



ARANESP® (darbepoetin alfa) For Injection INDICATIONS AND USAGE

Aranesp® is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.

CONTRAINDICATIONS

Aranesp® is contraindicated in patients with:

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

WARNINGS

Cardiovascular Events, Hemoglobin, and Rate of Rise of Hemoglobin

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

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

Hypertension

Patients with uncontrolled hypertension should not be treated with Aranesp®; blood pressure should be controlled adequately before initiation of therapy. Blood pressure may rise during treatment of anemia with Aranesp® or Epoetin alfa. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with Aranesp® or Epoetin alfa.

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

Seizures

During the first several months of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely. While the relationship between seizures and the rate of rise of hemoglobin is uncertain, it is recommended that the dose of Aranesp® be decreased if the hemoglobin increase exceeds 1.0 g/dL in any 2-week period.

Thrombotic Events

An increased incidence of thrombotic events has been observed in patients treated with erythropoietic agents. In patients with cancer who received Aranesp®, pulmonary emboli, thrombophlebitis and thrombosis occurred more frequently than in placebo controls.

Pure Red Cell Aplasia

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

Albumin (Human)

Aranesp® is supplied in 2 formulations with different excipients, one containing polysorbate 80 and another containing albumin (human), a derivative of human blood. Based on effective donor screening and product manufacturing processes, Aranesp® formulated with albumin carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS

General

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

Lack of Loss of Response to Aranesp®

A lack of response or failure to maintain a hemoglobin response with Aranesp® doses within the recommended dosing range should prompt a search for causative factors. Deficiencies of folic acid or vitamin B₁₂ should be excluded or corrected. Depending on the clinical setting, intercurrent infections, inflammatory or malignant processes, osteofibrosis, cystic, occult blood loss, hemolysis, severe aluminum toxicity, and bone marrow fibrosis may compromise an erythropoietic response. In the absence of another etiology, the patient should be evaluated for evidence of PRCA and sera should be tested for the presence of antibody to recombinant erythropoietins.

Hematology

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

In order to prevent the hemoglobin from exceeding the recommended target (12 g/dL) or rising too rapidly (greater than 1.0 g/dL in 2 weeks), the guidelines for dose and frequency of dose adjustments should be followed.

Allergic Reactions

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

Growth Factor Potential

Aranesp® is a growth factor that primarily stimulates RBC production. The possibility that Aranesp® can act as a growth factor for any tumor type, particularly myeloid malignancies, has not been evaluated. In the randomized, placebo-controlled study in 314 subjects with advanced lung cancer, there were no statistically significant differences in time-to-progression (TTP) or overall survival (OS) observed; however, the study was not designed to detect or exclude clinically meaningful differences in either TTP or OS.

Laboratory Tests

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

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

Information for Patients

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

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

Drug Interactions

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

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

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

Pregnancy Category C

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

Intravenous injection of Aranesp® to female rats every other day from day 6 of gestation through day 23 of lactation at doses of 2.5 mcg/kg/dose and higher resulted in offspring (F1 generation) with decreased body weights, which correlated with a low incidence of deaths, as well as delayed eye opening and delayed preputial separation. No adverse effects were seen in the F2 offspring. There are no adequate and well-controlled studies in pregnant women. Aranesp® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

ADVERSE REACTIONS

General

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

Cancer Patients Receiving Chemotherapy

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

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

Table 3: Adverse Events Occurring in ≥ 5% of Patients Receiving Chemotherapy Aranesp® (n = 873), Placebo (n = 221) BODY AS A WHOLE: Fatigue, 33%, 30%, Edema, 21%, 10%, Fever, 19%, 16%, CNS/PNS Dizziness, 14%, 8%, Headache, 12%, 9% GASTROINTESTINAL: Diarrhea, 22%, 12%, Constipation, 18%, 17% METABOLIC/NUTRITION: Dehydration, 5%, 3% MUSCULOSKELETAL: Arthralgia, 13%, 6%, Myalgia, 8%, 5% SKIN AND APPENDAGES: Rash, 7%, 3%

Table 4: Incidence of Other Clinically Significant Adverse Events in Patients Receiving Chemotherapy All Aranesp® (n = 873), Placebo (n = 221) Hypertension, 3.7%, 3.2%, Seizures/Convulsions (includes the preferred terms: Convulsions, Convulsions Grand Mal, and Convulsions Local), 0.6%, 0.5%, Thrombotic Events, 6.2%, 4.1%, Pulmonary Embolism, 1.3%, 0.0%, Thrombosis (includes: Thrombophlebitis, Thrombophlebitis Deep, Thrombosis Venous, Thrombosis Venous Deep, Thromboembolism, and Thrombosis), 5.6%, 4.1%.

Thrombotic and Cardiovascular Events

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

Immunogenicity

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

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

OVERDOSAGE

The maximum amount of Aranesp® that can be safely administered in single or multiple doses has not been determined. Doses over 3.0 mcg/kg/week for up to 28 weeks have been administered to CRF patients. Doses up to 8.0 mcg/kg every week and 15.0 mcg/kg every 3 weeks have been administered to cancer patients for up to 12-16 weeks. Excessive rise and rate of rise in hemoglobin concentration, however, have been associated with adverse events. In the event of polycythemia, Aranesp® should be temporarily withheld. If clinically indicated, phlebotomy may be performed.

Rx only

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

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