**BENEFIT DESCRIPTION AND LIMITATIONS OF COVERAGE**

**ITEM:** Aranesp® (darbepoetin alfa, injection)

**PRODUCT LINES:** Commercial HMO/PPO/CDHP

**COVERED UNDER:**
- **HMO:** Medical (provider setting); Rx (out patient)
- **PPO/CDHP:** Rx

**DESCRIPTION:** Darbepoetin alfa stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. The agent is manufactured by recombinant DNA technology. Darbepoetin alfa contains five N-linked oligosaccharide chains, whereas the other recombinant human erythropoietin (rHuEPO) products (epoetin alfa: Epogen®; Procrit®) contain three. The additional N-glycosylation sites increases the molecular weight of the glycoprotein and gives it an elimination half life that is three-fold longer than epoetin alfa, which allows prolongation of the dosing interval of darbepoetin alfa in certain conditions.

**CPT/HCPCS Code:** J0881, J0882

**Company Supplying:** Amgen

**Setting:** Intravenous (IV) or subcutaneous (SC)

**Coverage Criteria:** Express Scripts, Inc. monograph dated 8/03/2011

**Approval Period:** As stated by indication

**Recommended Authorization Criteria**

**WARNING:** Darbepoetin is contraindicated in patients with uncontrolled hypertension, as well as those with known hypersensitivity to the products or any of the excipients. The warning section of the package insert also provides clinical information regarding the increase in mortality, serious CV events, thrombembolic events and stroke noted with ESAs (darbepoetin, epoetin alfa [Epogen, Procrit] and epoetin beta [not marketed in the U.S.]). CRF patients had a greater risk of death, serious CV events and stroke when administering ESAs to target Hb levels of >13.0 g/dL as observed in clinical studies. In addition to the above warning, it is noted that CRF patients with an insufficient Hb response to ESA therapy may be at even greater risk for CV events compared with other patients. Darbepoetin and other ESAs increased the risk for death and serious CV events in controlled clinical trials involving cancer patients. These events involved myocardial infarction (MI), stroke, congestive heart failure (HF), and hemodialysis vascular access thrombosis. A rate of Hb rise of >1.0 g/dL over a period of two weeks may contribute to these risks.

Coverage of darbepoetin alfa is recommended in those who meet the following criteria:

**FDA-Approved Indications**

1. **Patients with CKD.**
   
   **A. Patients on dialysis.** Approve for 6 months if Hb < is 10.0 g/dL for initial therapy. If the patient has been previously receiving darbepoetin alfa or epoetin alfa, approve only if Hb is ≤ 11.0 g/dL.
B. Patients not on dialysis. Approve for 6 months if Hb is < 10.0 g/dL, regardless of whether this is initial therapy or the patient has been receiving darbepoetin alfa or epoetin alfa.

These recommendations for initiating and stopping therapy for CKD patients based on Hb values are derived from the FDA-approved dosing information for darbepoetin. The recommendation for the duration of therapy is based on the professional opinion of specialized physicians reviewing the data.

Other Uses with Supportive Evidence

2. Anemia due to myelodysplastic syndrome (MDS). Approve for 6 months for therapy initiation if Hb is \( \leq 12.0 \) g/dL. Therapy with darbepoetin is not recommended if Hb is > 12.0 g/dL in any situation. If the patient has previously been receiving darbepoetin or epoetin alfa, approve only if Hb is \( \leq 12.0 \) g/dL. An additional 6 months of darbepoetin may be allowed if Hb is \( \leq 12.0 \) g/dL.

Clinical practice guidelines from the NCCN (published in 2011) list darbepoetin as having a role in select patient populations with MDS. The guideline states that the agent has been effective in lower risk MDS and response rates have been between 40% and 60% (major and minor responses). Due to safety issues, the guidelines suggest that ESAs be used in the management of symptomatic anemia in MDS patients and to aim for a target Hb \( \leq 12.0 \) g/dL. Data suggests darbepoetin may provide some benefits in MDS. In the professional opinion of specialized physicians reviewing the data the criteria regarding Hb \( \leq 12.0 \) g/dL and the duration of therapy have been adopted.

3. Anemia associated with the use of ribavirin therapy for hepatitis C (in combination with interferon or pegylated interferon alfa 2a/2b products with or without direct-acting antiviral agents [i.e., boceprevir capsules {Victrelis™}, telaprevir tablets {Incivek™}]). Approve for 12 months of therapy if Hb is \( \leq 10.0 \) g/dL. If the patient has previously been receiving darbepoetin, approve only if Hb is \( \leq 12.0 \) g/dL. Therapy with darbepoetin is not recommended if Hb is > 12.0 g/dL in any situation.

Darbepoetin has been studied in a Phase II, open-label, three-center clinical trial with filgrastim for the treatment of anemia and neutropenia associated with combination therapy for hepatitis C. In this trial, Hb increased by 1.9 g/dL to 12.1 g/dL after 81 days of darbepoetin therapy and was utilized by 41 patients (of whom 26 also used filgrastim). Another assessment evaluated anemic patients placed on or switched from epoetin alfa to darbepoetin who had had hepatitis C and were also given ribavirin. The warning section of the darbepoetin product label states that PRCA has been noted in patients receiving ESAs while undergoing treatment for hepatitis C with interferon and ribavirin therapy. The pivotal trials with boceprevir allowed for administration of erythropoietin. One study stated that the use of erythropoietin was recommended when Hb dropped to < 10.0 g/dL; however, use was at the investigator’s discretion. Erythropoietin was to be stopped if Hb rebounded to \( \geq 12.0 \) g/dL. In the professional opinion of specialized physicians reviewing the data, the criteria regarding Hb have been adopted.

Other Uses with Supportive Evidence – Case-by-Case Consideration

4. Anemia in heart failure (HF). Patients will be evaluated by a pharmacist and/or physician on a case-by-case basis to determine a coverage recommendation for the client. A short trial with darbepoetin (< 2 months) may be authorized to determine
efficacy and/or safety. Patients that may be candidates include those that have more severe HF, have a Hb ≤ 10.0 g/dL, have anemia despite transfusions or have contraindications to transfusions (e.g., fluid overload). Therapy with darbepoetin is generally not recommended if Hb is > 12.0 g/dL. Further approval after initial therapy will be determined on a case-by-case basis. Darbepoetin has been used in HF patients and some benefits have been noted, such as an increase in exercise duration and improvement in some quality of life indices. 2009 guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA) for the management of HF do not recognize ESAs as a standard of care for HF patients with anemia. Further studies are ongoing.

6. Anemia of chronic disease/anemia of chronic inflammation (e.g., anemia in inflammatory bowel disease [ulcerative colitis, Crohn’s disease], rheumatoid arthritis, systemic lupus erythematosus). Patients will be evaluated by a pharmacist and/or physician on a case-by-case basis to determine a coverage recommendation for the client. A short trial of darbepoetin (3 months) may be authorized to determine responsiveness and improvement in clinical parameters (e.g., increase in Hb). Some patients that may be candidates include those with symptomatic anemia with low Hb (< 10.0 g/dL) who have anemia despite transfusions (e.g., transfusion dependent) or cannot tolerate or undergo transfusions. Other factors that may suggest appropriate treatment with ESAs include those with low erythropoietin levels or failure of other treatment modalities (e.g., iron supplementation). Other causes of anemia should have been ruled out and therapy with darbepoetin is generally not recommended if Hb is > 12.0 g/dL. Further approval after initial therapy will be determined on a case-by-case basis. ESAs have been used for anemia of chronic disease/inflammation. Some beneficial results regarding parameters related to anemia (e.g., increases in Hb) have been noted. It should be recognized, however, that use of ESAs for anemia of chronic disease/inflammation are not a standard of care and are generally not recommended.

Exclusions

Coverage of darbepoetin alfa is not recommended in the following circumstances:

1. Anemia associated with cancer in patients not receiving cancer chemotherapy. Darbepoetin is not indicated in cancer patients who are not receiving cancer chemotherapy. The ASCO/ASH guidelines for the use of epoetin and darbepoetin in adults patients with cancer recommend that ESAs not be used in treatment of anemia associated with malignancy in those who are not receiving concurrent myelosuppressive chemotherapy.

2. Anemia associated with acute myelogenous leukemias (AML), chronic myelogenous leukemias (CML) or other myeloid cancers. Darbepoetin is indicated for use in non-myeloid cancers when chemotherapy is given. AML and CML are examples of myeloid cancers.

3. Anemia associated with radiotherapy in cancer. Darbepoetin is not indicated for use in cancer patients who are given only radiation therapy.

4. To enhance athletic performance. Darbepoetin is not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

5. Anemia in patients due to acute blood loss. Use of darbepoetin is not appropriate in these types of situations.
6. Coverage is not recommended for circumstances *not* listed in the *Recommended Authorization Criteria*. Criteria will be updated as new published data are available.

**APPROVAL:**

| ENDORSED BY:     | Pharmacy & Therapeutics Committee | Original Date:  
1/17/2007 |
|------------------|-----------------------------------|--------------|
| APPROVED BY:     |                                   | Date:  1/18/2012;  
7/21/2010 |