decreased overall survival:

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

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

Cancer Study 5 was a Phase 3, multicenter, randomized (Epoetin alfa vs. placebo), double-blind study, in which patients with advanced non-small cell lung cancer receiving only palliative radiotherapy or no active therapy were treated with Epoetin alfa to achieve and maintain hemoglobin levels between 12 and 14 g/dL. Following an interim analysis of 70 of 300 patients planned, a significant difference in survival in favor of the patients on the placebo arm of the trial was observed (median survival 63 vs. 129 days; HR 1.84; $p = 0.04$).

Cancer Study 6 was a Phase 3, double-blind, randomized (Aranesp[®] vs. placebo), 16-week study in 989 anemic patients with active malignant disease, neither receiving nor planning to receive chemotherapy or radiation therapy. There was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions. The median survival was shorter in the Aranesp[®] treatment group (8 months) compared with the placebo group (10.8 months); HR 1.30, 95% CI: 1.07, 1.57.

Decreased locoregional progression-free survival and overall survival:

Cancer Study 3 (the 'ENHANCE' study) was a randomized controlled study in 351 head and neck cancer patients where Epoetin beta or placebo was administered to achieve target hemoglobins of 14 and 15 g/dL for women and men, respectively. Locoregional progression-free survival was significantly shorter in patients receiving Epoetin beta (HR 1.62, 95% CI: 1.22, 2.14, $p = 0.0008$) with a median of 406 days Epoetin beta vs. 745 days placebo. Overall survival was significantly shorter in patients receiving Epoetin beta (HR 1.39, 95% CI: 1.05, 1.84; $p = 0.02$).

Decreased locoregional control:

Cancer Study 4 (DAHANCA 10) was conducted in 522 patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy randomized to Aranesp[®] with radiotherapy or radiotherapy alone. An interim analysis on 484 patients demonstrated that locoregional control at 5 years was significantly shorter in patients receiving Aranesp[®] (RR 1.44, 95% CI: 1.06, 1.96; $p = 0.02$). Overall survival was shorter in patients receiving Aranesp[®] (RR 1.28, 95% CI: 0.98, 1.68; $p = 0.08$).

Hypertension

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

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

Seizures

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

Pure Red Cell Aplasia

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

Albumin (Human)

Aranesp[®] is supplied in two formulations with different excipients, one containing polysorbate 80 and another containing albumin (human), a derivative of human blood (see **DESCRIPTION**). Based on effective donor screening and product manufacturing processes, Aranesp[®] formulated with albumin carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS

General

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

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

Lack or Loss of Response to Aranesp®

A lack of response or failure to maintain a hemoglobin response with Aranesp® doses within the recommended dosing range should prompt a search for causative factors. Deficiencies of folic acid, iron, or vitamin B₁₂ should be excluded or corrected. Depending on the clinical setting, intercurrent infections, inflammatory or malignant processes, osteofibrosis cystica, occult blood loss, hemolysis, severe aluminum toxicity, and bone marrow fibrosis may compromise an erythropoietic response. In the absence of another etiology, the patient should be evaluated for evidence of PRCA and sera should be tested for the presence of antibodies to erythropoietin (see **WARNINGS: Pure Red Cell Aplasia**). See **DOSAGE AND ADMINISTRATION: Chronic Renal Failure Patients, Dose Adjustment** for management of patients with an insufficient hemoglobin response to Aranesp® therapy.

Hematology

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

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

Allergic Reactions

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

Patients with CRF Not Requiring Dialysis

Patients with CRF not yet requiring dialysis may require lower maintenance doses of Aranesp® than patients receiving dialysis. Though 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.

Laboratory Tests

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

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

Information for Patients

Patients should be informed of the increased risks of mortality, serious cardiovascular events, thromboembolic events, and tumor progression when used in off-label dose regimens or populations (see

WARNINGS). Patients should be informed of the possible side effects of Aranesp[®] and be instructed to report them to the prescribing physician. Patients should be informed of the signs and symptoms of allergic drug reactions and be advised of appropriate actions. Patients should be counseled on the importance of compliance with their Aranesp[®] treatment, dietary and dialysis prescriptions, and the importance of judicious monitoring of blood pressure and hemoglobin concentration should be stressed.

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

Drug Interactions

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

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

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

Pregnancy Category C

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

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

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

Nursing Mothers

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

Pediatric Use

Pediatric CRF Patients

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

Pediatric Cancer Patients

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

Geriatric Use

Of the 1598 CRF patients in clinical studies of Aranesp[®], 42% were age 65 and over, while 15% were age 75 and over. Of the 873 cancer patients in clinical studies receiving Aranesp[®] and concomitant chemotherapy, 45% were age 65 and over, while 14% were age 75 and over. No overall differences in safety or efficacy were observed between older and younger patients.

ADVERSE REACTIONS

General

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

Immunogenicity

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

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

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

Chronic Renal Failure Patients

Adult Patients

In all studies, the most frequently reported serious adverse 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: Increased Mortality, Serious Cardiovascular and Thromboembolic Events 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 2 reflect those adverse events occurring in at least 5% of patients treated with Aranesp[®].

Table 2. Adverse Events Occurring in \geq 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 2. 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.

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

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

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

Pediatric Patients

In Study N5, Aranesp® was administered to 81 pediatric CRF patients who had stable hemoglobin concentrations while previously receiving Epoetin alfa (see **CLINICAL STUDIES**). In this study, the most frequently reported serious adverse reactions with Aranesp® were fever and dialysis access infection. The most commonly reported adverse reactions were fever, headache, upper respiratory infection, hypertension, hypotension, injection site pain, and cough. Aranesp® administration was discontinued because of injection site pain in two patients and moderate hypertension in a third patient.

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

Thrombotic Events

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

Cancer Patients Receiving Chemotherapy

The incidence data described below reflect the exposure to Aranesp® in 873 cancer patients including patients exposed to Aranesp® QW (547, 63%), Q2W (128, 16%), and Q3W (198, 23%). Aranesp® was evaluated in seven studies that were active-controlled and/or placebo-controlled studies of up to 6 months duration. The Aranesp®-treated patient demographics were as follows: median age of 63 years (range of

20 to 91 years); 40% male; 88% Caucasian, 5% Hispanic, 4% Black, and 3% Asian. Over 90% of patients had locally advanced or metastatic cancer, with the remainder having early stage disease. Patients with solid tumors (e.g., lung, breast, colon, ovarian cancers) and lymphoproliferative malignancies (e.g., lymphoma, multiple myeloma) were enrolled in the clinical studies. All of the 873 Aranesp[®]-treated subjects also received concomitant cyclic chemotherapy.

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

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

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

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

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

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

^b Thrombosis includes: Thrombophlebitis, Thrombophlebitis Deep, Thrombosis Venous, Thrombosis Venous Deep, Thromboembolism, and Thrombosis.

In a randomized controlled trial of Aranesp® 500 mcg Q3W (n = 353) and Aranesp® 2.25 mcg/kg QW (n = 352), the incidences of all adverse events and of serious adverse events were similar between the two groups.

Thrombotic and Cardiovascular Events

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

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

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

Chronic Renal Failure Patients

Aranesp[®] 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. During therapy, hematological parameters should be monitored regularly. Doses must be individualized to ensure that hemoglobin is maintained at an appropriate level for each patient.

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

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

Starting Dose

Correction of Anemia

The recommended starting dose of Aranesp[®] for the correction of anemia in adult CRF patients is 0.45 mcg/kg body weight, administered as a single IV or SC injection once weekly. If hemoglobin excursions outside the recommended range occur, the Aranesp[®] dose should be adjusted as described below.

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

Maintenance Dose

The dose should be individualized to maintain hemoglobin levels within the range of 10 to 12 g/dL (see **Dose Adjustment**). If hemoglobin excursions outside the recommended range occur, the Aranesp[®] dose should be adjusted as described below. For many patients, the appropriate maintenance dose will be lower than the starting dose. Predialysis patients, in particular, may require lower maintenance doses. Some patients have been treated successfully with a SC dose of Aranesp[®] administered once every 2 weeks.

Dose Adjustment

The dose should be adjusted for each patient to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL. If hemoglobin excursions outside the recommended range occur, the Aranesp[®] dose should be adjusted as described below.

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

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

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

- do not administer higher Aranesp[®] doses and use the lowest dose that will maintain a hemoglobin level sufficient to avoid the need for recurrent RBC transfusions,
- evaluate and treat for other causes of anemia (see **PRECAUTIONS: Lack or Loss of Response to Aranesp[®]**), and
- thereafter, hemoglobin should continue to be monitored and if responsiveness improves, Aranesp[®] dose adjustments should be made as described above; discontinue Aranesp[®] if responsiveness does not improve and the patient needs recurrent RBC transfusions.

Conversion From Epoetin alfa to Aranesp[®]

The starting weekly dose of Aranesp[®] for adults and pediatric patients should be estimated on the basis of the weekly Epoetin alfa dose at the time of substitution (see **Table 6**). For pediatric patients receiving a weekly Epoetin alfa dose of < 1500 units/week, the available data are insufficient to determine an Aranesp[®] conversion dose. Because of variability, doses should be titrated to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL. Due to the longer serum half-life, Aranesp[®] should be administered less frequently than Epoetin alfa. Aranesp[®] should be administered once a week if a patient was receiving Epoetin alfa 2 to 3 times weekly. Aranesp[®] should be administered once every 2 weeks if a patient was receiving Epoetin alfa once per week. The route of administration (IV or SC) should be maintained.

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

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

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

Cancer Patients Receiving Chemotherapy

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

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

The recommended starting dose for Aranesp[®] administered once-every-3-weeks (Q3W) is 500 mcg as a SC injection.

For both dosing schedules, the dose should be adjusted for each patient to maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed the upper safety limit of 12 g/dL. If the rate of hemoglobin increase is more than 1 g/dL per 2-week period or when the hemoglobin reaches a level needed to avoid transfusion, the dose should be reduced by 40% of the previous dose. If the hemoglobin exceeds 12 g/dL, Aranesp[®] should be temporarily withheld until the hemoglobin approaches a level where transfusions may be required. At this point, therapy should be reinitiated at a dose 40% below the previous dose.

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

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

Preparation and Administration of Aranesp[®]

Do not shake Aranesp[®] or leave vials, syringes, or prefilled SureClick[™] autoinjectors exposed to bright light. After removing the vials, prefilled syringes, or autoinjectors 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, prefilled syringes, or autoinjectors of Aranesp[®] in their carton until use.

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

Do not dilute Aranesp[®].

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

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

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

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

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

See the accompanying "Information for Patients" leaflet for complete instructions on the preparation and administration of Aranesp[®] for patients, including injection site selection.

HOW SUPPLIED

Aranesp[®] is available in single-dose vials in two solutions, an albumin solution and a polysorbate solution. The words "Albumin Free" appear on the polysorbate container labels and the package main panels as

well as other panels as space permits. Aranesp® single-dose prefilled syringes and prefilled SureClick™ autoinjectors are available in albumin and polysorbate solutions. Both prefilled syringes and autoinjectors are supplied with a 27-gauge, ½-inch needle.

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

Aranesp® is available in the following packages:

Single-dose Vial, Polysorbate Solution

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

Single-dose Vial, Albumin Solution

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

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

1 Syringe/Pack, 4 Packs/Case	4 Syringes/Pack, 4 Packs/Case	4 Syringes/Pack, 10 Packs/Case
200 mcg/0.4 mL (NDC 55513-028-01)	200 mcg/0.4 mL (NDC 55513-028-04)	25 mcg/0.42 mL (NDC 55513-057-04)
300 mcg/0.6 mL (NDC 55513-111-01)	300 mcg/0.6 mL (NDC 55513-111-04)	40 mcg/0.4 mL (NDC 55513-021-04)
500 mcg/1 mL (NDC 55513-032-01)		60 mcg/0.3 mL (NDC 55513-023-04)
		100 mcg/0.5 mL (NDC 55513-025-04)
		150 mcg/0.3 mL (NDC 55513-027-04)

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

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

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

1 Autoinjector/Pack

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

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

60 mcg/0.3 mL
(NDC 55513-092-01)

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

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

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

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

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

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

1 Autoinjector/Pack

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

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

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

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

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

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

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

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

Storage

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

REFERENCES

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

Rx only

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

AMGEN®

Manufactured by:

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

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v - Issue Date:

Patient Information
Aranesp® (Air-uh-nesp)
darbepoetin alfa
Single-use Prefilled SureClick™ Autoinjector

This patient package insert contains information and directions for patients (and their caregivers) whose doctor has determined that they may receive injections of Aranesp® (Air-uh-nesp) at home. Please read it carefully. This patient package insert does not include all information about Aranesp® and does not replace talking with your doctor. You should discuss any questions about treatment with Aranesp® with your doctor. Only your doctor can prescribe Aranesp® and determine if it is right for you.

What is the most important information I should know about Aranesp®?

Aranesp® can cause serious side effects:

Chronic kidney failure patients:

- If your hemoglobin is kept too high, you have an increased chance of heart attack, stroke, heart failure, blood clots, and death. Your doctor should try to keep your hemoglobin between 10 and 12 g/dL.

Cancer patients:

- You may have an increased chance of dying sooner or your tumor (cancer) may grow faster if you take this drug.
- Your doctor should use the lowest dose of Aranesp® needed to help you avoid red blood cell transfusions.
- Once you have completed your chemotherapy course, Aranesp® treatment should be stopped.

All patients:

- Aranesp® treatment increases your chance of a blood clot. If you are scheduled for surgery, your doctor may prescribe a blood thinner to prevent blood clots.
- Blood clots can form at your vascular access if you are receiving hemodialysis. Call your doctor or dialysis center if you think your access is blocked.
- Blood clots can form in blood vessels (veins) in your leg (venous thrombosis). Blood clots may move from the legs to the lungs and block the blood circulation in the lungs (pulmonary embolus).

Call your doctor right away if you experience any of the following symptoms of a blood clot, while taking Aranesp®:

- chest pain
- shortness of breath
- pain in the legs with or without swelling

You will be asked to have blood tests that will check the number of red blood cells your body is producing. The blood tests will see if Aranesp® is working and if your hemoglobin level is getting too high. Your doctor may refer to the results of your blood tests as hemoglobin and hematocrit. 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. It is important to keep all appointments for blood tests to allow your doctor to adjust the dosage of Aranesp® as needed.

Please also read “**What are the possible side effects of Aranesp®?**” below.

What is Aranesp®?

Aranesp® is a man-made form of the protein human erythropoietin (ee-rith-row-po-eh-tin). Aranesp® works by stimulating your bone marrow to make red blood cells. After two to six weeks of treatment, your red blood cell counts may increase.

Aranesp® may be used to treat your anemia (a lower than normal number of red blood cells) if it is caused by:

- chronic kidney failure (you may or may not be on dialysis)
- chemotherapy used to treat cancer

Aranesp® does not improve symptoms of anemia, quality of life, fatigue, or patient well-being for patients with cancer.

Before receiving Aranesp®, you should talk with your doctor about the benefits and risks of Aranesp®.

Who should not take Aranesp®?

You should not take Aranesp® if you have:

- High blood pressure that is not controlled (uncontrolled hypertension).
- Antibodies to Aranesp® or other erythropoietins.

Talk to your doctor if you are not sure if you have these conditions or if you have any questions about this information.

What should I tell my doctor before taking Aranesp®?

Tell your doctor about all your health conditions and all the medicines you take, including prescription and over-the-counter medicines, vitamins, supplements, and herbals. Be sure to tell your doctor if you have:

- Heart disease
- High blood pressure
- Any history of seizures or strokes
- Blood disorders (such as sickle cell anemia, blood clotting disorders)

Tell your doctor if you are:

- Pregnant or nursing
- Planning to become pregnant

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 pass into human breast milk.

Talk to your doctor if you are not sure if you have these conditions or if you have any questions about this information.

Your doctor may monitor your blood pressure and the amount of iron in your blood before you start Aranesp® and while you are taking Aranesp®. You or your caregiver may also be asked to monitor your blood pressure every day and to report any changes. When the number of red blood cells increases, your blood pressure may also increase, so your doctor may prescribe new or more blood pressure medicine. You may be asked to have certain blood tests, such as hemoglobin, hematocrit or blood iron levels. Also, your doctor may prescribe iron for you to take. Follow your doctor's orders.

What are other possible side effects of Aranesp®?

Aranesp® may cause serious side effects. See "What is the most important information I should know about Aranesp®?"

Other side effects of Aranesp® include:

- Increased blood pressure; your doctor or caregiver may monitor your blood pressure more frequently.
- Infections
- Cough
- Chest pain
- Antibodies against Aranesp® that can block or reduce your body's ability to make red blood cells. If you experience unusual tiredness and lack of energy, **call your doctor**.
- Redness, swelling, pain, or itching at the site of injection. If you notice any signs of redness, swelling, or itching at the site of injection, talk to your doctor.
- Serious allergic reactions. 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).**

The needle cover on the prefilled syringe contains a derivative of latex. If you know you are allergic to latex, talk to your healthcare provider before using Aranesp®.

The most common side effects you may have when taking Aranesp® are:

- Increased blood pressure
- Decreased blood pressure
- Body or muscle aches
- Headache
- Diarrhea
- Shortness of breath
- Swelling in your arms or legs
- Fever
- Nausea or vomiting
- Infections
- Chest pain

Some side effects are more common depending on the reasons for which you are taking Aranesp®. Talk to your doctor for more information about side effects. Make sure to report any side effects to your doctor.

Aranesp® has other side effects that are not listed here. For a complete list, talk to your doctor.

Call your doctor right away if:

- You take more than the amount prescribed.
- You are currently taking Aranesp® and experience any of these symptoms, which may be a sign of a serious problem:
 - Unusual tiredness and lack of energy
 - Redness, swelling, pain, or itching at the site of injection and spreading rash over the whole body, shortness of breath, wheezing, a drop in blood pressure, swelling around the mouth or eyes, fast pulse, or sweating
 - Convulsion, confusion, dizziness, loss of consciousness
 - Increased blood pressure, chest pain, irregular heartbeats
 - Stroke, chest pain, shortness of breath, or pain with or without swelling in the legs
 - Blood clots in your hemodialysis vascular access port

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

After your doctor has determined that you can safely use Aranesp[®] at home, you 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 used vial, prefilled syringe or autoinjector. Your doctor will decide whether to use Aranesp[®] in vials, prefilled syringes, or prefilled autoinjectors. Do not change the way you use Aranesp[®] (including the dose of Aranesp[®]) without consulting your doctor. You should ask your doctor what to do if you miss a dose of Aranesp[®]. **You should always follow your doctor's instructions.**

How should I store Aranesp[®]?

- Always keep the single-use prefilled SureClick[™] autoinjector in the original box to protect Aranesp[®] from light. Do not leave the autoinjector exposed to light longer than necessary to inject Aranesp[®].
- Keep Aranesp[®] inside the refrigerator at 2° to 8°C (36° to 46°F). **DO NOT FREEZE.**
- When traveling, transport Aranesp[®] in its original box in an insulated container with an ice pack. To avoid freezing, make sure the Aranesp[®] prefilled SureClick[™] autoinjector does not touch the ice pack. Once you arrive, your Aranesp[®] should be placed in a refrigerator as soon as possible.

Do not use a prefilled SureClick[™] autoinjector that has been frozen, improperly left in light, or improperly refrigerated. It is important that Aranesp[®] be stored and used as stated in these instructions. Contact your pharmacist or healthcare provider with any questions about storage.

How do I take Aranesp[®]?

This section contains information on how to give yourself an injection of Aranesp[®] using the single-use, prefilled SureClick[™] autoinjector. You will need to give yourself the injection into the tissue just under the skin. This is called a subcutaneous injection. It is important that you do not try to give yourself the injection unless you have received special training from your doctor or nurse. **If you are not sure about giving the injection or you have any questions, please ask your doctor or nurse for help.**

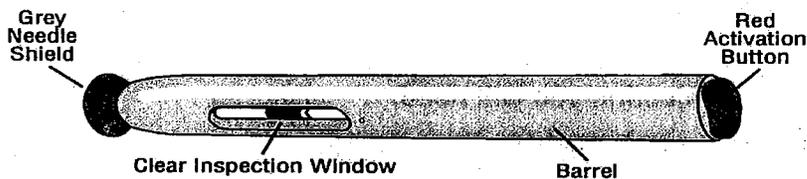
To give yourself a subcutaneous injection you will need:

- A new single-use Aranesp[®] prefilled SureClick[™] autoinjector
- Alcohol or sterile wipe
- A puncture-proof container so you can dispose of the used autoinjector safely

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

How do I prepare for an injection of Aranesp®?

1. Take your autoinjector out of the refrigerator. Keep the autoinjector in its box until you are ready to use it.
 - **Do not shake the autoinjector or leave exposed to bright light.** Vigorous shaking or exposure to light could cause the drug to become inactive. If the Aranesp® prefilled SureClick™ autoinjector has been shaken vigorously, the solution may appear foamy and it should not be used.
 - **Do not use an autoinjector that has been frozen, improperly left in light, or improperly refrigerated.**
2. Check that it is the correct dose that your doctor has prescribed.
3. Check the expiration date on the autoinjector label. **If the last day of the month shown has passed, do not use the autoinjector** and contact your pharmacist or healthcare provider for assistance.
4. Remove the autoinjector from the box. For a more comfortable injection, leave the autoinjector at room temperature for about 30 minutes. During this time, cover the autoinjector to protect the solution from light.
 - **Do not warm Aranesp®** in any other way (for example, do not warm it in a microwave or in hot water). **Do not** leave the autoinjector exposed to direct sunlight.
 - **Do not** remove the grey needle shield from the autoinjector until you are ready to inject.
 - **NEVER** put the grey needle shield back into the autoinjector.
5. Check the appearance of Aranesp® through the inspection window. It must be a clear and colorless liquid. **Do not inject the solution if it looks discolored or cloudy or contains lumps, flakes, or particles.** Contact your pharmacist or healthcare provider or call 1-866-55AMGEN for assistance.
6. **Wash your hands thoroughly.**
7. Find a comfortable, well-lit place and put everything you need where you can reach it (the autoinjector, alcohol or sterile wipe, and puncture-proof container).



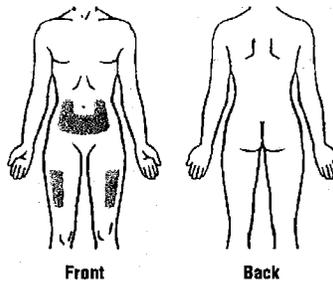
Where should I give my injection?

The recommended sites for injection using a single-use Aranesp® prefilled SureClick™ autoinjector are:

- The front center of thighs; and

- The back of the upper arms, only if someone else is injecting you

The abdomen can be considered when the thigh and back of arm are judged by your healthcare provider to be inappropriate.

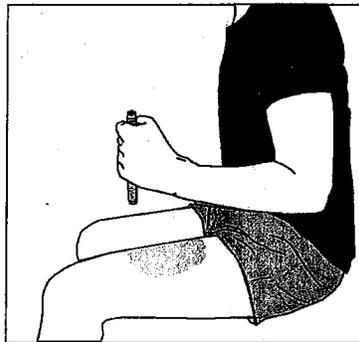


Be sure to change the site for each injection to avoid soreness at any one site.

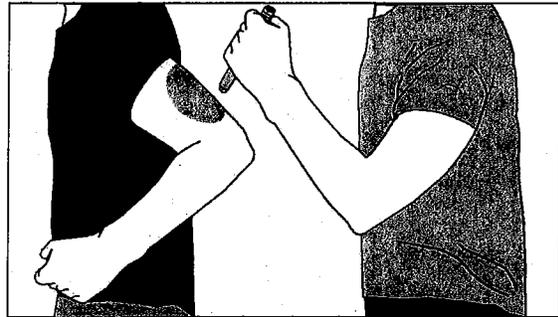
- Do not inject into areas where the skin is tender, bruised, red, or hard.
- Avoid areas with scars or stretch marks.

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.

How do I give an injection into the thigh or the back of the arm?



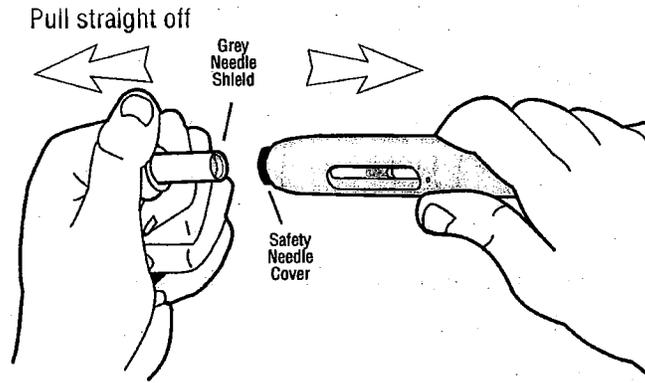
Do not pinch



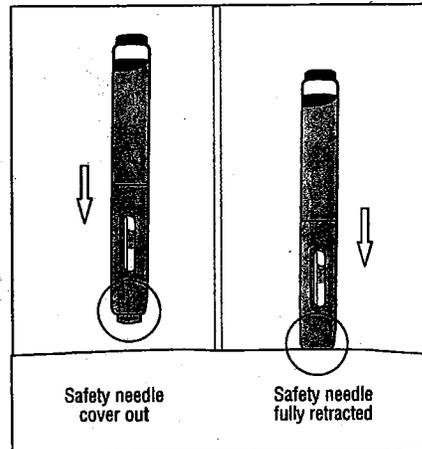
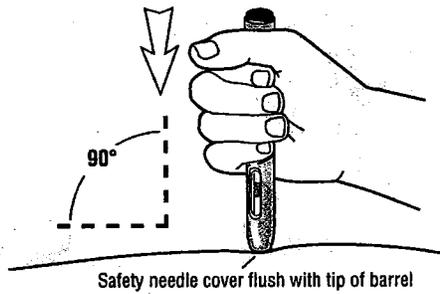
Do not pinch

1. Wipe the injection site with a new alcohol or sterile swab and allow your skin to dry. **Do not touch this area again before giving the injection.**

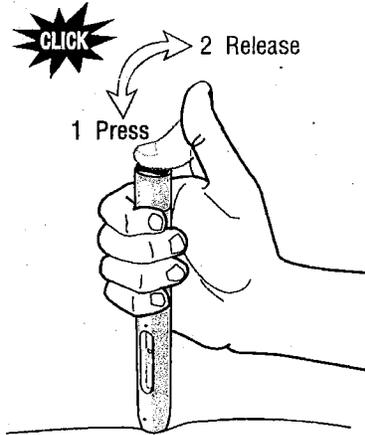
2. Pick up the prefilled SureClick™ autoinjector in one hand and smoothly remove the grey needle shield by pulling it straight off. Do not twist it off, and do not recap the grey needle shield, as either of these may damage the needle inside the autoinjector. The SureClick™ autoinjector has a cover that will protect you from needle sticks or loss of drug by accidental bumping or touching.



3. **Without** pressing the red activation button, place the open end of the autoinjector on the injection site, straight up at a right angle (90°) and push the safety needle cover firmly against the skin to unlock. **Continue to hold firmly against the skin.**

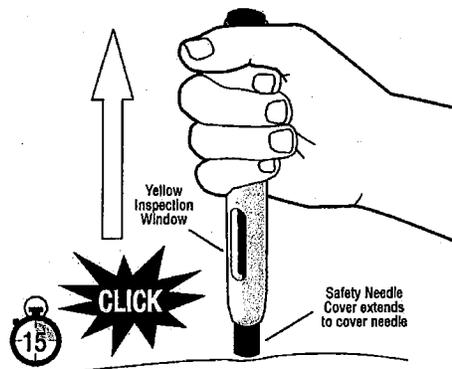


4. To start the injection, (1) press the red button (first click will sound) and (2) immediately release your thumb. This starts the injection. **Do not lift** the autoinjector off the skin.



5. **Wait until you hear the second 'click'.** Once you hear the second click, lift the autoinjector straight up from the injection site. The injection is finished. The safety needle cover on the autoinjector will automatically extend to cover the needle.

If you did not remove your thumb from the red button, the second 'click' cannot be heard. If this happens, slowly count to 15 before lifting the autoinjector from the injection site.

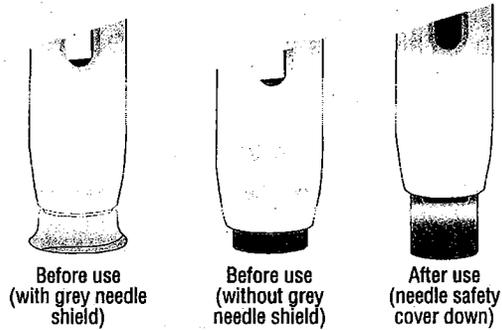


The needle safety cover will move down over the needle and lock into place. The inspection window will be yellow, confirming the injection is complete. Verify that the inspection window is yellow to ensure that the injection is complete before lifting the autoinjector. There is no need to replace the grey needle shield.

If the inspection window is not yellow, do not try to use the autoinjector again.

If you suspect you have not received the full dose, do not repeat the injection using a new autoinjector.

Call your healthcare provider or 1-866-55AMGEN for assistance.



If you notice a spot of blood at the injection site, dab away with a cotton ball or tissues. Do not rub the injection site. If needed, you may cover the injection site with a bandage.

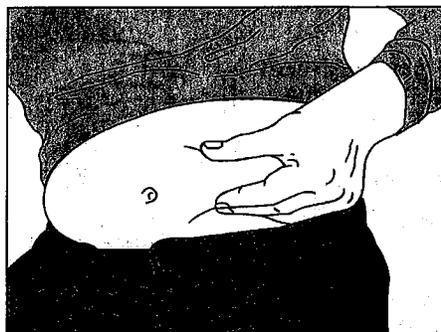
How do I inject into the abdomen?



Important skin pinch technique

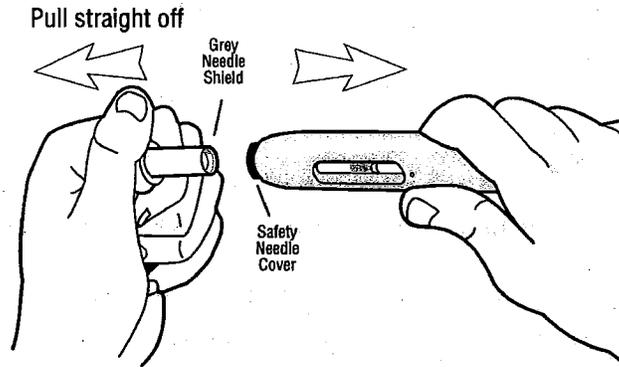
The objective of the skin pinch technique is to create a firm site for the injection.

- Choose a site at least 2 inches away from the belly button (navel).
- Pinch the skin of the abdomen **firmly** between the thumb and fingers creating a space at least 2 inches wide (twice the width of the tip of the autoinjector). It is important to maintain a firm skin pinch for the entire injection.



Pinch

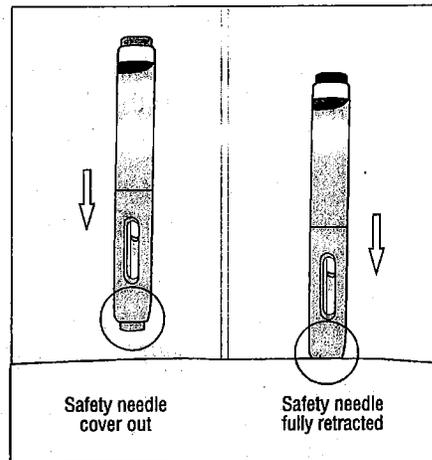
1. Wipe the injection site with a new alcohol or sterile swab and allow your skin to dry. **Do not touch this area again before giving the injection.**
2. Pick up the prefilled SureClick™ autoinjector in one hand and smoothly remove the grey needle shield by pulling it straight off. Do not twist it off, and do not recap the grey needle shield, as either of these may damage the needle inside the autoinjector. The SureClick™ autoinjector has a cover that will protect you from needle sticks or loss of drug by accidental bumping or touching.



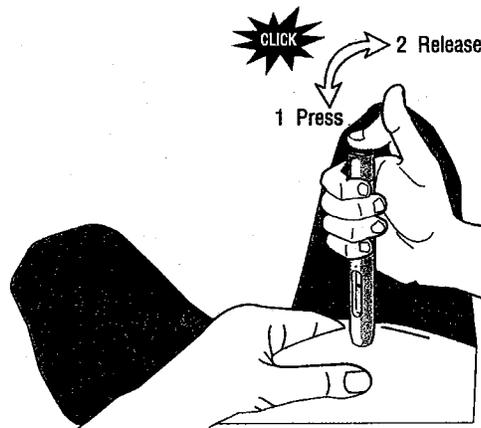
3. **Without** pressing the red activation button, place the open end of the autoinjector on the injection site, straight up at a right angle (90°) and push the safety needle cover firmly against the skin to unlock. **Continue to hold firmly against the skin.**



IMPORTANT: Press the autoinjector firmly enough against the skin so that the safety cover is fully retracted.

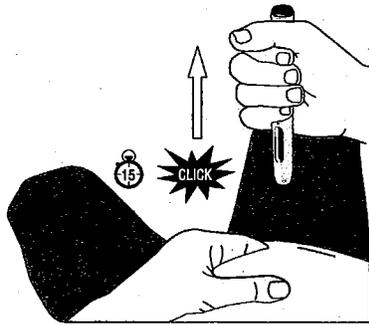


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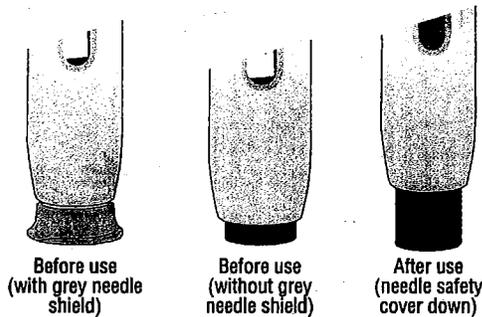


5. **Wait until you hear the second 'click'.** Once you hear the second click, lift the autoinjector straight up from the injection site. The injection is finished. The safety needle cover on the autoinjector will automatically extend to cover the needle.

If you did not remove your thumb from the red button, the second 'click' cannot be heard. If this happens, slowly count to 15 before lifting the autoinjector from the injection site.



The needle safety cover will move down over the needle and lock into place. The inspection window will be yellow, confirming the injection is complete. Verify that the inspection window is yellow to ensure that the injection is complete before lifting the autoinjector. There is no need to replace the grey needle shield.



If the inspection window is not yellow, do not try to use the autoinjector again. If you suspect you have not received the full dose, do not repeat the injection using a new autoinjector.

Call your healthcare provider or 1-866-55AMGEN for assistance.

If you notice a spot of blood at the injection site, dab away with a cotton ball or tissues. Do not rub the injection site. If needed, you may cover the injection site with a bandage.

Remember

If you have any problems, please do not be afraid to ask your healthcare provider for help and advice.

How do I dispose of used autoinjectors?

The Aranesp[®] prefilled SureClick[™] autoinjector should **NEVER** be reused. **NEVER** put the grey needle shield back into the autoinjector.

Dispose of the used autoinjector as instructed by your healthcare provider, or by following these steps:

1. Do not throw the used autoinjector in the household trash or recycle.
2. Place the used autoinjector 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. Puncture-resistant containers may also be purchased at your local pharmacy.
3. When the container is full, tape around the cap or lid to make sure the cap or lid does not come off.
 - 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, including autoinjectors. **Do not throw the disposal container in household trash. Do not recycle.**
 - **Always** keep the container out of the reach of children.

As with all medicines, you should keep Aranesp[®] out of the sight and reach of children.

General Information about Aranesp[®]

Doctors can prescribe medicines for conditions that are not in this leaflet. Use Aranesp[®] only for what your doctor prescribed. Do not give it to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet gives the most important information about Aranesp[®]. For more information, talk with your doctor or healthcare provider. You can also access more information at the following website: www.aranesp.com.

Active ingredient: darbepoetin alfa

Inactive ingredients: polysorbate solution or albumin solution

The logo for Amgen, consisting of the word "AMGEN" in a bold, black, sans-serif font with a registered trademark symbol (®) to the upper right of the letter "N".

Manufactured by:

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v - Issue Date:

Patient Information

Aranesp[®] (Air-uh-nesp)

darbepoetin alfa

Single-dose Vial/ Single-dose Prefilled Syringe (SingleJect[®])

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What is the most important information I should know about Aranesp[®]?

Aranesp[®] can cause serious side effects:

Chronic kidney failure patients:

- If your hemoglobin is kept too high, you have an increased chance of heart attack, stroke, heart failure, blood clots, and death. Your doctor should try to keep your hemoglobin between 10 and 12 g/dL.

Cancer patients:

- You may have an increased chance of dying sooner or your tumor (cancer) may grow faster if you take this drug.
- Your doctor should use the lowest dose of Aranesp[®] needed to help you avoid red blood cell transfusions.
- Once you have completed your chemotherapy course, Aranesp[®] treatment should be stopped.

All patients:

- Aranesp[®] treatment increases your chance of a blood clot. If you are scheduled for surgery, your doctor may prescribe a blood thinner to prevent blood clots.
- Blood clots can form at your vascular access if you are receiving hemodialysis. Call your doctor or dialysis center if you think your access is blocked.

- Blood clots can form in blood vessels (veins) in your leg (venous thrombosis). Blood clots may move from the legs to the lungs and block the blood circulation in the lungs (pulmonary embolus).

Call your doctor right away if you experience any of the following symptoms of a blood clot, while taking Aranesp®:

- chest pain
- shortness of breath
- pain in the legs with or without swelling

You will be asked to have blood tests that will check the number of red blood cells your body is producing. The blood tests will see if Aranesp® is working and if your hemoglobin level is getting too high. Your doctor may refer to the results of your blood tests as hemoglobin and hematocrit. 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. It is important to keep all appointments for blood tests to allow your doctor to adjust the dosage of Aranesp® as needed.

Please also read “**What are the possible side effects of Aranesp®?**” below.

What is Aranesp®?

Aranesp® is a man-made form of the protein human erythropoietin (ee-rith-row-po-eh-tin). Aranesp® works by stimulating your bone marrow to make red blood cells. After two to six weeks of treatment, your red blood cell counts may increase.

Aranesp® may be used to treat your anemia (a lower than normal number of red blood cells) if it is caused by:

- chronic kidney failure (you may or may not be on dialysis)
- chemotherapy used to treat cancer

Aranesp® does not improve symptoms of anemia, quality of life, or patient well-being for patients with cancer.

Before receiving Aranesp®, you should talk with your doctor about the benefits and risks of Aranesp®.

Who should not take Aranesp®?

You should not take Aranesp® if you have:

- High blood pressure that is not controlled (uncontrolled hypertension).
- Antibodies to Aranesp® or other erythropoietins.

Talk to your doctor if you are not sure if you have these conditions or if you have any questions about this information.

What should I tell my doctor before taking Aranesp®?

Tell your doctor about all your health conditions and all the medicines you take, including prescription and over-the-counter medicines, vitamins, supplements, and herbals. Be sure to tell your doctor if you have:

- Heart disease
- High blood pressure
- Any history of seizures or strokes
- Blood disorders (such as sickle cell anemia, blood clotting disorders)

Tell your doctor if you are:

- Pregnant or nursing
- Planning to become pregnant

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 pass into human breast milk.

Talk to your doctor if you are not sure if you have these conditions or if you have any questions about this information.

Your doctor may monitor your blood pressure and the amount of iron in your blood before you start Aranesp® and while you are taking Aranesp®. You or your caregiver may also be asked to monitor your blood pressure every day and to report any changes. When the number of red blood cells increases, your blood pressure may also increase, so your doctor may prescribe new or more blood pressure medicine. You may be asked to have certain blood tests, such as hemoglobin, hematocrit or blood iron levels. Also, your doctor may prescribe iron for you to take. Follow your doctor's orders.

What are other possible side effects of Aranesp®?

Aranesp® may cause serious side effects. See **"What is the most important information I should know about Aranesp®?"**

Other side effects of Aranesp® include:

- Increased blood pressure; your doctor or caregiver may monitor your blood pressure more frequently.
- Infections
- Cough
- Chest pain
- Antibodies against Aranesp[®] that can block or reduce your body's ability to make red blood cells. If you experience unusual tiredness and lack of energy, **call your doctor**.
- Redness, swelling, pain, or itching at the site of injection. If you notice any signs of redness, swelling, or itching at the site of injection, talk to your doctor.
- Serious allergic reactions. 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)**.

The needle cover on the prefilled syringe contains a derivative of latex. If you know you are allergic to latex, talk to your healthcare provider before using Aranesp[®].

The most common side effects you may have when taking Aranesp[®] are:

- Increased blood pressure
- Decreased blood pressure
- Body or muscle aches
- Headache
- Diarrhea
- Shortness of breath
- Swelling in your arms or legs
- Fever
- Nausea or vomiting
- Infections
- Chest pain

Some side effects are more common depending on the reasons for which you are taking Aranesp[®]. Talk to your doctor for more information about side effects. Make sure to report any side effects to your doctor.

Aranesp[®] has other side effects that are not listed here. For a complete list, talk to your doctor.

Call your doctor right away if:

- You take more than the amount prescribed.
- You are currently taking Aranesp[®] and experience any of these symptoms, which may be a sign of a serious problem:

- Unusual tiredness and lack of energy
- Redness, swelling, pain, or itching at the site of injection and spreading rash over the whole body, shortness of breath, wheezing, a drop in blood pressure, swelling around the mouth or eyes, fast pulse, or sweating
- Convulsion, confusion, dizziness, loss of consciousness
- Increased blood pressure, chest pain, irregular heartbeats
- Stroke, chest pain, shortness of breath, or pain with or without swelling in the legs
- Blood clots in your hemodialysis vascular access port

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

After your doctor has determined that you can safely use Aranesp[®] at home, you 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 to use Aranesp[®] in vials or prefilled syringes. Do not change the way you use Aranesp[®] (including the dose of Aranesp[®]) without consulting your doctor. You should ask your doctor what to do if you miss a dose of Aranesp[®]. **You should always follow your doctor's instructions.**

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.

How should I store Aranesp[®]?

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.

How do I take 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.

Setting up for an injection

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 Aranesp[®]. If the Aranesp[®] vial or prefilled syringe has been shaken vigorously, the solution may appear foamy and it should not be used.

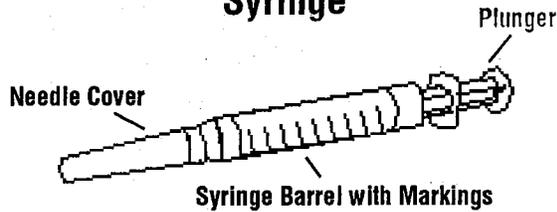
5. Assemble the supplies you will need for an injection:

- Aranesp[®] vial and the correct disposable syringe and needle

Vial



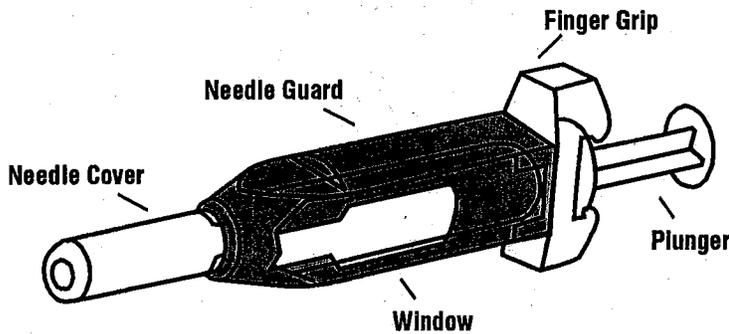
Disposable Syringe



OR

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

Prefilled Syringe



- 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.

Alcohol Swab

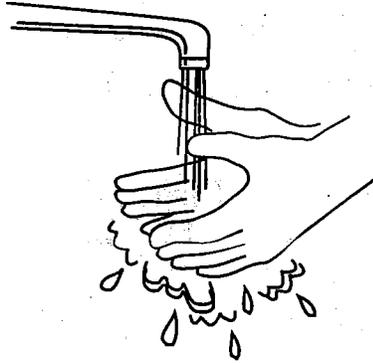


Cotton Ball



- Puncture-proof disposal container

6. Wash your hands with soap and warm water.

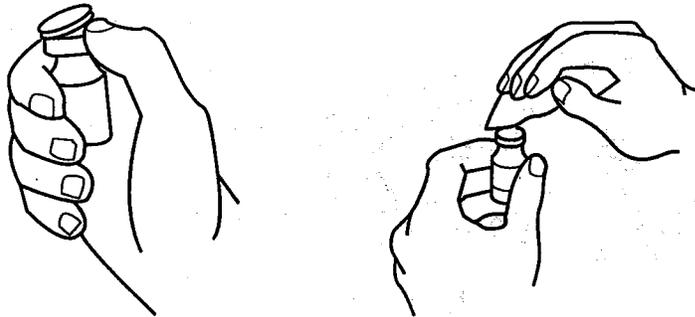


How to prepare the dose of Aranesp®

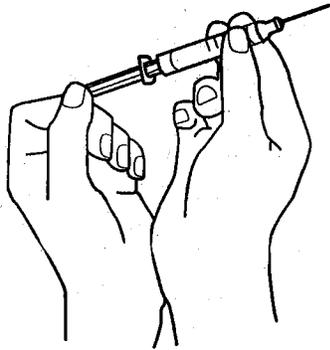
If you are using Aranesp® in a vial, follow the instructions in Section A. If you are using Aranesp® in a prefilled syringe, follow the instructions in Section B.

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

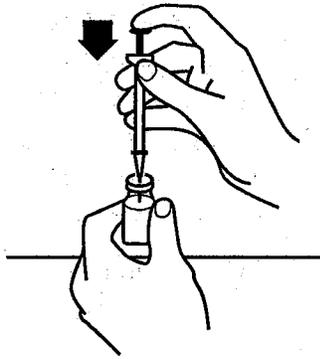
1. Take the color cap off the vial. Clean the rubber stopper with one alcohol swab.



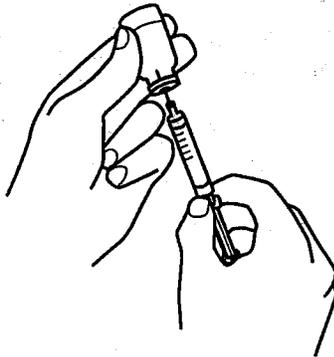
2. Check the package containing the syringe. If the package has been opened or damaged, do not use that syringe. You should dispose of that syringe in the puncture-proof disposal container. If the syringe package is undamaged, open the package and remove the syringe.
3. Pull the needle cover straight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

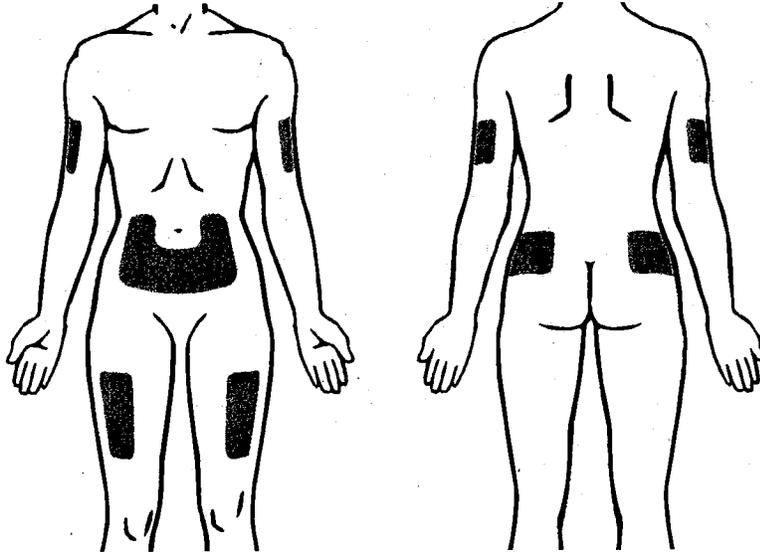
Go directly to the section “Selecting and preparing the injection site.”

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

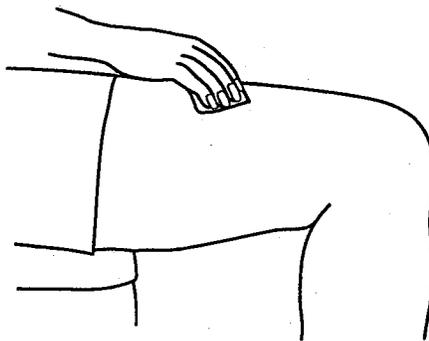


Front

Back

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.

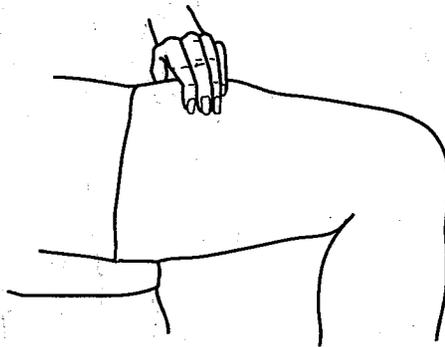


Injecting the dose of Aranesp® from a vial or prefilled syringe

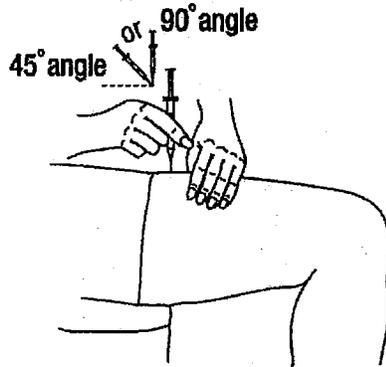
For patients not on hemodialysis:

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.

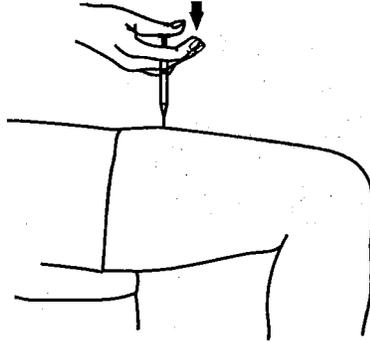
Note: If using a prefilled syringe with a needle guard, hold the syringe barrel through the two needle guard windows when giving the injection.



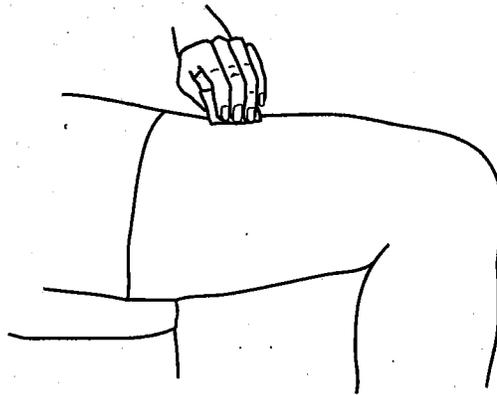
2. Holding the syringe like a pencil, use a quick “dart like” motion to insert the needle either straight up and down (90 degree angle) or at a slight angle (45 degrees) into the skin.



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.



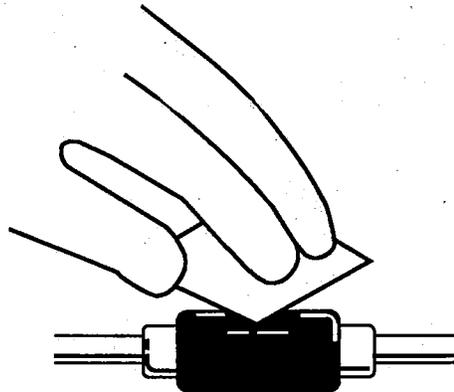
5. You should **ONLY** use a disposable syringe and Aranesp[®] vial or prefilled syringe once. You should discard the disposable syringe and vial or prefilled syringe with any remaining Aranesp[®].

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."

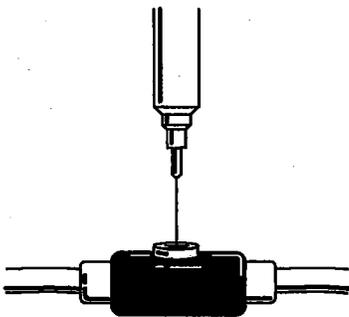
For patients on hemodialysis:

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

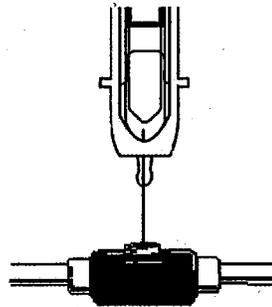


2. Insert the needle of the syringe into the cleaned venous port and push the plunger all the way down to inject all the Aranesp[®].

Using
disposable syringe



Using prefilled syringe
with needle guard

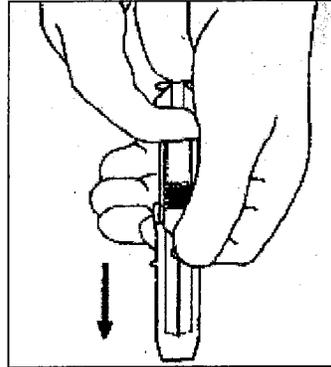
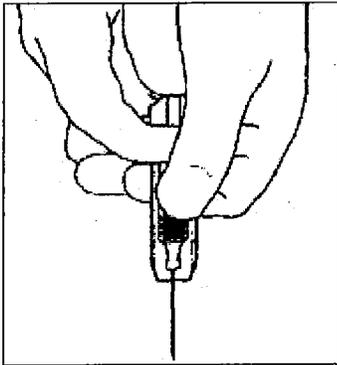


Remove the syringe from the venous port.

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.**

General Information about Aranesp[®]

Doctors can prescribe medicines for conditions that are not in this leaflet. Use Aranesp[®] only for what your doctor prescribed. Do not give it to other people, even if they have the same symptoms that you have. It may harm them.