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Darbepoetin Alfa

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Drug Name: Darbepoetin alfa is manufactured and marketed as Aranesp™ by Amgen Inc. (Thousand Oaks, CA).

Classification: Darbepoetin alfa is classified as a hematologic growth factor.

Action: Darbepoetin alfa's mechanism of action is to stimulate erythropoiesis similar to endogenous erythropoietin. Erythropoietin is produced in the kidney in response to hypoxia and then interacts with progenitor stem cells to increase red blood cell production. In patients with chronic renal failure (CRF), this production is impaired and results in anemia. In patients with cancer receiving chemotherapy, the cause may be multifactorial because of the treatment or the disease. Darbepoetin alfa is a protein almost identical to erythropoietin that is produced in Chinese hamster ovary cells by recombinant DNA technology. Darbepoetin alfa is different from recombinant human erythropoietin in that it contains two additional N-linked oligosaccharide chains. The two additional N-glycosylation sites result from amino acid substitutions in the erythropoietin peptide backbone. The additional carbohydrate chains increase the molecular weight of the glycoprotein, which allows a longer half-life and less frequent administration.

Indications: Darbepoetin alfa is indicated for anemia associated with CRF and for the treatment of anemia in patients with nonmyeloid malignancies where the anemia is caused by concomitantly administered chemotherapy.

Metabolism: Liver

Excretion: Liver

Half-life: Time-to-peak concentration varies among patients with CRF and cancer. After subcutaneous (SC) administration, the peak concentration for patients with CRF occurs at 34 hours (range 24–72 hours) and at 90 hours for patients with cancer (range 71–123 hours).

Effect on blood counts: In clinical trials with darbepoetin alfa, an increase in hemoglobin is seen two to six weeks after the initiation of treatment.

Adverse reactions and events: Darbepoetin alfa and other erythropoietic therapies have very similar side-effect profiles. In clinical trials associated with this classification of drugs, an increased incidence of adverse events occurs when the hemoglobin increase is greater than 1 g/dl in a two-week period. The adverse events included acute myocardial infarction; vascular thrombosis; congestive heart failure; exacerbation of hypertension; neurologic events, including seizures and stroke; fluid overload and edema; and cardiac arrest.

Patients with uncontrolled hypertension should not be treated with darbepoetin alfa until their blood pressure is controlled adequately. In clinical trials, 40% of patients with CRF required an increase in antihypertensive medications with the increase in their hemoglobin. Seizures have occurred in patients with CRF who were participating in clinical trials of darbepoetin alfa and epoetin alfa. Thrombotic events such as pulmonary emboli, thrombophlebitis, and thrombosis occurred more frequently in patients who received darbepoetin alfa than in placebo controls.

In the literature, pure red cell aplasia has been reported to occur in patients with CRF in association with recombinant erythropoietin agent administration. This development is unclear but should be considered in patients who have a loss of response to darbepoetin alfa. These patients should be evaluated for neutralizing and binding antibodies.

Serious allergic reactions are rare but have included skin rash and urticaria.

In patients with cancer, the most common adverse effects were nausea and vomiting, diarrhea, fatigue, and edema. Hypertension, hypotension, diarrhea, headache, infection, and myalgia were the most common adverse effects in patients with CRF.

Route and dosage: Darbepoetin alfa may be administered via IV or SC injection. The IV dose is used most commonly in patients with CRF. The goal with darbepoetin alfa is for the dose to be adjusted for each patient to achieve and maintain a target hemoglobin level not to exceed 12 g/dl. In many patients, the maintenance dose will be lower than the starting dose. The recommended starting dose of darbepoetin alfa for patients with cancer is 2.25 mcg/kg administered as a weekly SC injection. In clinical practice, the starting dose may be 1.5–2.25 mcg/kg once weekly, or 3–5 mcg/kg once every two weeks. If less than a 1.0 g/dl increase in hemoglobin occurs after six weeks of therapy, the dose of darbepoetin alfa should be increased up to 4.5 mcg/kg. If hemoglobin increases by more than 1.0 g/dl in a two-week period, or if the hemoglobin exceeds 12 g/dl, the dose should be reduced by approximately 25%. If the hemoglobin exceeds 13 g/dl, doses should be withheld until the hemoglobin falls to 12 g/dl. At this point, therapy should be restarted at a dose approximately 25% below the previous dose. Ongoing research is being conducted to evaluate the safety and efficacy of administering darbepoetin alfa every three to four weeks, as well as administering a loading dose to quickly increase the hemoglobin level, then tapering off the dose to maintain adequate hemoglobin.

The recommended dose in patients with CRF is 0.45 mcg/kg for a starting dose. As

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