

Approved: 3-23-06

S-NESP-US-PI-9.3 + Q3W\_C

Aranesp®  
(darbepoetin alfa)  
For Injection

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6 **DESCRIPTION**

7 Aranesp® is an erythropoiesis stimulating protein, closely related to erythropoietin, that is  
8 produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Aranesp® is a  
9 165-amino acid protein that differs from recombinant human erythropoietin in containing  
10 5 N-linked oligosaccharide chains, whereas recombinant human erythropoietin contains 3  
11 chains<sup>1</sup>. The two additional N-glycosylation sites result from amino acid substitutions in the  
12 erythropoietin peptide backbone. The additional carbohydrate chains increase the approximate  
13 molecular weight of the glycoprotein from 30,000 to 37,000 daltons. Aranesp® is formulated as a  
14 sterile, colorless, preservative-free protein solution for intravenous (IV) or subcutaneous (SC)  
15 administration.

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

18 **Single-dose prefilled syringes** are available containing 25, 40, 60, 100, 150, 200, 300, or  
19 500 mcg of Aranesp®. To reduce the risk of accidental needlesticks to users, each prefilled  
20 syringe is equipped with a needle guard that covers the needle during disposal.

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

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

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

31 **CLINICAL PHARMACOLOGY**

32 **Mechanism of Action**

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

42 **Pharmacokinetics**

43 *Adult Patients*

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

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46 Following intravenous (IV) administration in CRF patients, Aranesp<sup>®</sup> serum concentration-time  
47 profiles were biphasic, with a distribution half-life of approximately 1.4 hours and a mean terminal  
48 half-life of 21 hours. The terminal half-life of Aranesp<sup>®</sup> was approximately 3-fold longer than that  
49 of epoetin alfa when administered intravenously.

50 Following subcutaneous (SC) administration, absorption is slow and rate limiting. The observed  
51 half-life in CRF patients, which reflected the rate of absorption, was 49 hours (range: 27 to  
52 89 hours). Peak concentrations occurred at 34 hours (range: 24 to 72 hours). The bioavailability  
53 of Aranesp<sup>®</sup> as measured in CRF patients after SC administration was 37% (range: 30% to 50%).

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

60 Over the dose range of 0.45 to 4.5 mcg/kg Aranesp<sup>®</sup> administered IV or SC on a once-weekly  
61 (QW) schedule and 4.5 to 15 mcg/kg administered SC on a once-every-3-week (Q3W) schedule,  
62 systemic exposure was approximately proportional to dose. No evidence of accumulation was  
63 observed beyond an expected < 2-fold increase in blood levels when compared to the initial dose.

64

### 65 *Pediatric Patients*

66 Aranesp<sup>®</sup> pharmacokinetics were studied in 12 pediatric CRF patients (age 3-16 years) receiving  
67 or not receiving dialysis. Following a single IV or SC Aranesp<sup>®</sup> dose, C<sub>max</sub> and half-life were  
68 similar to those obtained in adult CRF patients. Following a single SC dose, the average  
69 bioavailability was 54% (range: 32% to 70%), which was higher than that obtained in adult CRF  
70 patients.

## 71 **CLINICAL STUDIES**

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

### 74 *Chronic Renal Failure Patients*

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

### 80 **De Novo Use of Aranesp<sup>®</sup>**

81 In two open-label studies, Aranesp<sup>®</sup> or Epoetin alfa was administered for the correction of anemia  
82 in CRF patients who had not been receiving prior treatment with exogenous erythropoietin.  
83 Study N1 evaluated CRF patients receiving dialysis; Study N2 evaluated patients not requiring  
84 dialysis (predialysis patients). In both studies, the starting dose of Aranesp<sup>®</sup> was 0.45 mcg/kg  
85 administered once weekly. The starting dose of Epoetin alfa was 50 U/kg 3 times weekly in  
86 Study N1 and 50 U/kg twice weekly in Study N2. When necessary, dosage adjustments were  
87 instituted to maintain hemoglobin in the study target range of 11 to 13 g/dL. (Note: The  
88 recommended hemoglobin target is lower than the target range of these studies. See **DOSAGE**  
89 **AND ADMINISTRATION: General** for recommended clinical hemoglobin target.) The primary  
90 efficacy endpoint was the proportion of patients who experienced at least a 1.0 g/dL increase in  
91 hemoglobin concentration to a level of at least 11.0 g/dL by 20 weeks (Study N1) or 24 weeks

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92 (Study N2). The studies were designed to assess the safety and effectiveness of Aranesp® but  
93 not to support conclusions regarding comparisons between the two products.

94 In Study N1, the hemoglobin target was achieved by 72% (95% CI: 62%, 81%) of the 90 patients  
95 treated with Aranesp® and 84% (95% CI: 66%, 95%) of the 31 patients treated with Epoetin alfa.  
96 The mean increase in hemoglobin over the initial 4 weeks of Aranesp® treatment was 1.10 g/dL  
97 (95% CI: 0.82 g/dL, 1.37 g/dL).

98 In Study N2, the primary efficacy endpoint was achieved by 93% (95% CI: 87%, 97%) of the  
99 129 patients treated with Aranesp® and 92% (95% CI: 78%, 98%) of the 37 patients treated with  
100 Epoetin alfa. The mean increase in hemoglobin from baseline through the initial 4 weeks of  
101 Aranesp® treatment was 1.38 g/dL (95% CI: 1.21 g/dL, 1.55 g/dL).

### 102 **Conversion From Other Recombinant Erythropoietins**

103 Two adult studies (N3 and N4) and one pediatric study (N5) were conducted in patients with CRF  
104 who had been receiving other recombinant erythropoietins. The studies compared the abilities of  
105 Aranesp® and other erythropoietins to maintain hemoglobin concentrations within a study target  
106 range of 9 to 13 g/dL in adults and 10 to 12.5 g/dL in pediatric patients. (Note: The  
107 recommended hemoglobin target is lower than the target range of these studies. See **DOSAGE  
108 AND ADMINISTRATION: General** for recommended clinical hemoglobin target.) CRF patients  
109 who had been receiving stable doses of other recombinant erythropoietins were randomized to  
110 Aranesp®, or to continue with their prior erythropoietin at the previous dose and schedule. For  
111 patients randomized to Aranesp®, the initial weekly dose was determined on the basis of the  
112 previous total weekly dose of recombinant erythropoietin.

#### 113 *Adult Patients*

114 Study N3 was a double-blind study conducted in North America, in which 169 hemodialysis  
115 patients were randomized to treatment with Aranesp® and 338 patients continued on Epoetin alfa.  
116 Study N4 was an open-label study conducted in Europe and Australia in which 347 patients were  
117 randomized to treatment with Aranesp® and 175 patients were randomized to continue on  
118 Epoetin alfa or Epoetin beta. Of the 347 patients randomized to Aranesp®, 92% were receiving  
119 hemodialysis and 8% were receiving peritoneal dialysis.

120 In Study N3, a median weekly dose of 0.53 mcg/kg Aranesp® (25<sup>th</sup>, 75<sup>th</sup> percentiles: 0.30,  
121 0.93 mcg/kg) was required to maintain hemoglobin in the study target range. In Study N4, a  
122 median weekly dose of 0.41 mcg/kg Aranesp® (25<sup>th</sup>, 75<sup>th</sup> percentiles: 0.26, 0.65 mcg/kg) was  
123 required to maintain hemoglobin in the study target range.

#### 124 *Pediatric Patients*

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

131

### 132 **Cancer Patients Receiving Chemotherapy**

#### 133 *Once-Weekly (QW) Dosing*

134 The safety and effectiveness of Aranesp® in reducing the requirement for RBC transfusions in  
135 patients undergoing chemotherapy was assessed in a randomized, placebo-controlled, double-  
136 blind, multinational study (C1). This study was conducted in anemic (Hgb ≤ 11 g/dL) patients with  
137 advanced, small cell or non-small cell lung cancer, who received a platinum-containing

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138 chemotherapy regimen. Patients were randomized to receive Aranesp<sup>®</sup> 2.25 mcg/kg (n = 156) or  
139 placebo (n = 158) administered as a single weekly SC injection for up to 12 weeks. The dose  
140 was escalated to 4.5 mcg/kg/week at week six, in subjects with an inadequate response to  
141 treatment, defined as less than 1 g/dL hemoglobin increase. There were 67 patients in the  
142 Aranesp<sup>®</sup> arm who had their dose increased from 2.25 to 4.5 mcg/kg/week, at any time during the  
143 treatment period.

144 Efficacy was determined by a reduction in the proportion of patients who were transfused over the  
145 12 week treatment period. A significantly lower proportion of patients in the Aranesp<sup>®</sup> arm, 26%  
146 (95% CI: 20%, 33%) required transfusion compared to 60% (95% CI: 52%, 68%) in the placebo  
147 arm (Kaplan-Meier estimate of proportion; p < 0.001 by Cochran - Mantel - Haenszel test). Of the  
148 67 patients who received a dose increase, 28% had a 2 g/dL increase in hemoglobin over  
149 baseline, generally occurring between weeks 8 to 13. Of the 89 patients who did not receive a  
150 dose increase, 69% had a 2g/dL increase in hemoglobin over baseline, generally occurring  
151 between weeks 6 to 13.

152

### 153 *Once-Every-3-Week (Q3W) Dosing*

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

165 Efficacy was determined by a comparison of the Kaplan-Meier estimates of the proportion of  
166 patients who received at least one RBC transfusion between day 29 and the end of treatment.  
167 Three hundred thirty five patients in the Q3W group and 337 patients in the QW group remained  
168 on study through or beyond day 29 and were evaluated for efficacy. Twenty seven percent (95%  
169 CI: 22%, 32%) of patients in the Q3W group and 34% (95% CI: 29%, 39%) in the weekly group  
170 required a RBC transfusion. The observed difference in the transfusion rates (QW-Q3W) was -  
171 6.7% (95% CI: -13.8%, 0.4%).

## 172 **INDICATIONS AND USAGE**

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

## 177 **CONTRAINDICATIONS**

Aranesp<sup>®</sup> is contraindicated in patients with:

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

178 **WARNINGS**

179 **Cardiovascular Events, Hemoglobin, and Rate of Rise of Hemoglobin**

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

184 In a clinical trial of Epoetin alfa (rHuEPO) treatment in hemodialysis patients with clinically evident  
185 cardiac disease, patients were randomized to a target hemoglobin of either  $14 \pm 1$  g/dL or  
186  $10 \pm 1$  g/dL<sup>2</sup>. Higher mortality (35% vs 29%) was observed in the 634 patients randomized to a  
187 target hemoglobin of 14 g/dL than in the 631 patients assigned a target hemoglobin of 10 g/dL.  
188 The reason for the increased mortality observed in this study is unknown; however, the incidence  
189 of nonfatal myocardial infarction, vascular access thrombosis, and other thrombotic events was  
190 also higher in the group randomized to a target hemoglobin of 14 g/dL.

191 In patients treated with Aranesp<sup>®</sup> or other recombinant erythropoietins in Aranesp<sup>®</sup> clinical trials,  
192 increases in hemoglobin greater than approximately 1.0 g/dL during any 2-week period were  
193 associated with increased incidence of cardiac arrest, neurologic events (including seizures and  
194 stroke), exacerbations of hypertension, congestive heart failure, vascular  
195 thrombosis/ischemia/infarction, acute myocardial infarction, and fluid overload/edema. It is  
196 recommended that the dose of Aranesp<sup>®</sup> be decreased if the hemoglobin increase exceeds  
197 1.0 g/dL in any 2-week period, because of the association of excessive rate of rise of hemoglobin  
198 with these events.

199 **Hypertension**

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

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

212 **Seizures**

213 Seizures have occurred in patients with CRF participating in clinical trials of Aranesp<sup>®</sup> and  
214 Epoetin alfa. During the first several months of therapy, blood pressure and the presence of  
215 premonitory neurologic symptoms should be monitored closely. While the relationship between  
216 seizures and the rate of rise of hemoglobin is uncertain, it is recommended that the dose of  
217 Aranesp<sup>®</sup> be decreased if the hemoglobin increase exceeds 1.0 g/dL in any 2-week period.

218 **Thrombotic Events and Increased Mortality**

219 An increased incidence of thrombotic events has been observed in patients treated with  
220 erythropoietic agents. In patients with cancer who received Aranesp<sup>®</sup>, pulmonary emboli,  
221 thrombophlebitis and thrombosis occurred more frequently than in placebo controls (see  
222 **ADVERSE REACTIONS: Cancer Patients Receiving Chemotherapy, Table 4**).

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223 In a randomized controlled study with another erythropoietic product in 939 women with  
224 metastatic breast cancer receiving chemotherapy, patients received either weekly Epoetin alfa or  
225 placebo for up to a year. This study was designed to prevent anemia (maintain hemoglobin  
226 levels between 12 and 14 g/dL or hematocrit between 36 and 42%). Treatment with Epoetin alfa  
227 was associated with a higher rate of fatal thrombotic events (1.1% Epoetin alfa vs 0.2% placebo)  
228 in the first 4 months of the study. Based on Kaplan-Meier estimates, the proportion of subjects  
229 surviving at 12 months after randomization was lower in the Epoetin alfa group than in the  
230 placebo group (70% vs 76%),  $p = 0.012$ , log rank. However, due to insufficient monitoring and  
231 data collection, reliable comparisons cannot be made concerning the effect of Epoetin alfa on  
232 overall time to disease progression, progression-free survival, and overall survival. Until further  
233 information is available, the recommended target hemoglobin should not exceed 12 g/dL in men  
234 or women.

### 235 **Pure Red Cell Aplasia**

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

### 248 **Albumin (Human)**

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

## 255 **PRECAUTIONS**

### 256 **General**

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

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### 260 **Lack or Loss of Response to Aranesp®**

261 A lack of response or failure to maintain a hemoglobin response with Aranesp® doses within the  
262 recommended dosing range should prompt a search for causative factors. Deficiencies of folic  
263 acid, iron or vitamin B<sub>12</sub> should be excluded or corrected. Depending on the clinical setting,  
264 intercurrent infections, inflammatory or malignant processes, osteofibrosis cystica, occult blood  
265 loss, hemolysis, severe aluminum toxicity, and bone marrow fibrosis may compromise an  
266 erythropoietic response. In the absence of another etiology, the patient should be evaluated for  
267 evidence of PRCA and sera should be tested for the presence of antibodies to erythropoietin (see  
268 **WARNINGS: Pure Red Cell Aplasia**).

### 269 **Hematology**

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

274 In order to prevent the hemoglobin from exceeding the recommended target (12 g/dL) or rising  
275 too rapidly (greater than 1.0 g/dL in 2 weeks), the guidelines for dose and frequency of dose  
276 adjustments should be followed (see **WARNINGS** and **DOSAGE AND ADMINISTRATION:**  
277 **Dose Adjustment**).

### 278 **Allergic Reactions**

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

### 284 **Patients With CRF Not Requiring Dialysis**

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

### 291 **Dialysis Management**

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

### 295 **Tumor Growth Factor Potential**

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

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

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306 Two additional studies explored the effect on survival and/or disease progression following  
307 administrations of two other erythropoietic products (ie, Epoetin alfa and Epoetin beta) with higher  
308 hemoglobin targets. The first study was a randomized controlled study in 939 women with  
309 metastatic breast cancer receiving chemotherapy where patients received either weekly Epoetin  
310 alfa or placebo for up to a year. This study was designed to prevent anemia (maintain  
311 hemoglobin levels between 12 and 14 g/dL or hematocrit between 36 and 42%). Mortality at 12  
312 months was significantly higher in the Epoetin alfa arm (see **WARNINGS: Thrombotic Events  
313 and Increased Mortality**). This difference was observed primarily in the first 4 months of the  
314 study with more deaths attributed to breast cancer progression in the Epoetin alfa group (6%  
315 Epoetin alfa vs 3% placebo). Due to insufficient monitoring and data collection, reliable  
316 comparisons cannot be made concerning the effect of Epoetin alfa on overall time to disease  
317 progression, progression-free survival, and overall survival. The second study was a randomized  
318 controlled study in 351 head and neck cancer patients where Epoetin beta or placebo was  
319 administered to achieve target hemoglobins of 14 and 15 g/dL for women and men, respectively.  
320 Locoregional progression-free survival was significantly shorter (median of 406 days Epoetin beta  
321 vs 745 days placebo,  $p = 0.04$ ) in patients receiving Epoetin beta.

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

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

### 327 **Laboratory Tests**

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

333 In order to ensure effective erythropoiesis, iron status should be evaluated for all patients before  
334 and during treatment, as the majority of patients will eventually require supplemental iron therapy.  
335 Supplemental iron therapy is recommended for all patients whose serum ferritin is below  
336 100 mcg/L or whose serum transferrin saturation is below 20%.

### 337 **Information for Patients**

338 Patients should be informed of the possible side effects of Aranesp<sup>®</sup> and be instructed to report  
339 them to the prescribing physician. Patients should be informed of the signs and symptoms of  
340 allergic drug reactions and be advised of appropriate actions. Patients should be counseled on  
341 the importance of compliance with their Aranesp<sup>®</sup> treatment, dietary and dialysis prescriptions,  
342 and the importance of judicious monitoring of blood pressure and hemoglobin concentration  
343 should be stressed.

344 It is recommended that Aranesp<sup>®</sup> should be administered by a healthcare professional. In those  
345 rare cases where it is determined that a patient can safely and effectively administer Aranesp<sup>®</sup> at  
346 home, appropriate instruction on the proper use of Aranesp<sup>®</sup> should be provided for patients and  
347 their caregivers, including careful review of the accompanying "Information for Patients" insert.  
348 Patients and caregivers should also be cautioned against the reuse of needles, syringes, or drug  
349 product, and be thoroughly instructed in their proper disposal. A puncture-resistant container for  
350 the disposal of used syringes and needles should be made available to the patient.

### 351 **Drug Interactions**

352 No formal drug interaction studies of Aranesp<sup>®</sup> have been performed.

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### 353 **Carcinogenesis, Mutagenesis, and Impairment of Fertility**

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

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

363 **Impairment of Fertility:** When administered intravenously to male and female rats prior to and  
364 during mating, reproductive performance, fertility, and sperm assessment parameters were not  
365 affected at any doses evaluated (up to 10 mcg/kg/dose, administered 3 times weekly). An  
366 increase in post implantation fetal loss was seen at doses equal to or greater than  
367 0.5 mcg/kg/dose, administered 3 times weekly.

### 368 **Pregnancy Category C**

369 When Aranesp® was administered intravenously to rats and rabbits during gestation, no evidence  
370 of a direct embryotoxic, fetotoxic, or teratogenic outcome was observed at doses up to  
371 20 mcg/kg/day. The only adverse effect observed was a slight reduction in fetal weight, which  
372 occurred at doses causing exaggerated pharmacological effects in the dams (1 mcg/kg/day and  
373 higher). No deleterious effects on uterine implantation were seen in either species. No  
374 significant placental transfer of Aranesp® was observed in rats. An increase in post implantation  
375 fetal loss was observed in studies assessing fertility (see **PRECAUTIONS: Carcinogenesis,  
376 Mutagenesis, and Impairment of Fertility: Impairment of Fertility**).

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

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

### 383 **Nursing Mothers**

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

### 386 **Pediatric Use**

#### 387 *Pediatric CRF Patients*

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

#### 393 *Pediatric Cancer Patients*

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

395

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### 396 **Geriatric Use**

397 Of the 1598 CRF patients in clinical studies of Aranesp<sup>®</sup>, 42% were age 65 and over, while  
398 15% were 75 and over. Of the 873 cancer patients in clinical studies receiving Aranesp<sup>®</sup> and  
399 concomitant chemotherapy, 45% were age 65 and over, while 14% were 75 and over. No overall  
400 differences in safety or efficacy were observed between older and younger patients.

### 401 **ADVERSE REACTIONS**

#### 402 **General**

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

#### 406 **Immunogenicity**

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

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

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

426

#### 427 **Chronic Renal Failure Patients**

##### 428 *Adult Patients*

429 In all studies, the most frequently reported serious adverse reactions with Aranesp<sup>®</sup> were  
430 vascular access thrombosis, congestive heart failure, sepsis, and cardiac arrhythmia. The most  
431 commonly reported adverse reactions were infection, hypertension, hypotension, myalgia,  
432 headache, and diarrhea, (see **WARNINGS: Cardiovascular Events, Hemoglobin, and Rate of  
433 Rise of Hemoglobin, and Hypertension**). The most frequently reported adverse reactions  
434 resulting in clinical intervention (e.g., discontinuation of Aranesp<sup>®</sup>, adjustment in dosage, or the  
435 need for concomitant medication to treat an adverse reaction symptom) were hypotension,  
436 hypertension, fever, myalgia, nausea, and chest pain.

437 The data described below reflect exposure to Aranesp<sup>®</sup> in 1598 CRF patients, including 675  
438 exposed for at least 6 months, of whom 185 were exposed for greater than 1 year. Aranesp<sup>®</sup> was  
439 evaluated in active-controlled (n = 823) and uncontrolled studies (n = 775).

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

446 The population encompassed an age range from 18 to 91 years. Fifty-seven percent of the  
447 patients were male. The percentages of Caucasian, Black, Asian, and Hispanic patients were  
448 83%, 11%, 3%, and 1%, respectively. The median weekly dose of Aranesp<sup>®</sup> was 0.45 mcg/kg  
449 (25<sup>th</sup>, 75<sup>th</sup> percentiles: 0.29, 0.66 mcg/kg).

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

454 The data in Table 1 reflect those adverse events occurring in at least 5% of patients treated with  
455 Aranesp<sup>®</sup>.

Table 1. Adverse Events Occurring in  $\geq 5\%$  of CRF Patients

Event	Patients Treated With Aranesp <sup>®</sup> (n = 1598)
<b>APPLICATION SITE</b>	
Injection-site Pain	7%
<b>BODY AS A WHOLE</b>	
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%
<b>CARDIOVASCULAR</b>	
Hypertension	23%
Hypotension	22%
Cardiac Arrhythmias/Cardiac Arrest	10%
Angina Pectoris/Cardiac Chest Pain	8%
Thrombosis Vascular Access	8%
Congestive Heart Failure	6%
<b>CNS/PNS</b>	
Headache	16%
Dizziness	8%
<b>GASTROINTESTINAL</b>	
Diarrhea	16%
Vomiting	15%
Nausea	14%
Abdominal Pain	12%
Constipation	5%
<b>MUSCULO-SKELETAL</b>	
Myalgia	21%
Arthralgia	11%
Limb Pain	10%
Back Pain	8%
<b>RESISTANCE MECHANISM</b>	
Infection <sup>a</sup>	27%
<b>RESPIRATORY</b>	
Upper Respiratory Infection	14%
Dyspnea	12%
Cough	10%
Bronchitis	6%
<b>SKIN AND APPENDAGES</b>	
Pruritus	8%

<sup>a</sup> Infection includes sepsis, bacteremia, pneumonia, peritonitis, and abscess.

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

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

457 *Pediatric Patients*

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

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

467 **Thrombotic Events**

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

473 **Cancer Patients Receiving Chemotherapy**

474 The incidence data described below reflect the exposure to Aranesp® in 873 cancer patients  
 475 including patients exposed to Aranesp QW (547, 63%), Q2W (128, 16%), and Q3W (198, 23%).  
 476 Aranesp® was evaluated in seven studies that were active-controlled and/or placebo-controlled  
 477 studies of up to 6 months duration. The Aranesp®-treated patient demographics were as follows:  
 478 median age of 63 years (range of 20 to 91 years); 40% male; 88% Caucasian, 5% Hispanic, 4%  
 479 Black, and 3% Asian. Over 90% of patients had locally advanced or metastatic cancer, with the  
 480 remainder having early stage disease. Patients with solid tumors (e.g., lung, breast, colon,  
 481 ovarian cancers), and lymphoproliferative malignancies (e.g., lymphoma, multiple myeloma) were  
 482 enrolled in the clinical studies. All of the 873 Aranesp®-treated subjects also received  
 483 concomitant cyclic chemotherapy.

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

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493 observed in controlled studies in which patients received Aranesp<sup>®</sup> or other recombinant  
494 erythropoietins.

495

496 **Table 3. Adverse Events Occurring in  $\geq 5\%$  of Patients Receiving Chemotherapy**

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

**Table 4. Incidence of Other Clinically Significant Adverse Events in Patients Receiving Chemotherapy**

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

<sup>a</sup> Seizures/Convulsions include the preferred terms: Convulsions, Convulsions Grand Mal, and Convulsions Local.

<sup>b</sup> Thrombosis includes: Thrombophlebitis, Thrombophlebitis Deep, Thrombosis Venous, Thrombosis Venous Deep, Thromboembolism, and Thrombosis.

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

500

#### 501 **Thrombotic and Cardiovascular Events**

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

#### 507 **OVERDOSAGE**

508 The maximum amount of Aranesp<sup>®</sup> that can be safely administered in single or multiple doses  
509 has not been determined. Doses over 3.0 mcg/kg/week for up to 28 weeks have been  
510 administered to CRF patients. Doses up to 8.0 mcg/kg every week and 15.0 mcg/kg every 3  
511 weeks have been administered to cancer patients for up to 12-16 weeks. Excessive rise and  
512 rate of rise in hemoglobin concentration, however, have been associated with adverse events  
513 (see **WARNINGS** and **DOSAGE AND ADMINISTRATION: Dose Adjustment**). In the event of  
514 polycythemia, Aranesp<sup>®</sup> should be temporarily withheld (see **DOSAGE AND ADMINISTRATION:**  
515 **Dose Adjustment**). If clinically indicated, phlebotomy may be performed.

#### 516 **DOSAGE AND ADMINISTRATION**

##### 517 **General**

518 **IMPORTANT:** Aranesp<sup>®</sup> dosing regimens are different for each of the indications  
519 described in this section of the package insert. Aranesp<sup>®</sup> should be administered under  
520 the supervision of a healthcare professional.

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

### 524 **Chronic Renal Failure Patients**

525 Aranesp® is administered either IV or SC as a single weekly injection. *In patients on*  
526 *hemodialysis, the IV route is recommended.* The dose should be started and slowly adjusted  
527 as described below based on hemoglobin levels. If a patient fails to respond or maintain a  
528 response, this should be evaluated (see **WARNINGS: Pure Red Cell Aplasia, PRECAUTIONS:**  
529 **Lack or Loss of Response to Aranesp®** and **PRECAUTIONS: Laboratory Tests**). When  
530 Aranesp® therapy is initiated or adjusted, the hemoglobin should be followed weekly until  
531 stabilized and monitored at least monthly thereafter.

532 For patients who respond to Aranesp® with a rapid increase in hemoglobin (e.g., more than  
533 1.0 g/dL in any 2-week period), the dose of Aranesp® should be reduced (see **DOSAGE AND**  
534 **ADMINISTRATION: Dose Adjustment**) because of the association of excessive rate of rise of  
535 hemoglobin with adverse events (see **WARNINGS: Cardiovascular Events, Hemoglobin, and**  
536 **Rate of Rise of Hemoglobin**).

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

### 539 **Starting Dose**

#### 540 **Correction of Anemia**

541 The recommended starting dose of Aranesp® for the correction of anemia in adult CRF patients is  
542 0.45 mcg/kg body weight, administered as a single IV or SC injection once weekly. Because of  
543 individual variability, doses should be titrated to not exceed a target hemoglobin concentration of  
544 12 g/dL (see **DOSAGE AND ADMINISTRATION: Dose Adjustment**). For many patients, the  
545 appropriate maintenance dose will be lower than this starting dose. Predialysis patients, in  
546 particular, may require lower maintenance doses. Also, some patients have been treated  
547 successfully with a SC dose of Aranesp® administered once every 2 weeks.

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

#### 550 **Conversion From Epoetin alfa to Aranesp®**

551 The starting weekly dose of Aranesp® for adults and pediatric patients should be estimated on the  
552 basis of the weekly Epoetin alfa dose at the time of substitution (see **Table 5**). For pediatric  
553 patients receiving a weekly Epoetin alfa dose of <1500 units/week, the available data are  
554 insufficient to determine an Aranesp conversion dose. Because of individual variability, doses  
555 should be titrated to maintain the target hemoglobin. Due to the longer serum half-life, Aranesp®  
556 should be administered less frequently than Epoetin alfa. Aranesp® should be administered once  
557 a week if a patient was receiving Epoetin alfa 2 to 3 times weekly. Aranesp® should be  
558 administered once every 2 weeks if a patient was receiving Epoetin alfa once per week. The  
559 route of administration (IV or SC) should be maintained.

**Table 5. Estimated Aranesp<sup>®</sup> Starting Doses (mcg/week) for Patients  
Based on Previous Epoetin alfa Dose (Units/week)**

Previous Weekly Epoetin alfa Dose (Units/week)	Weekly Aranesp <sup>®</sup> 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<sup>®</sup> conversion dose.

560 **Dose Adjustment**

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

563 Increases in dose should not be made more frequently than once a month. If the hemoglobin is  
564 increasing and approaching 12 g/dL, the dose should be reduced by approximately 25%. If the  
565 hemoglobin continues to increase, doses should be temporarily withheld until the hemoglobin  
566 begins to decrease, at which point therapy should be reinitiated at a dose approximately 25%  
567 below the previous dose. If the hemoglobin increases by more than 1.0 g/dL in a 2-week period,  
568 the dose should be decreased by approximately 25%.

569 If the increase in hemoglobin is less than 1.0 g/dL over 4 weeks and iron stores are adequate  
570 (see **PRECAUTIONS: Laboratory Tests**), the dose of Aranesp<sup>®</sup> may be increased  
571 by approximately 25% of the previous dose. Further increases may be made at 4-week intervals  
572 until the specified hemoglobin is obtained.

573 **Maintenance Dose**

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

577 **Cancer Patients Receiving Chemotherapy**

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

579  
580 The recommended starting dose for Aranesp<sup>®</sup> administered weekly is 2.25 mcg/kg as a SC  
581 injection.  
582

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

585 For both dosing schedules, the dose should be adjusted for each patient to maintain a target  
586 hemoglobin not to exceed 12 g/dL. If the hemoglobin exceeds 13 g/dL, doses should be  
587 temporarily withheld until the hemoglobin falls to 12 g/dL. At this point, therapy should be  
588 reinitiated at a dose 40% below the previous dose. If the rate of hemoglobin increase is more  
589 than 1.0 g/dL per 2-week period or when the hemoglobin exceeds 11 g/dL, the dose should be  
590 reduced by 40% of the previous dose.

591 For patients receiving weekly administration, if there is less than a 1.0 g/dL increase in  
592 hemoglobin after 6 weeks of therapy, the dose of Aranesp® should be increased up to 4.5  
593 mcg/kg.

594

### 595 **Preparation and Administration of Aranesp®**

596 Do not shake Aranesp® or leave vials or syringes exposed to bright light. After removing the vials  
597 or prefilled syringes from the cartons, keep them covered to protect from room light until  
598 administration. Vigorous shaking or exposure to light may denature Aranesp® causing it to  
599 become biologically inactive. Always store vials or prefilled syringes of Aranesp® in their carton  
600 until use.

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

604 Do not dilute Aranesp®.

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

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

609 Following administration of Aranesp® from the prefilled syringe, activate the UltraSafe® Needle  
610 Guard. Place your hands behind the needle, grasp the guard with one hand, and slide the guard  
611 forward until the needle is completely covered and the guard clicks into place. NOTE: If an  
612 audible click is not heard, the needle guard may not be completely activated. The prefilled  
613 syringe should be disposed of by placing the entire prefilled syringe with guard activated into an  
614 approved puncture-proof container.

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

### 617 **HOW SUPPLIED**

618 Aranesp® is available in single-dose vials in two solutions, an albumin solution and a polysorbate  
619 solution. The words "Albumin Free" appear on the polysorbate container labels and the package  
620 main panels as well as other panels as space permits. Aranesp® albumin solution is also  
621 available in single-dose prefilled syringes supplied with a 27 gauge, ½ inch needle. To reduce  
622 the risk of accidental needlesticks to users, each prefilled syringe is equipped with an UltraSafe®  
623 Needle Guard that covers the needle during disposal. Aranesp® is available in the following  
624 packages:

625

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**625 Single-dose Vial, Polysorbate Solution**

<b>1 Vial/Pack, 4 Packs/Case</b>	<b>4 Vials/Pack, 4 Packs/Case</b>	<b>4 Vials/Pack, 10 Packs/Case</b>
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)

**626 Single-dose Vial, Albumin Solution**

<b>1 Vial/Pack, 4 Packs/Case</b>	<b>4 Vials/Pack, 4 Packs/Case</b>	<b>4 Vials/Pack, 10 Packs/Case</b>
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)

627

628

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628 **Single-dose Prefilled Syringe (SingleJect®) With a 27 gauge, ½ inch Needle With an**  
629 **UltraSafe® Needle Guard, Polysorbate Solution**

<b>1 Syringe/Pack, 4 Packs/Case</b>	<b>4 Syringes/Pack, 4 Packs/Case</b>	<b>4 Syringes/Pack, 10 Packs/Case</b>
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)

630 **Single-dose Prefilled Syringe (SingleJect®) With a 27 gauge, ½ inch Needle With an**  
631 **UltraSafe® Needle Guard, Albumin Solution**

<b>1 Syringe/Pack, 4 Packs/Case</b>	<b>4 Syringes/Pack, 4 Packs/Case</b>	<b>4 Syringes/Pack, 10 Packs/Case</b>
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)

632 **Storage**

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

634 **REFERENCES**

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**S-NESP-US-PI-9.3 + Q3W\_C**

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640 This product, or its use, may be covered by one or more US Patents, including US Patent  
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