

## PRODUCT MONOGRAPH

**Pr Aranesp<sup>®</sup>**  
(darbepoetin alfa)

Single-use Vials<sup>†</sup>  
(15, 60, 325 mcg/vial)

SingleJect<sup>®</sup> Prefilled Syringes  
(10, 15<sup>‡</sup>, 20, 30, 40, 50, 60, 80, 100, 130, 150, 200, 250<sup>‡</sup>, 300, 400<sup>‡</sup>, 500 mcg/syringe)

Subcutaneous Injection; Intravenous Injection

Erythropoiesis Regulating Hormone

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Submission Control #: 215710

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**Pr Aranesp<sup>®</sup>**  
(darbepoetin alfa)

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
<b>Chronic Kidney Disease (CKD):</b> subcutaneous (SC) or intravenous (IV) <b>Cancer:</b> subcutaneous	<b>Pre-filled Syringes:</b> 10, 15 <sup>†</sup> , 20, 30, 40, 50, 60, 80, 100, 130, 150, 200, 250 <sup>‡</sup> , 300, 400 <sup>‡</sup> , 500 mcg/syringe <b>Liquid in Vials<sup>†</sup>:</b> 15, 60, 325 mcg/vial	Not Applicable*

\* For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section

<sup>†</sup> Single-use vial presentation is not available in Canada.

<sup>‡</sup> 15, 250, 400 mcg/syringe pre-filled syringes are not available in Canada.

**DESCRIPTION**

ARANESP (darbepoetin alfa) is an erythropoiesis-stimulating agent produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. The final processed form is a 165-amino acid protein containing 5 N-linked oligosaccharide chains and 1 O-linked oligosaccharide chain. ARANESP has a molecular weight of 37.1 kd (based on known amino acid and carbohydrate structure).

**INDICATIONS AND CLINICAL USE**

**Treatment of Anemia in Chronic Kidney Disease**

ARANESP (darbepoetin alfa) is indicated for the treatment of anemia associated with chronic kidney disease (CKD), including patients on dialysis and patients not on dialysis.

ARANESP is not intended for patients who require immediate correction of severe anemia or emergency transfusions.

Blood pressure should be adequately controlled prior to initiation of ARANESP therapy and must be closely monitored and controlled during treatment.

ARANESP is not indicated for other causes of anemia such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding which should be managed appropriately.

## **Treatment of Anemia due to Chemotherapy in Patients with Non-Myeloid Malignancies**

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

- In patients with a long life expectancy, the decision to administer erythropoiesis-stimulating agents (ESAs) should be based on a benefit-risk assessment with the participation of the individual patient. This should take into account the specific clinical context such as (but not limited to) the type of tumour and its stage, the degree of anemia, life expectancy, the environment in which the patient is being treated and known risks of transfusions and ESAs.
- If appropriate, red blood cell transfusion should be the preferred treatment for the management of anemia in patients with a long life expectancy and who are receiving myelosuppressive chemotherapy.
- ARANESP is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy.

## **CONTRAINDICATIONS**

ARANESP (darbepoetin alfa) is contraindicated in patients:

- with uncontrolled hypertension
- who develop Pure Red Cell Aplasia (PRCA) following treatment with any ESAs
- with known hypersensitivity to the active substance or any of the excipients
- with sensitivity to mammalian cell-derived products

## WARNINGS AND PRECAUTIONS

### SERIOUS WARNINGS AND PRECAUTIONS

#### All Patients

- To minimize the risks for death, serious adverse cardiovascular reactions, and stroke, follow the recommended dosage for each indication for ARANESP and other erythropoiesis-stimulating agents (ESAs) (see **WARNINGS AND PRECAUTIONS: Increased Mortality, Serious Adverse Cardiovascular Reactions, Thromboembolic Events and Stroke, and DOSAGE AND ADMINISTRATION**).
- Patients with uncontrolled hypertension should not be treated with ARANESP; blood pressure should be adequately controlled before initiation of therapy with ARANESP.
- ARANESP should be used with caution in patients with a history of seizures.
- Antibody-mediated Pure Red Cell Aplasia (PRCA) has been reported after months to years of treatment with ESAs.

#### Chronic Kidney Disease Patients

- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target hemoglobin levels of 130 g/L and above. Individualize dosing to achieve and maintain hemoglobin levels within the range of 100 to 115 g/L, not to exceed 120 g/L.

#### Cancer Patients

- ESAs increased the risks for death, serious adverse cardiovascular reactions and thromboembolic events in some controlled clinical trials.
- ESAs shortened overall survival and/or increased the risk of tumour progression or recurrence in some clinical studies in patients with breast, head and neck, lymphoid, cervical and non-small cell lung cancers when dosed to target a hemoglobin level of  $\geq 120$  g/L.
- To minimize the above risks, use the lowest dose needed to avoid red blood cell (RBC) transfusions.
- Use ESAs only for treatment of anemia due to concomitant myelosuppressive chemotherapy.
- If appropriate, red blood cell transfusion should be the preferred treatment for the management of anemia in patients with a long life expectancy and who are receiving myelosuppressive chemotherapy.
- Discontinue ARANESP following the completion of a chemotherapy course.

## **Carcinogenesis, Mutagenesis**

(See TOXICOLOGY)

## **Cardiovascular**

### **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 rHuEPO. In ARANESP CKD clinical trials, approximately 40% of patients 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 CKD treated with ARANESP or rHuEPO.

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

### **Increased Mortality, Serious Adverse Cardiovascular Reactions, Thromboembolic Events and Stroke**

Patients with chronic kidney disease experienced greater risks for death, serious adverse cardiovascular reactions and stroke when administered ESAs to target hemoglobin levels of 130 g/L and above in clinical studies. No trial has identified a hemoglobin target level, dose or dosing strategy that does not increase these risks. Patients with chronic kidney disease and an insufficient hemoglobin response to ESA therapy may be at even greater risk for adverse cardiovascular reactions and mortality than other patients. Serious adverse cardiovascular reactions included myocardial infarction, stroke, congestive heart failure, and an increased risk of serious arterial and venous thromboembolic events including hemodialysis vascular access thrombosis. A rate of hemoglobin rise of > 10 g/L over 2 weeks may contribute to these risks (see **CLINICAL TRIALS, Chronic Kidney Disease Patients, Increased Mortality, Serious Adverse Cardiovascular Reactions, Thromboembolic Events and Stroke**). ARANESP and other ESAs increased the risks for death and serious adverse cardiovascular reactions and thromboembolic events in some controlled clinical trials of patients with cancer. A rate of hemoglobin rise of > 10 g/L over 2 weeks may contribute to these risks.

CKD patients with hypo-responsiveness to ESAs may be at an increased risk for mortality and adverse cardiovascular reactions. These patients should be evaluated for treatable conditions (see **WARNINGS AND PRECAUTIONS: Lack or Loss of Response to ARANESP** and **DOSAGE AND ADMINISTRATION: Dose Adjustment for CKD Patients**). These risks should be carefully weighed against the benefit to be derived from treatment with ESAs, particularly in cancer patients with increased risk factors of thrombotic events, such as patients with a prior history of thrombovascular events (TVEs) (e.g., deep venous thrombosis or pulmonary embolism) (see **CLINICAL TRIALS** and **DOSAGE AND ADMINISTRATION: Chronic Kidney Disease Patients; Cancer Patients Receiving Chemotherapy**).

To minimize the risks for death and serious adverse cardiovascular reactions, follow the recommended dosage for each indication for ARANESP and other ESAs. For CKD patients, individualize dosing to achieve and maintain hemoglobin levels within the recommended range of 100 to 115 g/L, not to exceed 120 g/L. For patients with cancer, use the lowest dose sufficient to avoid blood transfusions. The rate of hemoglobin increase should not exceed 10 g/L in any 2 week period (see **DOSAGE AND ADMINISTRATION**).

An increased incidence of thromboembolic events has been observed in patients treated with erythropoietic agents. The anticipated benefits of ARANESP must be weighed against the potential for increased risks associated with therapy in the following populations: patients at risk for thrombosis; patients with pre-existing vascular disease; and in those patients with a known intolerance to antithrombotic agents.

An increased incidence of deep vein thrombosis (DVT) in patients receiving ESAs and undergoing surgical orthopedic procedures has been observed. Increased mortality was observed in patients receiving ESAs who were undergoing coronary artery bypass surgery. ARANESP is not authorized for reduction in allogeneic RBC transfusions in patients scheduled for surgical procedures.

### **Hematologic**

The safety and efficacy of ARANESP (darbepoetin alfa) therapy has not been established in patients with underlying hematologic diseases (e.g., hemolytic anemia, sickle cell anemia, thalassemia, porphyria).

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 serum transferrin saturation is below 20%.

## **Neurologic**

### **Seizures**

Use with caution in patients with a history of seizures. Seizures have occurred in patients participating in clinical trials of ARANESP and rHuEPO. During the first several months of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely. Patients should be cautioned to avoid potentially hazardous activities such as driving heavy machinery during this period. 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 10 g/L in any 2-week period in CKD patients or 15 g/L in any 3-week period in cancer patients.

### **Sensitivity/Resistance**

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

### **Severe Cutaneous Reactions**

Blistering and skin exfoliation reactions including Erythema multiforme and Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN), have been reported in a small number of patients treated with ARANESP in the post-marketing environment. Discontinue ARANESP therapy immediately if a severe cutaneous reaction, such as SJS/TEN, is suspected. As it is not known whether this is a class effect of ESAs, no recommendation can be made about switching to another ESA.

### **Lack or Loss of Response to ARANESP**

A lack of response or failure to maintain a hemoglobin response with ARANESP (darbepoetin alfa) doses within the recommended dosing range should prompt a search for causative factors. Deficiencies of iron, folic acid, or vitamin B<sub>12</sub> should be excluded or corrected. Depending on the clinical setting, intercurrent infections, inflammatory or malignant processes, osteofibrosis cystica, occult blood loss, severe aluminum toxicity, bone marrow fibrosis, insufficient dialysis and malnutrition may compromise an erythropoietic response.

If patients are hyporesponsive, or fail to respond to other erythropoietic agents, Pure Red Cell Aplasia (PRCA) or anti-erythropoietin antibody formation should be excluded. Patients with confirmed antibody-mediated PRCA should not be switched to ARANESP. See **DOSAGE**

**AND ADMINISTRATION: Dose Adjustment for CKD Patients** for the management of patients with an insufficient hemoglobin response to ARANESP therapy.

### **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 CKD patients receiving ARANESP by subcutaneous administration. For additional information on the use of ESAs and PRCA reactions in non-CKD patients, see **ADVERSE REACTIONS, Adverse Drug Reaction (ADR) Post-Marketing**.

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. If anti-erythropoietin antibody-associated anemia is suspected, withhold ARANESP and other ESAs. Contact Amgen Canada (1-866-502-6436) 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 ESAs as antibodies may cross react (see **ADVERSE REACTIONS, Immunogenicity**).

Suspected cases of PRCA in association with ARANESP should be reported to Amgen who may assist in this evaluation.

### **Sexual Function/Reproduction**

No data are available from human studies with regard to impairment of fertility (see **TOXICOLOGY**).

### **Special Populations**

#### **Chronic Kidney Disease Patients**

##### ***Patients With CKD Not Requiring Dialysis***

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

### ***Dialysis Management***

Therapy with ARANESP results in an increase in the number of red blood cells (RBCs) and a decrease in plasma volume, which could reduce dialysis efficiency; patients who are marginally dialyzed may require adjustments in their dialysis prescription.

The importance of compliance with a prescribed diet should be reinforced. Notably hyperkalemia is not uncommon in this patient population.

### **Cancer Patients**

#### **Increased Mortality and/or Increased Risk of Tumour Progression or Recurrence**

Erythropoiesis-stimulating agents (ESAs), when administered to target a hemoglobin level of > 120 g/L, shortened the time to tumour progression in patients with advanced head and neck cancer receiving radiation therapy. ESAs also shortened survival in patients with metastatic breast cancer and in patients with lymphoid malignancy receiving chemotherapy when administered to target a hemoglobin level  $\geq$  120 g/L.

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 level of  $\geq$  120 g/L.

An increased risk of death was observed in a clinical study when ESAs were administered to target hemoglobin of 120 g/L in patients with active malignant disease who were not being treated with either chemotherapy or radiation therapy. ARANESP is not indicated for use in patients with cancer who have anemia that is not associated with chemotherapy (see **CLINICAL TRIALS, Cancer Patients, Tumour Progression, Increased Mortality and Thromboembolic Events**).

In view of the above, where appropriate red blood cell transfusion should be the preferred treatment for the management of anemia in patients with cancer. The decision to administer ESAs should be based on a benefit-risk assessment with the participation of the individual patient. This should take into account the specific clinical context such as (but not limited to) the type of tumour and its stage, the degree of anemia, life-expectancy, the environment in which the patient is being treated, and known risks of transfusions and ESAs.

### **Pregnant Women**

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.

Reproductive studies in rats showed no significant placental transfer of ARANESP. Studies in rats and rabbits, in which ARANESP was administered during gestation, showed no evidence of direct embryotoxic, fetotoxic, or teratogenic properties at doses up to 40 times the human dose. The only adverse effect observed was a slight reduction in fetal weight, which was seen at doses causing exaggerated pharmacological effects in the dams. No treatment effects on uterine implantation were seen in either species.

## **Nursing Women**

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.

## **Pediatrics**

The safety and efficacy of ARANESP in pediatric patients has not been established.

## **Geriatrics**

### ***Chronic Kidney Disease Patients***

The results of clinical trials with ARANESP suggest no increased safety risk with increasing age. Of more than 1500 patients with CKD treated with ARANESP, 43% were 65 years of age or older. Of these geriatric patients, 35% were 75 years of age or older. Regardless of age, the administration of ARANESP, either IV or SC, resulted in a dose-dependent and sustained increase in hemoglobin. No differences in dose requirements between geriatric and younger adults were observed. No overall differences in safety or efficacy were observed between these subjects and younger subjects. A greater sensitivity in older patients cannot be ruled out.

### ***Cancer Patients***

Of the 873 cancer patients in clinical studies receiving ARANESP and concomitant chemotherapy, 45% were age 65 and over, while 14% were 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients.

## **Monitoring and Laboratory Tests**

### **Chronic Kidney Disease Patients**

In order to avoid an excessive rate of rise or exceeding the recommended hemoglobin range of 100 to 115 g/L, not to exceed 120 g/L, the guidelines for dose and frequency of dose adjustments should be followed. 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: Chronic Kidney Disease Patients**). 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%.

### **Cancer Patients**

The hemoglobin concentration after initiation of ARANESP therapy should be monitored at regular intervals to assess the need to modify dose based on the individual patient's response (see **DOSAGE AND ADMINISTRATION: Cancer Patients Receiving Chemotherapy**).

## **ADVERSE REACTIONS**

### **All Patients**

#### **Thrombotic/Vascular Events**

The following thrombotic/vascular events have been reported in patients receiving ESAs (some with fatal outcomes): venous and arterial thromboses and embolism (such as deep venous thrombosis, arterial thrombosis, pulmonary emboli, aneurysms, retinal thrombosis, clotting of vascular access), cerebrovascular accidents (including cerebral infarction and cerebral hemorrhage) and transient ischemic attacks.

#### **Chronic Kidney Disease Patients**

In all studies with CKD patients, 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 AND PRECAUTIONS: Increased Mortality, Serious Adverse Cardiovascular Reactions, Thromboembolic Events and Stroke**). The most frequently reported adverse reactions resulting in clinical intervention (eg, 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 CKD 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 CKD, 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 ESAs.

The data in Table 1 reflect those adverse events occurring in at least 5% of CKD patients treated with ARANESP.

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

<b>Event</b>	<b>CKD Patients Treated With ARANESP (n = 1598)</b>
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%

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

<b>Event</b>	<b>CKD Patients Treated With ARANESP (n = 1598)</b>
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.

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

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

<b>Event</b>	<b>CKD Patients Treated With ARANESP (n = 1598)</b>
Acute Myocardial Infarction	2%
Seizure	1%
Stroke	1%
Transient Ischemic Attack	1%

Vascular access thrombosis occurred in CKD clinical trials at an annualized rate of 0.22 events per patient year of ARANESP therapy. Rates of thrombotic events (eg, vascular access thrombosis, venous thrombosis, and pulmonary emboli) with ARANESP therapy were similar to those observed with rHuEPO therapy in these trials.

### **Cancer Patients Receiving Chemotherapy**

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

The most frequently reported serious adverse events included death (10%), fever (4%), pneumonia (3%), dehydration (3%), vomiting (2%), and dyspnea (2%). The most commonly reported adverse events were fatigue, edema, nausea, vomiting, diarrhea, fever, and dyspnea (see **Table 3**). The most commonly reported adverse reaction was injection site pain (see **Table 4**).

Except for those events listed in Table 3, 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 events leading to 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 ESAs.

**Table 3. Adverse Events<sup>a</sup> Occurring in  $\geq 5\%$  of Cancer Patients Receiving Chemotherapy**

<b>Event</b>	<b>All ARANESP (n = 873)</b>	<b>Placebo (n = 221)</b>
<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%

<sup>a</sup> An adverse event is defined as an event that presents during treatment but does not necessarily have a causal relationship to ARANESP.

**Table 4. Adverse Reactions Occurring in  $\geq 1\%$  of Cancer Patients Receiving Chemotherapy**

<b>Event</b>	<b>ARANESP (N = 873)</b>	<b>Placebo (N = 221)</b>
	n (%)	n (%)
Number of Patients with an Adverse Reaction <sup>b</sup>	98 (11)	14 (6)
Injection Site Pain	36 (4)	6 (3)

<sup>b</sup> An adverse reaction is defined as an event determined to be causally related to treatment with ARANESP.

Adverse reactions occurring in less than 1% of cancer patients treated with ARANESP include the following events:

*Application Site:* injection site ecchymosis, injection site edema, injection site paresthesia, injection site rash, injection site reaction.

*Body as a Whole:* fever, pain, peripheral edema, rigors, allergic reaction, fatigue, malaise, chest pain.

*CNS/PNS:* headache, dizziness, insomnia, cerebrovascular disorder, hypertonia, hypoesthesia, peripheral neuropathy, paresthesia.

*Cardiovascular:* hypertension, hypotension.

*Gastrointestinal:* diarrhea, nausea, vomiting, constipation, abdominal pain, anorexia, dry mouth, dyspepsia, tongue edema, GI hemorrhage, oral moniliasis, mucositis.

*Hematologic:* ecchymosis, hematoma, thrombocytopenia.

*Metabolic/Nutrition:* hypomagnesemia.

*Musculo-Skeletal:* involuntary muscular contraction, skeletal pain, myalgia, limb pain, arthralgia, back pain, joint stiffness, muscle weakness.

*Resistance Mechanism:* Herpes Zoster, sepsis.

*Respiratory:* dyspnea, cough, pulmonary embolism, hemoptysis, rhinitis, sore throat.

*Skin & Appendages:* increased sweating, erythema, skin lesion, rash, pruritus, maculopapular rash, dry skin, skin ulceration.

*Special Senses:* parosmia, taste perversion.

*Urinary Disorders:* nocturia.

*Vascular Disorders:* deep venous thrombosis, thrombosis.

*Vision Disorders:* abnormal lacrimation, abnormal vision.

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

<b>Event</b>	<b>All ARANESP (n = 873)</b>	<b>Placebo (n = 221)</b>
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.

Once-every-3-week dosing in chemotherapy-treated patients was assessed in a 705 patient active-controlled, double-blind study with 4 months of ARANESP treatment. The incidence of adverse reactions was similar between subjects treated with ARANESP at the starting dose of 500 mcg once every 3 weeks and ARANESP at the starting dose of 2.25 mcg/kg/week.

### **Thrombotic Events and Adverse Cardiovascular Reactions**

Overall, the incidence of thrombotic events was 6.2% for ARANESP and 4.1% for placebo. The following events were reported more frequently in ARANESP-treated patients than in placebo controls: pulmonary embolism, thromboembolism, thrombosis, and thrombophlebitis (deep and/or superficial). In addition, edema of any type was more frequently reported in ARANESP-treated (21%) patients than in patients who received placebo (10%) (see Table 3).

### **Immunogenicity**

As with all therapeutic proteins, there is a potential for immunogenicity. Radioimmunoprecipitation assays were performed on sera from 1534 CKD patients and 833 cancer patients treated with ARANESP. High-titer antibodies were not detected, but assay sensitivity may be inadequate to reliably detect lower titers. Since the incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may additionally be influenced by several factors including sample handling, concomitant medications, and underlying disease, comparison of the incidence of antibodies to ARANESP with the incidence of antibodies to other products may be misleading.

## **Adverse Drug Reaction (ADR) Post-Marketing**

In the post-marketing experience, the following have been reported in patients treated with ARANESP:

- Very rare cases of PRCA associated with neutralizing anti-erythropoietin antibodies (see **WARNINGS AND PRECAUTIONS: Pure Red Cell Aplasia**)
- Convulsions/seizures
- Serious allergic reactions including anaphylactic reaction, angioedema, allergic bronchospasm, skin rash and urticaria
- Severe cutaneous reactions including blistering, skin exfoliation, erythema multiforme and SJS/TEN (see **WARNINGS AND PRECAUTIONS, Severe Cutaneous Reactions**)

Cases of PRCA have been rarely reported in patients with hepatitis C treated with interferon and ribavirin, when ESAs are used concomitantly. ESAs are not approved for the management of anemia associated with hepatitis C.

## **DRUG INTERACTIONS**

No formal drug interaction studies of ARANESP with other medications commonly used in CKD or cancer patients have been performed.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

**IMPORTANT: See WARNINGS AND PRECAUTIONS: SERIOUS WARNINGS AND PRECAUTIONS Box, and Increased Mortality, Serious Adverse Cardiovascular Reactions, Thromboembolic Events and Stroke. ARANESP dosing regimens are different for each of the indications described in the INDICATIONS AND CLINICAL USE section of this product monograph. ARANESP should be administered under the supervision of a healthcare professional. Due to the longer serum half-life, ARANESP should be administered less frequently than Epoetin alfa (for example, where Epoetin alfa is administered three times a week, ARANESP should be administered weekly). When changing the route of administration, the same dose should be used and the hemoglobin monitored so that the appropriate dose adjustments can be made to keep the hemoglobin at the desired concentration.**

### **Chronic Kidney Disease Patients**

ARANESP is administered either IV or SC as a single injection administered weekly or once every two weeks. The dose should be started and slowly adjusted as described below based on hemoglobin levels. If a patient fails to respond or maintain a response, other etiologies should be considered and evaluated (see **WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests; Lack or Loss of Response to ARANESP, Pure Red Cell Aplasia**). When ARANESP therapy is initiated or adjusted, the hemoglobin should be followed weekly until stabilized and monitored at least monthly thereafter.

For patients who respond to ARANESP with a rapid increase in hemoglobin (eg, more than 10 g/L in any 2-week period), the dose of ARANESP should be reduced (see **DOSAGE AND ADMINISTRATION: Dose Adjustment for CKD Patients**) because of the association of excessive rate of rise of hemoglobin with adverse events (see **WARNINGS AND PRECAUTIONS: Increased Mortality, Serious Adverse Cardiovascular Reactions, Thromboembolic Events and Stroke**).

It should be recognized that subcutaneous administration of recombinant human proteins may increase the risk of immunogenicity. In patients on hemodialysis, the IV route is recommended.

### **Correction of Anemia in Chronic Kidney Disease Patients**

The treatment of anemia in chronic renal failure patients should be individualized. The choice of the treatment modality (iron, erythropoiesis-stimulating agent, blood transfusion) and of the amount of therapeutic product administered should take into consideration the overall condition and treatment plan for the patient (e.g., presence of concomitant conditions, risk factors, plan for renal transplant, etc.) as well as national guidelines. ESA therapy should only be initiated if hemoglobin is less than 100 g/L.

The recommended starting dose of ARANESP for the correction of anemia in CKD patients is 0.45 mcg/kg body weight, administered as a single IV or SC injection once weekly. Doses should be titrated to achieve and maintain the hemoglobin within the recommended range of 100 to 115 g/L, not to exceed 120 g/L. If hemoglobin excursions outside the recommended range occur ARANESP dose should be adjusted using the dosing recommendations below (see **DOSAGE AND ADMINISTRATION: Dose Adjustment for CKD Patients**). For many patients, the appropriate maintenance dose will be lower than this starting dose. CKD patients not receiving dialysis, in particular, may require lower maintenance doses. Also, some patients have been treated successfully with a SC dose of ARANESP administered once every 2 weeks.

### **Conversion to ARANESP from Recombinant Human Erythropoietin in CKD Patients**

The clinical studies demonstrated that the relationship between baseline rHuEPO and maintenance ARANESP is nonlinear across the dosing spectrum. Consequently, the starting weekly dose of ARANESP should be estimated on the basis of the weekly Epoetin alfa dose at

the time of substitution (see Table 6). Due to the longer serum half-life, ARANESP should be administered less frequently than rHuEPO. Patients receiving rHuEPO 2 or 3 times weekly should change to once weekly ARANESP at a dose equivalent to their total weekly dose of rHuEPO. Patients receiving rHuEPO once per week should change to ARANESP once every 2 weeks at a dose that is equivalent to the sum of 2 weekly doses of rHuEPO. The same route of administration should be used. For patients prescribed prefilled syringes the calculated dose should be rounded upward to the next available syringe strength.

**Table 6. Estimated ARANESP Starting Dose (mcg/week) Based on Previous Epoetin alfa Dose (Units/week) for CKD Patients**

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

Patients should be carefully monitored to ensure appropriate dose adjustments in order to maintain appropriate hemoglobin levels (see **DOSAGE AND ADMINISTRATION: Dose Adjustment for CKD Patients**).

Data from approximately 800 patients receiving ARANESP in clinical studies were analysed to assess the dose required to maintain hemoglobin; no difference was observed between the average weekly dose administered by the IV or SC routes of administration.

Because of intersubject variability, titration to the optimal therapeutic ARANESP dose is required for individual patients. When a patient's hemoglobin is stabilized within the recommended range it should be monitored monthly and adjustments made as described below (see **DOSAGE AND ADMINISTRATION: Dose Adjustment for CKD Patients**).

### **Dose Adjustment for CKD Patients**

The dose of ARANESP should be individualized to achieve and maintain the hemoglobin within the recommended range of 100 to 115 g/L, not to exceed 120 g/L. If hemoglobin excursions outside the recommended range occur ARANESP dose should be adjusted using the dosing recommendations below.

Because of the time required for erythropoiesis and the red cell half-life, an interval of 2 to 6 weeks may occur between the time of a dose adjustment and a significant change in hemoglobin. Increases in dose should not be made more frequently than once a month. If the hemoglobin is increasing and approaching 120 g/L, the dose should be reduced by approximately 25%. If after a dose reduction, the hemoglobin continues to increase, or if the hemoglobin is 120 g/L or above, the dose 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 10 g/L in a 2-week period, the dose should be decreased by approximately 25%.

After ARANESP initiation or dose increase, if the increase in hemoglobin is less than 10 g/L over 4 weeks and iron stores are adequate (see **WARNINGS AND PRECAUTIONS: Hematologic**), 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 desired response is attained.

For patients whose hemoglobin does not attain a level within the range of 100 to 120 g/L 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 **WARNINGS AND PRECAUTIONS: Increased Mortality, Serious Adverse Cardiovascular Reactions, Thromboembolic Events and Stroke**), and
- thereafter, hemoglobin should continue to be monitored and if responsiveness improves, ARANESP dose adjustments should be made as described above; use caution when increasing the dose for patients with lack or loss of response, discontinue ARANESP if responsiveness does not improve and the patient needs recurrent RBC transfusions.

### **Maintenance Dose for CKD Patients**

ARANESP dosage should be individualized to maintain the hemoglobin within the recommended range of 100 to 115 g/L, not to exceed 120 g/L. If hemoglobin excursions outside the recommended range occur, ARANESP dose should be adjusted using the dosing recommendations above. If the hemoglobin exceeds 120 g/L, the dose should be temporarily withheld until the Hb has decreased to within the recommended range. Doses must be individualized to ensure that hemoglobin is maintained at an appropriate level for each patient.

### **Cancer Patients Receiving Chemotherapy**

ARANESP should not be initiated at hemoglobin levels  $\geq$  100 g/L. Two dosing regimens may be used in adults; 500 mcg SC once every 3 weeks or 2.25 mcg/kg SC once weekly. ARANESP administration should be discontinued following the completion of a chemotherapy course.

Discontinue ARANESP if after 8 weeks of therapy there is no response as measured by increased hemoglobin levels or decreased need for RBC transfusions.

### **Once-Every-Three-Week (Q3W) Dosing**

The recommended starting dose for ARANESP administered once every 3 weeks is 500 mcg as a SC injection.

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 120 g/L. Hemoglobin levels should be monitored, prior to dosing, at least every 3 weeks until the lowest level sufficient to avoid the need for RBC transfusion is reached and thereafter.

Doses of ARANESP should be decreased by approximately 40% (eg, 300 mcg once every 3 weeks) when the hemoglobin reaches a level needed to avoid red blood cell transfusion or increases by more than 10 g/L in a 2-week period or 15 g/L in any 3-week period. If the hemoglobin exceeds a level needed to avoid transfusion, ARANESP should be temporarily withheld until the hemoglobin approaches a level where RBC transfusions may be required. At this point, therapy should be reinitiated at a dose 40% below the previous dose (eg, 300 mcg once every 3 weeks).

### **Once-Weekly Dosing**

The recommended starting dose of ARANESP administered weekly is 2.25 mcg/kg as a SC injection. 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 120 g/L.

If the increase in hemoglobin is inadequate ( $\leq 10$  g/L) or if the response is not satisfactory in terms of reducing RBC transfusion requirements after approximately 6 weeks of therapy, the dose of ARANESP should be increased up to 4.5 mcg/kg/week. For patients prescribed prefilled syringes the calculated dose should be rounded upward to the next available syringe strength.

Hemoglobin levels should be monitored, prior to dosing, on a weekly basis until the lowest level sufficient to avoid the need for RBC transfusion is reached, and every 3 weeks thereafter. Doses of ARANESP should be decreased by 40% as the hemoglobin reaches a level needed to avoid RBC transfusion or the rate of hemoglobin increase is more than 10 g/L in a 2-week period or 15 g/L in a 3-week period. If the hemoglobin exceeds a level needed to avoid RBC transfusion, doses should be temporarily withheld until the hemoglobin approaches a level where RBC transfusions may be required. At this point, therapy should be reinitiated at a dose 40% below the previous dose.

## **Administration**

### **Information for Patients**

In those situations in which the physician determines that a patient can safely and effectively self-administer ARANESP, the patient should be instructed as to the proper dosage and administration technique. Patients should be referred to the “**CONSUMER INFORMATION**” section of the monograph. This is intended as a guide for patients; however, it is not a disclosure of all possible side effects. Patients should be informed of the signs and symptoms of allergic drug reactions and advised of appropriate actions.

Following administration of ARANESP from the prefilled syringe, the patient should activate the UltraSafe<sup>®</sup> Needle Guard by placing their hands behind the needle, grasping the guard with one hand, and sliding 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.

If home use is prescribed for a patient, the patient should be thoroughly instructed in the importance of proper disposal of syringes and cautioned against the reuse of needles and syringes, or drug product. A puncture-resistant container for the disposal of used syringes and needles should be available to the patient. The full container should be disposed of according to the directions provided by the physician, pharmacist or nurse.

### **OVERDOSAGE**

If overdose occurs, the patient’s hemoglobin, blood pressure, and any premonitory neurologic symptoms should be carefully monitored.

The maximum amount of ARANESP (darbepoetin alfa) that can be safely administered in single or multiple doses has not been determined. Therapy with ARANESP can result in polycythemia if the hemoglobin is not carefully monitored and the dose appropriately adjusted. Severe hypertension (including hypertensive crisis and malignant hypertension) has been observed following overdose with ARANESP (see **WARNINGS AND PRECAUTIONS, Cardiovascular, Hypertension**). If the recommended hemoglobin range is exceeded, ARANESP should be temporarily withheld until the hemoglobin returns to the recommended range; ARANESP therapy may then be resumed using a lower dose (see **DOSAGE AND ADMINISTRATION**). If clinically indicated, phlebotomy may be performed.

For management of a suspected drug overdose, contact your regional Poison Control Centre.
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## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

ARANESP (darbepoetin alfa) is an erythropoiesis-stimulating agent produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. The final processed form is a 165-amino acid protein containing 5 N-linked oligosaccharide chains, whereas endogenous erythropoietin (EPO) or recombinant human erythropoietin (rHuEPO) contain only 3. Erythropoietin is a glycoprotein that is the primary regulator of erythropoiesis through specific interaction with the erythropoietin receptor on the erythroid progenitor cells in the bone marrow. The production of erythropoietin primarily occurs in and is regulated by the kidney in response to changes in tissue oxygenation. Hypoxia and anemia generally result in an increase in endogenous erythropoietin production, which in turn stimulates erythropoiesis. ARANESP stimulates erythropoiesis by the same mechanism as endogenous erythropoietin.

Endogenous erythropoietin production is impaired in patients with chronic kidney disease (CKD) and EPO deficiency is the primary cause of their anemia. ARANESP has been shown to stimulate erythropoiesis in anemic CKD patients resulting in the correction of anemia and maintenance of hemoglobin levels within a defined target range in patients not previously receiving rHuEPO. In patients previously maintained on rHuEPO who were switched to ARANESP, hemoglobin levels were maintained within a defined target range.

The etiology of anemia in cancer patients is multifactorial. Erythropoietin deficiency and a blunted response of erythroid progenitor cells to endogenous erythropoietin contribute significantly towards anemia in these patients. ARANESP has been shown to stimulate erythropoiesis, resulting in increased hemoglobin levels and a reduced need for red blood cell (RBC) transfusions in cancer patients.

### **Pharmacokinetics**

Due to its increased sialic acid containing carbohydrate content, ARANESP has an approximately 3-fold longer terminal half-life than rHuEPO and consequently a greater *in vivo* activity when administered by either the subcutaneous (SC) or intravenous (IV) route. Receptor-binding studies indicate that ARANESP has a reduced binding affinity to the EPO receptor compared with rHuEPO, explained by the addition of sialic acids; however, the relationship between the increased amount of sialic acid-containing carbohydrate on the molecule and an increase in serum half-life accounts for the observed greater biological effect with ARANESP. The pharmacokinetics of ARANESP were studied in adults with chronic kidney disease and adult cancer patients receiving chemotherapy.

## **Chronic Kidney Disease Patients**

Following IV administration to adult CKD patients, ARANESP serum concentration-time profiles are biphasic, with a distribution half-life of approximately 1.4 hours and mean terminal half-life of approximately 21 hours.

Following SC administration, the absorption is slow and rate-limiting, and the terminal half-life is 49 hours (range: 27 to 89 hours), which reflects the absorption half-life. The peak concentration occurs at 34 hours (range: 24 to 72 hours) post-SC administration in adult CKD patients, and bioavailability is approximately 37% (range: 30% to 50%).

The distribution of ARANESP in adult CKD patients is predominantly confined to the vascular space (approximately 60 mL/kg). The pharmacokinetic parameters indicate dose-linearity over the therapeutic dose range. With once weekly dosing, steady-state serum levels are achieved within 4 weeks with < 2-fold increase in peak concentration when compared to the initial dose. Accumulation was negligible following both IV and SC dosing over 1 year of treatment.

## **Cancer Patients**

Following SC administration of 2.25 mcg/kg/week to adult cancer patients (n = 26), a mean peak concentration of 10.6 ng/mL (range: 1.23 to 25.2 ng/mL) was achieved at a mean time of 90.5 hours (range: 70.8 to 123 hours). The data were consistent with dose-linear pharmacokinetics over a wide dose range (0.5 to 8.0 mcg/kg weekly and 3.0 to 9.0 mcg/kg every 2 weeks). Upon multiple dosing over 12 weeks (dosing every week or every 2 weeks), the pharmacokinetic properties did not change. The expected moderate increases (< 2-fold) in ARANESP serum concentrations upon multiple dosing were observed as steady state was approached. Accumulation was negligible across a wide range of doses at once weekly and once every 2 weeks dosing schedules. Although the accumulation potential of ARANESP is unknown for longer-term (i.e., > 12 weeks) treatment in cancer patients, the extent (< 2-fold) accumulation observed at 12 weeks was the same as that observed at 4 weeks.

Over the dose range of 4.5 to 15 mcg/kg administered on a once-every-3-week (Q3W) schedule to cancer patients receiving chemotherapy, ARANESP pharmacokinetics were approximately linear with respect to dose, and no evidence of accumulation was observed.

Following SC administration of 6.75 mcg/kg (equivalent to 500 mcg for a 74-kg patient) on a Q3W schedule to cancer patients, peak concentrations occurred at 71 hours (range: 28 to 120 hours), and a terminal half-life of 74 hours (range: 24 to 144 hours) was observed. No evidence of marked (> 2-fold) accumulation was observed upon Q3W SC dosing of 6.75 mcg/kg. Exposure to ARANESP when administered on a Q3W schedule (6.75 mcg/kg), either on the same day of chemotherapy or mid cycle was comparable, with mean AUC values differing by less than 28% between groups. Although approximately 30-70% differences in mean terminal half-life or peak concentration values were observed between groups, no clinically significant differences in efficacy or safety between groups was observed, suggesting limited clinical

significance of the findings. Following IV or SC administration of 4.5 mcg/kg on a Q3W schedule, mean trough or 1- to 2-week postdose ARANESP serum levels were comparable between the IV and SC groups after multiple dosing.

## STORAGE AND STABILITY

Store at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. Protect from light. Do not use ARANESP beyond the expiry date shown on the label.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

### Dosage Forms

The following dosage forms are available for ARANESP (darbepoetin alfa):

**Table 7. SingleJect® Prefilled Syringes**

Quantity of ARANESP	Volume	ARANESP Concentration
10 mcg	0.4 mL	25 mcg/mL
15 mcg <sup>‡</sup>	0.38 mL	40 mcg/mL
20 mcg	0.5 mL	40 mcg/mL
30 mcg	0.3 mL	100 mcg/mL
40 mcg	0.4 mL	100 mcg/mL
50 mcg	0.5 mL	100 mcg/mL
60 mcg	0.3 mL	200 mcg/mL
80 mcg	0.4 mL	200 mcg/mL
100 mcg	0.5 mL	200 mcg/mL
130 mcg	0.65 mL	200 mcg/mL
150 mcg	0.3 mL	500 mcg/mL
200 mcg	0.4 mL	500 mcg/mL
250 mcg <sup>‡</sup>	0.5 mL	500 mcg/mL
300 mcg	0.6 mL	500 mcg/mL
400 mcg <sup>‡</sup>	0.8 mL	500 mcg/mL
500 mcg	1.0 mL	500 mcg/mL

<sup>‡</sup>15, 250, 400 mcg/syringe pre-filled syringes are not available in Canada.

To reduce the risk of accidental needle sticks to users, each prefilled syringe is equipped with an UltraSafe® Needle Guard that is manually activated to cover the needle during disposal.

**Table 8. Single-dose Vials<sup>†</sup>**

Quantity of ARANESP	Volume	ARANESP Concentration
15 mcg	1.0 mL	15 mcg/mL
60 mcg	1.0 mL	60 mcg/mL
325 mcg	1.0 mL	325 mcg/mL

**Composition**

Vials<sup>†</sup> and syringes contain the following in sterile Water for Injection, USP (per 1.0 mL). The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex).

**Table 9. Inactive Ingredients**

	Each 1 mL contains <sup>a</sup>
Polysorbate 80	0.05 mg
Sodium Phosphate Monobasic Monohydrate	2.12 mg
Sodium Phosphate Dibasic Anhydrous	0.66 mg
Sodium Chloride	8.18 mg
Water for Injection, USP	Up to 1 mL

<sup>a</sup> ARANESP is formulated as a sterile, colorless solution, pH 6.2 ± 0.2

ARANESP does not contain any preservatives.

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<sup>†</sup> Single-dose vial presentation is not available in Canada.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

<b>Proper name:</b>	darbepoetin alfa
<b>Chemical name:</b>	Novel Erythropoiesis-Stimulating Agent
<b>Molecular mass:</b>	37.1 kd (based on known amino acid and carbohydrate structure)

#### Product Characteristics

Aranesp<sup>®</sup> (darbepoetin alfa) is an erythropoiesis-stimulating agent produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. The final processed form is a 165-amino acid protein containing 5 N-linked oligosaccharide chains and 1 O-linked oligosaccharide chain.

### CLINICAL TRIALS

#### Chronic Kidney Disease Patients

The safety and effectiveness of ARANESP have been assessed in multicenter studies. Two studies evaluated the safety and efficacy of ARANESP for the correction of anemia in adult patients with CKD, 2 studies assessed the ability of ARANESP to maintain hemoglobin concentrations in adult patients with CKD who had been receiving other ESAs, and 2 studies assessed a manufacturing change.

#### De Novo Use of ARANESP

In two open-label studies, ARANESP or rHuEPO were administered for the correction of anemia in CKD patients who had not been receiving prior treatment with exogenous erythropoietin. Study 1 evaluated CKD patients receiving dialysis; Study 2 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 rHuEPO was 50 U/kg 3 times weekly in Study 1 and 50 U/kg twice weekly in Study 2. When necessary, dosage adjustments were instituted to maintain hemoglobin in the study target range of 110 to 130 g/L (see **DOSAGE AND ADMINISTRATION: Chronic Kidney Disease Patients** for recommended clinical hemoglobin target). The primary efficacy endpoint was the proportion of patients who experienced at least a 10 g/L increase in hemoglobin concentration to a level of at least 110 g/L by 20 weeks (Study 1) or 24 weeks (Study 2). The studies were designed to assess the safety and

effectiveness of ARANESP but not to support conclusions regarding comparisons between the 2 products.

In Study 1, 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 rHuEPO. The mean increase in hemoglobin over the initial 4 weeks of ARANESP treatment was 11.0 g/L (95% CI: 8.2 g/L, 13.7 g/L).

In Study 2, 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 rHuEPO. The mean increase in hemoglobin from baseline through the initial 4 weeks of ARANESP treatment was 13.8 g/L (95% CI: 12.1 g/L, 15.5 g/L).

### **Conversion From Other ESAs**

Two studies (Studies 3 and 4) were conducted in adult patients with CKD who had been receiving ESAs and compared the abilities of ARANESP and erythropoietic agents to maintain hemoglobin concentrations within a study target range of 90 to 130 g/L (see **DOSE AND ADMINISTRATION** for recommended clinical hemoglobin target). CKD patients who had been receiving stable doses of ESAs 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 ESA. Study 3 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 4 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 3, 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 4, 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.

### **Other Studies**

Study 5 (N = 446) was a multicenter, randomized, double-blind, 28-week, study of the efficacy and safety of darbepoetin alfa manufactured by 2 processes for the treatment of anemia in patients with CKD receiving hemodialysis. Study 6 (N = 1127) was an open-label, single-arm, multicenter study to assess the safety of darbepoetin alfa manufactured by the modified process administered for up to 1 year to CKD patients who were receiving or not receiving dialysis. The hemoglobin target range for Study 5 was 100 to 130 g/L and 110 to 130 g/L for Study 6.

Study 5 demonstrated comparability between the two manufacturing processes in terms of safety and efficacy. The results demonstrate that darbepoetin alfa manufactured by the modified process is equivalent to darbepoetin alfa manufactured using the original process for hemoglobin maintenance and dosing. Mean (SD) hemoglobin concentrations were comparable at baseline (118 [8.0] vs 118 [7.8] g/L) and during the evaluation period (116 [10.7] vs 118 [10.4]). Mean (SD) weekly doses ( $\mu\text{g}/\text{week}$ ) were also comparable in both groups at baseline (36.54 [24.16] vs 37.32 [27.84]) and during the evaluation period (32.09 [26.47] vs 31.10 [26.63]). Safety results were similar in both darbepoetin alfa groups and no new safety information was identified. Safety findings from Study 6 similarly demonstrated no new safety information.

### **Increased Mortality, Serious Adverse Cardiovascular Reactions, Thromboembolic Events and Stroke**

In a clinical trial of Epoetin alfa treatment in hemodialysis patients with clinically evident cardiac disease, patients were randomized to a target hemoglobin of either  $140 \pm 10$  g/L or  $100 \pm 10$  g/L. Higher mortality (35% versus 29%) was observed in the 634 patients randomized to a target hemoglobin of 140 g/L than in the 631 patients assigned a target hemoglobin of 100 g/L. 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 140 g/L.

A randomized prospective trial (CHOIR) evaluated 1432 anemic chronic renal failure patients who were not undergoing dialysis. Patients were assigned to epoetin alfa treatment targeting a maintenance hemoglobin concentration of 135 g/L or 113 g/L. A major adverse cardiovascular reaction (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,  $p = 0.03$ ).

In a randomized, double-blind, placebo-controlled study of 4038 patients, there was an increased risk of stroke when ARANESP was administered to patients with anemia, type 2 diabetes, and CKD who were not on dialysis. Patients were randomized to ARANESP treatment targeted to a hemoglobin level of 130 g/L or to placebo. Placebo patients received ARANESP only if their hemoglobin levels were less than 90 g/L. A total of 101 patients receiving ARANESP experienced stroke compared to 53 patients receiving placebo (5% vs. 2.6%; HR 1.92, 95% CI: 1.38, 2.68;  $p < 0.001$ ).

In CKD patients treated with ARANESP or ESAs in ARANESP clinical trials, increases in hemoglobin greater than approximately 10 g/L during any 2-week period were associated with increased incidence of cardiac arrest, neurologic events (including seizures and stroke), exacerbations of hypertension, congestive heart failure, vascular thrombosis/ischemia/infarction, acute myocardial infarction, and fluid overload/edema.

## **Cancer Patients**

### **Cancer Patients Receiving Chemotherapy**

The use of ARANESP in anemic cancer patients undergoing chemotherapy was evaluated in seven studies that were active controlled and/or placebo controlled for up to 6 months duration, at a variety of dosing schedules (1 dose per week, 1 dose every 2 weeks, and 1 dose every 3 weeks). Patients were treated with ARANESP at doses as low as 3.0 mcg/kg administered once every two weeks and as low as 6.75 mcg/kg administered once every three weeks.

### **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  $\leq$  110 g/L) 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.

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). This represents a greater than 50% reduction in the percentage of patients requiring RBC transfusions ( $p < 0.001$ ). In this double-blind, placebo-controlled phase 3 study, the safety profile of ARANESP was shown to be similar to that of the placebo-control group (see **ADVERSE REACTIONS**).

### **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  $<$  110 g/L) patients with non-myeloid malignancies receiving multicycle chemotherapy. Patients were randomized to receive either a starting dose of ARANESP 500 mcg Q3W (n = 353) or a starting dose of ARANESP 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 if hemoglobin increased by more than 10 g/L in a 14-day period, and study drug was withheld if hemoglobin exceeded 130 g/L.

Efficacy was determined by a reduction in the proportion of patients who received at least one RBC transfusion between week 5 and the end of treatment at week 16. A similar proportion of patients in the ARANESP Q3W and weekly groups required a RBC transfusion between weeks

5 and 16 (see Table 10). Sixty-seven percent of the patients in the Q3W group vs 75% of the patients in the QW group had dose reductions.

**Table 10. Percentage (95% CI) of Patients Receiving at Least One RBC Transfusion Between Week 5 and 16**

	<b>Q3W ARANESP dosing</b>	<b>QW ARANESP dosing</b>	<b>Difference</b>
<b>RBC transfusion</b>	23% (19%, 28%)	30% (25%, 35%)	-6.8% (-13.6%, 0.1%)

Note: Percentages are estimated using Kaplan-Meier methodology

In a randomized, placebo-controlled, dose-finding trial evaluating Q3W doses of ARANESP ranging from 4.5 mcg/kg to 15 mcg/kg, the minimally effective starting dose with respect to reducing RBC transfusion requirements was 4.5 mcg/kg.

Other randomized clinical studies have been conducted to assess the safety and efficacy of ARANESP administered Q3W. In a randomized, controlled trial, the impact of the timing of once-per-chemotherapy-cycle ARANESP dosing was evaluated with ARANESP given either on the same day as chemotherapy or administered in the middle of the chemotherapy cycle. The results indicated that ARANESP administered on the same day as myelotoxic chemotherapy did not result in any clinically relevant difference in RBC transfusion requirement or safety profile compared with mid-cycle dosing. In a separate trial where cancer patients receiving chemotherapy were randomized to either subcutaneous or intravenous administration of ARANESP, no clinically relevant differences in RBC transfusion requirements or safety were observed.

### **Tumour Progression, Increased Mortality and Thromboembolic Events**

To assess tumour growth factor potential, the effect of ARANESP on tumour progression and survival was evaluated through long-term surveillance of patients treated in the pivotal clinical study. After a median observation period of approximately 1 year, the median time to disease progression in the ARANESP group (n = 155) was 29 weeks (95% CI: 22, 33) compared with 22 weeks (95% CI: 18, 25) in the placebo group (n = 159). The median time to death in the ARANESP group (n = 155) was 43 weeks (95% CI: 37, not estimable) compared with 35 weeks (95% CI: 29, 48) in the placebo group (n = 159). Statistically significant differences in time-to-progression (TTP) or overall survival (OS) were not observed. However, the study was not designed to detect or exclude clinically meaningful differences in either TTP or OS.

In clinical trials of ARANESP in anemic cancer patients receiving chemotherapy, a hemoglobin increase of > 20 g/L per 4-week period was associated with an increased incidence of thrombosis. For anemic cancer patients receiving chemotherapy, it is recommended that the dose of ARANESP be decreased if the rate of hemoglobin increase is more than 15 g/L per 3-week period.

A phase III double-blind, randomized, placebo-controlled trial evaluated 989 cancer patients with active malignant disease, not being treated with either chemotherapy or radiation therapy. The median number of days since the last prior chemotherapy and the first dose received by patients was 91.5 days and 83.0 days for the placebo group and ARANESP group, respectively. Per protocol, no patient had received chemotherapy in the 4 weeks preceding the study. This study showed no statistically-significant reduction in the proportion of patients receiving RBC transfusions, and more deaths in the ARANESP group than in the placebo group (26% vs 20%) at 16 weeks (completion of treatment phase). With a median survival follow-up of 4.3 months, the absolute number of deaths at the end of the study was also higher in the ARANESP group (49% vs 46%, HR 1.29, 95% CI: 1.08, 1.55). An increased risk of death was observed in this study where ARANESP was administered to target a hemoglobin of 120 g/L. ARANESP is not indicated for use in patients with cancer who have anemia that is not associated with chemotherapy.

Randomized, controlled trials with decreased survival and/or decreased locoregional control are summarized in Table 11.

**Table 11. Randomized, Controlled Trials with Decreased Survival and/or Decreased Locoregional Control**

<b>Tumour (n)</b>	<b>Hemoglobin Target</b>	<b>Achieved Hemoglobin (Median Q1, Q3)</b>	<b>Primary Endpoint</b>	<b>Adverse Outcome for ESA-containing Arm</b>
<b>Chemotherapy</b>				
Metastatic breast cancer (n = 939)	120-140 g/L	129 g/L 122, 133 g/L	12-month overall survival	Decreased 12-month survival
Lymphoid malignancy (n = 344)	130-150 g/L (M) 130-140 g/L (F)	110 g/L 98, 121 g/L	Proportion of patients achieving a hemoglobin response	Decreased overall survival
Early breast cancer (n = 733)	125-130 g/L	131 g/L 125, 137 g/L	Relapse-free and overall survival	Lower observed 3-year relapse-free and overall survival*
Cervical cancer (n = 114)	120-140 g/L	127 g/L 121, 133 g/L	Progression-free and overall survival and locoregional control	Lower observed 3-year progression-free and overall survival and locoregional control*
<b>Radiotherapy Alone</b>				
Head and neck cancer (n = 351)	≥150 g/L (M) ≥140 g/L (F)	Not available	Locoregional progression-free survival	Decreased 5-year locoregional progression-free survival Decreased overall survival
Head and neck cancer (n = 522)	140-155 g/L	Not available	Locoregional disease control	Decreased locoregional disease control
<b>No Chemotherapy or Radiotherapy</b>				
Non-small cell lung cancer (n = 70)	120-140 g/L	Not available	Quality of life	Decreased overall survival
Non-myeloid malignancy (n = 989)	120-130 g/L	106 g/L 94, 118 g/L	RBC transfusions	Decreased overall survival

\* Not statistically significant

A systematic review of 57 randomized controlled trials (including the BEST, ENHANCE, and EPO-CAN 20) evaluating 9353 patients with cancer compared erythropoiesis-stimulating agents (ESAs) plus RBC transfusion with RBC transfusion alone for prophylaxis or treatment of anemia in cancer patients with or without concurrent antineoplastic therapy. Sub-group analysis of patients treated for chemotherapy-induced anemia from this systematic review demonstrates an overall survival odds ratio (OR) of 0.92 (95% CI: 0.78, 1.09) for platinum-based chemotherapy and 1.10 (95% CI: 0.96, 1.24) for chemotherapy without platinum. Use of ESAs for treatment of chemotherapy-induced anemia was associated with an OR of 0.99 (95% CI: 0.72, 1.36). An overall survival hazard ratio of 1.08 (95% CI: 0.99, 1.18; 42 trials and 8167 patients) was observed in all ESA-treated patients, including those receiving chemotherapy, radiotherapy, and no active treatment. An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06; 35 trials and 6769 patients) was observed in ESA-treated patients.

## **DETAILED PHARMACOLOGY**

Human erythropoietin is an endogenous glycoprotein hormone that is the primary regulator of erythropoiesis through specific interaction with the erythropoietin receptor on the erythroid progenitor cells in the bone marrow. The production of erythropoietin primarily occurs in and is regulated by the kidneys in response to changes in tissue oxygenation. Research has determined that the sialic acid containing carbohydrate moieties of erythropoietin have a significant effect on serum clearance and that serum clearance is the primary determinant of *in vivo* activity.

ARANESP (darbepoetin alfa) stimulates erythropoiesis by the same mechanism as the endogenous hormone. Treatment of anemia with ARANESP in CKD and cancer patients has been associated with a reduction in RBC transfusions.

ARANESP has 5 N-linked carbohydrate chains whereas the endogenous hormone and recombinant human erythropoietin (rHuEPO) have 3. Due to its increased carbohydrate content ARANESP has a longer terminal half-life than rHuEPO and consequently a greater *in vivo* activity. Despite these molecular changes, darbepoetin alfa and rHuEPO have identical modes of action and ARANESP retains the very narrow specificity for the erythropoietin receptor demonstrated by rHuEPO.

### **Pharmacokinetics**

Preclinical studies indicate that ARANESP undergoes limited distribution, with the intact form being predominantly confined to the vascular space. ARANESP undergoes extensive metabolism, presumably by sialidases, with subsequent rapid removal of the desialylated form by hepatic receptors. Intact ARANESP undergoes negligible renal excretion (< 2% in rats). Degradation products are recovered in the urine (57% of dose) and feces (24% of dose).

The pharmacokinetic properties of ARANESP have been studied in healthy adult subjects, adult and pediatric CKD patients, and adult cancer patients.

Following IV administration to adult CKD patients, ARANESP serum concentration time profiles are biphasic, with a distribution half-life of approximately 1.4 hours and mean terminal half-life of approximately 21 hours. Following SC administration, the absorption is slow and rate-limiting and the terminal half-life is 49 hours (range: 27 to 89 hours), which reflects the absorption half-life. The peak concentration occurs at 34 hours (range: 24 to 72 hours) post-SC administration in adult CKD patients, and bioavailability is approximately 37% (range: 30% to 50%).

Confirming the results of the preclinical studies, the distribution of ARANESP in adult CKD patients is predominantly confined to the vascular space (approximately 60 mL/kg). Characterization of pharmacokinetic parameters indicated dose-linearity over the therapeutic dose range. With once weekly dosing, steady-state serum levels are achieved within 4 weeks with < 2-fold increase in peak concentration. Accumulation was minimal following both IV and SC dosing over 1 year of treatment.

The pharmacokinetic properties of ARANESP have been studied in adult cancer patients receiving chemotherapy. Following SC administration of 2.25 mcg/kg to adult cancer patients, a mean peak concentration of 10.6 ng/mL (SD: 5.93; n = 26) was achieved at a mean time of 90.5 hours (SD 19.7). The data were consistent with dose-linear pharmacokinetics over a wide dose range (0.5 to 8.0 mcg/kg weekly and 3.0 to 9.0 mcg/kg every 2 weeks). Upon multiple dosing over 12 weeks (dosing every week or every 2 weeks), the pharmacokinetic properties did not change. The expected moderate increases (< 2-fold) in ARANESP serum concentrations upon multiple dosing were observed as steady state was approached. Accumulation was negligible across a wide range of doses at once weekly and once every 2 weeks dosing schedules.

## **Special Populations**

### **Pediatrics**

Following IV or SC administration in children 3 to 16 years old, the mean terminal half-life was 22 hours for IV administration (range: 12 to 30 hours) and 43 hours (range: 16 to 86 hours) for SC administration. The SC bioavailability was 54% (range: 32% to 70%).

Comparison of the limited data available for the pharmacokinetics of ARANESP in pediatric CKD patients with that of adults suggests that the disposition of ARANESP is similar in adult and pediatric subjects. However, following SC administration, ARANESP appears to be absorbed at a more rapid rate than compared with adults. Precaution need be noted, since additional study is required as this observation has not been thoroughly investigated.

## Geriatrics

The pharmacokinetic parameters estimated for adult subjects < 65 years old and ≥ 65 years old were similar, for both IV and SC dosing.

## Renal Insufficiency

As there is minimal renal excretion of intact ARANESP, alterations in renal function are not expected to affect its pharmacokinetics. Following SC dosing of ARANESP to healthy subjects peak concentration occurred 36 hours post dose and the terminal half-life was 60 hours (range: 28 to 144 hours) compared to 49 hours (range: 27 to 89 hours) in CKD patients.

## TOXICOLOGY

In preclinical studies ARANESP (darbepoetin alfa) was well tolerated up to the highest doses studied, administered as a single IV dose, in rats (200 mcg/kg) and dogs (150 mcg/kg).

ARANESP was administered IV to rats and dogs in multiple dose studies at up to 300 mcg/kg/week and 150 mcg/kg/week respectively (as a once and three times per week dosing schedule). The studies ranged from one week to six months in both species. Studies up to one month also included SC administration.

In all studies and in both species ARANESP produced the expected pharmacological effects on hematological parameters consisting of marked increases in hemoglobin, hematocrits, red blood cell counts and reticulocytes. At higher exposures (based on area under the concentration/time curve) these effects were exaggerated. Histopathological changes such as myelofibrosis and splenic hypertrophy were all considered to be sequelae to the increased viscosity of the blood, vascular congestion and/or blood stasis leading to decreased tissue perfusion.

ARANESP did not show any evidence of genotoxic effects in the standard battery of tests designed to identify hazards with respect to DNA damage. Neither did ARANESP reveal any mutagenic potential nor did it have any effect on the proliferation of non-hematological cells *in vitro* or *in vivo*. In the chronic toxicity studies no tumorigenic or unexpected mitogenic responses were observed in any tissue type.

## **Carcinogenesis, Mutagenesis**

ARANESP was not evaluated in standard carcinogenicity bioassays. ARANESP did not alter the proliferative response of non-hematological cells *in vitro* or *in vivo*. In chronic toxicity studies, no tumorigenic or unexpected mitogenic responses were observed in any tissue type. 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 recombinant human erythropoietin (rHuEPO). Neither molecule bound to human tissues other than those expressing the EPO receptor.

ARANESP was negative in the *in vitro* bacterial and CHO cell assays used to detect mutagenicity and in the *in vivo* mouse micronucleus assay to detect clastogenicity.

Studies in rats and rabbits showed no relevant evidence of harmful effects with respect to pregnancy, embryo/fetal development, parturition or postnatal development. However, a slight reduction in fetal weights was observed at doses causing toxicities due to exaggerated pharmacological effects in the dams. No placental transfer or alteration of fertility was detected.

When administered to rats before mating, reproductive performance, fertility, and sperm assessment parameters were not affected at any doses evaluated (up to 10 mcg/kg/day). An increase in post-implantation fetal loss was seen with ARANESP doses of 0.5 mcg/kg/day and higher.

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**PART III: CONSUMER INFORMATION**

**Pr Aranesp®**  
(darbepoetin alfa)

**Single-use Vials<sup>†</sup> and SingleJect® Prefilled Syringes**

This section is part III of a three-part “Product Monograph” published when ARANESP was approved in Canada and is designed specifically for patients who will be receiving ARANESP and their caregivers. This leaflet is a summary and will not tell you everything about ARANESP. Contact your doctor or pharmacist if you have any questions about ARANESP.

<sup>†</sup>Single-use vials are not available in Canada.

**ABOUT THIS MEDICATION****What is ARANESP used for?**

ARANESP is used to treat anemia associated with chronic kidney disease (kidney failure) or anemia associated with chemotherapy administration in cancer patients.

**What is Anemia?**

Anemia is a condition where your blood does not contain enough red blood cells. Red blood cells are responsible for carrying oxygen to your organs and body tissues. If the number of red blood cells in your blood is decreased, the amount of oxygen delivered throughout your body is also decreased. This may cause several symptoms that are typical of anemia including fatigue, weakness and shortness of breath.

**Anemia and kidney failure**

In kidney failure, the kidneys do not produce enough of the natural hormone, erythropoietin, which encourages your bone marrow to produce more red blood cells.

**Anemia and cancer**

When chemotherapy is given to cancer patients, the body may not be able to produce enough and/or respond adequately enough to its own erythropoietin, the natural hormone that encourages bone marrow to make more red blood cells. As a result, not enough red blood cells are produced in order to overcome the effect of chemotherapy.

**How does ARANESP work?**

In cancer, when chemotherapy is given to cancer patients, the body may not be able to produce enough and/or respond adequately enough to its own erythropoietin, the natural hormone that encourages bone marrow to make red blood cells. If your kidneys are no longer able to produce enough erythropoietin you may benefit by receiving ARANESP. ARANESP will stimulate your bone marrow to produce more red blood cells. Like the natural hormone erythropoietin, the

active ingredient of ARANESP, “darbepoetin alfa”, travels through the blood and binds to specific cells in the bone marrow. This signals the bone marrow to produce more red blood cells and release them into the blood. As a result, the number of red blood cells circulating in the blood increases and they can deliver more oxygen to your organs and tissues. This helps in managing the symptoms that are associated with anemia. It takes a few weeks for this process to occur.

Your doctor will know when ARANESP is working because your blood tests will show an increase in the number of red blood cells. He/she may refer to the results of your blood tests as hemoglobin and/or hematocrit, and will check these tests while you are being treated with ARANESP. These blood tests may be done more often at the beginning of your treatment or if your dose of ARANESP changes. The increase in the number of red blood cells is not immediate; it may take several weeks. The amount of time it takes to reach the red blood cell level that is right for you, and the dose of ARANESP needed to make the red blood cell level rise, is different for each person. You may need several ARANESP dose adjustments before you reach your correct dose of ARANESP and the correct dose may change over time. Your doctor will also check your blood pressure regularly. In some cases, your doctor may recommend that you take iron supplements.

**Who should not take ARANESP?**

- People with uncontrolled high blood pressure should not take ARANESP.
- People who are allergic to other erythropoietins, medicines made using mammalian cells, or any of the ingredients (for example, polysorbate 80) in ARANESP should not take ARANESP.
- Patients who make antibodies (develop Pure Red Cell Aplasia) following treatment with any erythropoiesis- stimulating agent (ESA).

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

**How long will it take to feel better?**

Because it will take your bone marrow some time to make more red blood cells, it may take a few weeks before you notice any effects.

**I have been treated with Epoetin alfa for my renal failure; what can I expect from ARANESP?**

In clinical trials, ARANESP has proved to be as efficacious in correcting and regulating anemia as Epoetin alfa, in patients with chronic kidney disease who have been switched from Epoetin alfa to ARANESP as well as in new patients. Because ARANESP has been designed to work in your body for a longer period of time, it is possible to achieve the same results with fewer injections.

**What is the medicinal ingredient in ARANESP?**

darbepoetin alfa

**What are the nonmedicinal ingredients in ARANESP?**

Polysorbate 80  
Sodium Chloride  
Sodium Phosphate Dibasic Anhydrous  
Sodium Phosphate Monobasic Monohydrate

**What dosage forms does ARANESP come in?**

ARANESP is available as a liquid for injection, and comes in vials<sup>†</sup> or syringes. The needle cover on the single-use prefilled syringe contains dry natural rubber (latex), which should not be handled by persons sensitive to this substance.

<sup>†</sup>Single-use vials are not available in Canada.

**WARNINGS AND PRECAUTIONS****All Patients**

- To minimize the risks for death and serious cardiovascular (heart and blood vessel-related) side effects, your doctor will follow the recommended dosage for each indication.
- Patients with uncontrolled high blood pressure should not be treated with ARANESP; blood pressure should be adequately controlled before receiving ARANESP.
- ARANESP should be used with caution in patients with a history of seizures.
- Antibody-mediated Pure Red Cell Aplasia (PRCA) has been reported after months to years of treatment with erythropoiesis-stimulating agents (ESAs). If you develop PRCA, you may suddenly become severely anemic and this could result in a dependency on blood transfusions.

**Chronic Kidney Disease 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 will try to keep your hemoglobin between 100 and 115 g/L, not to exceed 120 g/L.

**Cancer Patients**

- If you are a cancer patient and your hemoglobin is kept too high (over 120 g/L),
  - your tumour may grow faster,
  - you have an increased chance of heart attack, stroke, blood clots and death.
- Your doctor should use the lowest dose of ARANESP needed to avoid red blood cell (RBC) transfusions.
- In some instances, red blood cell transfusion should be the preferred treatment option.
- Once you have finished your chemotherapy course, ARANESP should be discontinued.

Do not take ARANESP if you are allergic to other erythropoietic agents, ARANESP or to any of the other ingredients in ARANESP.

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

It is important to keep all appointments for blood tests to allow your doctor to adjust the dosage of ARANESP as needed.

Over time, many patients also need to take iron. Your doctor will know when or if you need an iron supplement from your laboratory test results. Do not change the dose of ARANESP.

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

If you have a hemodialysis vascular access, continue to check the access to make sure it is working. Call your doctor or dialysis center right away if you have any problems or questions. Always call your doctor if you do not feel well while using ARANESP.

Pure Red Cell Aplasia (PRCA), in association with antibodies, has been observed in patients treated with ESAs. PRCA is a condition in which severe and sudden anemia (characterized by symptoms such as severe tiredness/fatigue, and shortness of breath on mild exertion) develops due to failure of the bone marrow to produce red blood cells. PRCA could result in a dependency on blood transfusions. Should you be diagnosed with PRCA, your doctor will stop your ARANESP therapy and may initiate treatment with blood transfusions to help increase your red blood cell count. PRCA has been reported predominantly in patients with chronic kidney disease. PRCA has been reported in a very rare number of patients exposed to ARANESP subcutaneously (under your skin).

If you are a cancer patient you should be aware that ARANESP is a red blood cell growth factor and in some circumstances your cancer may grow faster. You should discuss treatment options for your anemia with your doctor.

**Special Warnings:**

Please tell your doctor if you are suffering or have suffered from:

- High blood pressure
- Heart disease (e.g., angina)
- Epileptic fits (seizures)

It is important to tell your doctor if you:

- Are pregnant
- Think you may be pregnant
- Plan to get pregnant, or
- Are breast-feeding

**INTERACTIONS WITH THIS MEDICATION**

As with all medicines, you must tell your doctor what other medications you are taking.

**PROPER USE OF THIS MEDICATION****Usual dose:**

ARANESP is given to patients as an injection. The method of injection depends on your clinical condition as indicated below.

For patients with chronic kidney disease, one of the following methods will be used:

- under your skin (subcutaneous); or
- into the venous line connecting the hemodialysis machine to your vein (intravenous), if you are on hemodialysis

You and your doctor will determine which is best for you. Your doctor will determine how much you must take and how often you need to take it. ARANESP is given once a week or in some cases, once every two weeks. Your doctor will try to keep your hemoglobin between 100 and 115 g/L, not to exceed 120 g/L.

For cancer patients, there is only one method for injection as follows:

- under your skin (subcutaneous)

Your doctor will determine how much you must take and how often you need to take it. ARANESP is typically given once a week or in some cases, once every two or three weeks. Your doctor should use the lowest dose of ARANESP needed to help you avoid RBC transfusions. Once you have finished your chemotherapy course, ARANESP should be discontinued.

**Overdose:**

If self-administering this medication, be sure to adhere to the prescribed dose.

Severe hypertension (including hypertensive crisis and malignant hypertension) has been observed following overdose with ARANESP. If there is a significant increase in your blood pressure seek immediate medical attention.

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**

You should ask your doctor what to do if you miss a dose of ARANESP.

**Administration:**

**IMPORTANT: TO HELP AVOID CONTAMINATION AND POSSIBLE INFECTION DUE TO INJECTION, PLEASE READ AND FOLLOW THESE INSTRUCTIONS CAREFULLY.**

The following section contains step-by-step instructions on self-administering ARANESP by subcutaneous (under-the-skin) injection. Part A of these instructions describes the process of setting up for your injection. Part B of these instructions contains specific instructions for patients who have been prescribed ARANESP vials<sup>†</sup>. If you have been prescribed ARANESP prefilled syringes, you can ignore Part B. Part C provides directions on selecting and preparing the injection site and the process of self-injection. Part D provides instructions on the activation of the needle guard on used prefilled syringes. Part E provides instructions on the safe disposal of used needles.

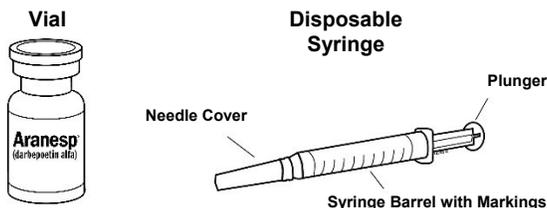
It is important that you do not try to give yourself the injection until you have received special training from your doctor or nurse. It is also important that you dispose of the used needles in a puncture-proof container. Do not use ARANESP in a prefilled syringe if the grey cover on the needle is off, or the needle guard (yellow sleeve on the syringe) has been activated (pulled to extend over the needle).

Always follow the instructions provided by your doctor, nurse or pharmacist concerning the dosage and administration of ARANESP. Do not change the dose or method of administration of ARANESP, without consulting your doctor. If you are not sure about giving the injection or you have any questions, please ask your doctor, nurse or pharmacist for help.

<sup>†</sup>Single-use vials are not available in Canada.

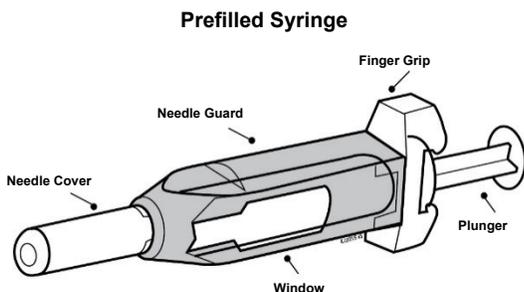
**Part A - Setting up for the injection**

1. Find a comfortable, clean, well-lit working place with a flat surface such as a table.
2. Remove the ARANESP vial<sup>†</sup> or prefilled syringe from the refrigerator and place it on your flat working surface. Allow it to reach room temperature. This should take about 30 minutes. Do not leave the vial<sup>†</sup> or prefilled syringe in direct sunlight and do not use it if it has been frozen.
3. Inspect the vial<sup>†</sup> or prefilled syringe. Check that the strength on the vial<sup>†</sup> or syringe is the strength that your doctor prescribed for you. Check the date on the label to be sure that the product has not expired. ARANESP should be a clear, colourless solution. If the solution has particles or is discoloured, do not use it, and check with a doctor, nurse, or pharmacist. **DO NOT SHAKE THE VIAL<sup>†</sup> OR PREFILLED SYRINGE.** Shaking may damage the ARANESP. If the product has been shaken vigorously, the solution may appear foamy and it should not be used.
4. Assemble the supplies you will need for an injection:  
ARANESP vial<sup>†</sup> and the correct disposable syringe and needle



**OR**

ARANESP prefilled syringe with a transparent (clear) yellow plastic needle guard attached



5. In addition to your medication, you will need alcohol swabs, a cotton ball or piece of gauze, and a puncture-proof container for disposal of used needles. When you have all these materials assembled, and are ready to begin, wash your hands well with soap and warm water.



<sup>†</sup>Single-use vials are not available in Canada.

**Part B - ARANESP vials<sup>†</sup>**

If you are using ARANESP vials<sup>†</sup>, the doctor or nurse will give you instructions on how to measure your dose of ARANESP and draw it from the vial into the syringe. Only use the syringe that your doctor prescribes. This dose will be measured in millilitres. You should only use a syringe that is marked in tenths of millilitres 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. Each ARANESP vial is designed to be used only once. Do not put the needle through the rubber stopper more than once. Use only disposable syringes and needles. Use the syringes and needles only once and dispose of them as instructed by your doctor or nurse (see Part D below).

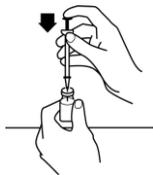
1. Take the yellow color cap off the vial. Clean the rubber stopper with one alcohol swab.



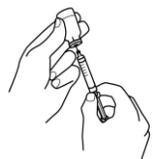
2. Check the package containing the syringe. If the package has been opened or damaged, do not use that syringe. You should dispose of that syringe in the puncture-proof disposal container (see Part D below). If the syringe package is undamaged, open the package and remove the syringe.
3. Pull the needle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



- Keep the vial on your flat working surface and insert the needle straight down through the rubber stopper.
- Push the plunger of the syringe down to inject the air from the syringe into the vial of ARANESP.



- Keeping the needle inside the vial, turn the vial upside down. Make sure that the tip of the needle is in the ARANESP liquid.



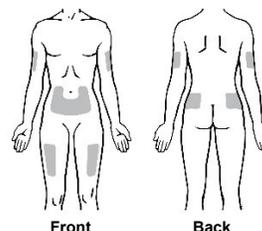
- Keeping the vial upside down, slowly pull back on the plunger to fill the syringe with ARANESP liquid to the number (mL or cc) that matches the dose your doctor prescribed.
- Keeping the needle in the vial, check for air bubbles in the syringe. If there are air bubbles, gently tap the syringe with 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.
- 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.

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† Single-use vials are not available in Canada.

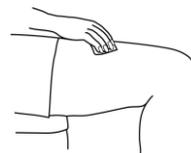
### **Part C - Preparing Injection Site and Self-Injecting ARANESP**

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



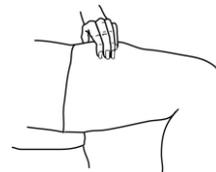
Choose a new site each time you inject ARANESP. Choosing a new site can help avoid soreness at any one site. Do not inject ARANESP into an area that is tender, red, bruised, or hard or that has scars or stretch marks.

- Clean the injection site with a new alcohol swab.

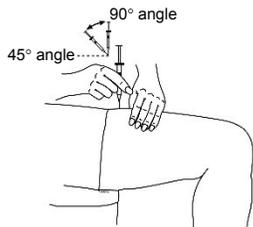


- Hold the syringe in the hand that you will use to inject ARANESP. Use the other hand to pinch a fold of skin at the cleaned injection site.

NOTE: If using a prefilled syringe with a needle guard, pull the needle cover straight off the needle and hold the syringe barrel through the two needle guard windows when giving the injection.



4. 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.



5. After the needle is inserted, let go of the skin. Inject the prescribed dose subcutaneously as directed by your doctor, nurse or pharmacist.



6. 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.

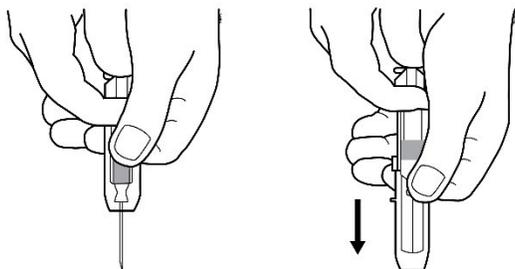


You should ONLY use a syringe and vial<sup>†</sup> once. You should discard the vial<sup>†</sup> with any remaining ARANESP.

<sup>†</sup> Single-use vials are not available in Canada.

#### **Part D – 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.**



#### **Part E - Disposing of syringes and needles**

Dispose of the syringe and needle or the syringe with activated needle guard as instructed by your doctor, nurse, or pharmacist, or by following these steps:

- Do NOT throw the needle or syringe in the household trash or recycle.
- Do NOT put the needle cover (the cap) back on the needle. Place all used needles and syringes in a hard plastic container, or a metal container with a plastic lid. Do not use glass or clear plastic containers, or any container that will be recycled or returned to a store.
- Properly label the container to indicate its contents. If a metal container such as a coffee can with a plastic lid is used, cut a small hole in the plastic lid and tape the lid onto the metal container. When the container is full, cover the hole and dispose of the container according to your doctor’s, nurse’s, or pharmacist’s instructions.
- If an opaque (do not use clear plastic), hard plastic container with a screw-on cap is used, always screw the cap on tightly after each use. When the container is full, tape around the cap or lid and dispose of the container according to the instructions provided by your doctor, nurse, or pharmacist. There may be special local laws that they will discuss with you.
- Always store the container out of the reach of children.
- You should always first check with your doctor, nurse, or pharmacist for instructions on how to properly dispose of a filled container. There may be local laws for disposal of used needles and syringes. Do not throw the container in household trash. Do not recycle.

#### **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

If you get headaches, particularly sudden stabbing migraine-like headaches or you start to feel confused or have seizures you should tell your doctor immediately. These may be the warning signs of a sudden rise in blood pressure and may need urgent treatment.

For hemodialysis patients there may be a chance of blood clots (thrombosis) forming in your vascular access (a channel that bypasses normal blood circulation).

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

You may notice stinging around the area that you were injected. This stinging will only last for a short period of time and may be more common at the start of your treatment. Some people have also had infections, fevers, headaches, muscle aches or soreness, nausea, and chest pain. If you experience any of these symptoms, you should call your doctor. If any of these symptoms persist or you notice any side effects that are not

mentioned in this leaflet, please tell your doctor, nurse or pharmacist.

Other signs that may appear at the site of injection are redness, swelling, or itching. This may indicate an allergy to the components of ARANESP, or it may indicate a local reaction. If you have a local reaction, consult your doctor.

Serious allergic reactions have been observed, including sudden life-threatening allergic reactions with drop in blood pressure, fast pulse, difficulty breathing and sweating (anaphylaxis), swelling of the face, lips, mouth, tongue or throat (angioedema), shortness of breath (allergic bronchospasm), skin rash/rash over the whole body, hives. If you think you are having a serious allergic reaction, stop taking ARANESP and notify your doctor or emergency medical personnel immediately.

<b>SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM</b>				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Increase in blood pressure (symptoms may include headaches, confusion, seizures)		√	
	Diarrhea		√	
	Infections		√	
	Fever		√	
	Muscle aches		√	
	Nausea		√	
	Chest Pain		√	
Uncommon	Blood clots		√	
	Stroke		√	
	Allergic reaction		√	√
Unknown	Severe Cutaneous Reactions (symptoms may include a rash, which may be severe, may cover your whole body and can also include blisters or areas of skin coming off)		√	√

This is not a complete list of side effects. For any unexpected effects while taking ARANESP, contact your doctor or pharmacist.

**HOW TO STORE IT**

You should store ARANESP in the refrigerator (between 2°C and 8°C), but not in the freezer. Do not let ARANESP freeze and do not use ARANESP if you think that it has been frozen. You can take ARANESP out of the refrigerator and let it warm to room temperature (approximately 30 minutes) before injecting it. ARANESP does not contain any preservatives so you should not use it if you have it at room temperature (up to 25°C) for longer than 24 hours.

Always keep the ARANESP vials<sup>†</sup> or syringes in the original pack and do not leave them in direct sunlight.

The expiry date for ARANESP is stamped on the pack and on the vial<sup>†</sup> or syringe label. Do not use ARANESP after the last day of the month and year shown.

As with all medicines, you should keep ARANESP out of the reach and sight of children.

<sup>†</sup> Single-use vials are not available in Canada.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:

Canada Vigilance Program  
 Health Canada  
 Postal Locator 1908C  
 Ottawa, Ontario  
 K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

NOTE: *Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Amgen Canada Inc., at: 1-866-502-6436

This leaflet was prepared by Amgen Canada Inc.

UltraSafe<sup>®</sup> is a registered trademark of Safety Syringes, Inc.

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