Medicare's ESA NCD

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CMS
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Timeline

- March 9, 2007: FDA Black Boxed Warnings
- March 14, 2007: CMS opens NCA
- May 10, 2007: FDA ODAC Meeting
- May 14, 2007: CMS posts Proposed DM
- July 30, 2007: CMS posts Final DM

EPOGEN®
(Epoetin alfa)
FOR INJECTION

WARNINGS: Erythropoiesis-Stimulating Agents

Use the lowest dose of EPOGEN® that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion (see DOSAGE AND ADMINISTRATION).

EPOGEN® and other erythropoiesis-stimulating agents (ESAs) increased the risk for death and for serious cardiovascular events when administered to target a hemoglobin of greater than 12 g/dL (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events).

Cancer Patients: Use of ESAs

- **shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a hemoglobin of greater than 12 g/dL;**
- **shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to target a hemoglobin of greater than 12 g/dL;**
- **increased the risk of death when administered to target a hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for this population.**

(See WARNINGS: Increased Mortality and/or Tumor Progression)

Patients receiving ESAs pre-operatively for reduction of allogeneic red blood cell transfusions: A higher incidence of deep venous thrombosis was documented in patients receiving EPOGEN® who were not receiving prophylactic anticoagulation. Antithrombotic prophylaxis should be strongly considered when EPOGEN® is used to reduce allogeneic red blood cell transfusions (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events).

ODAC Recommendations

- further marketing authorization be contingent upon additional restriction in product labeling;
- further marketing authorization be contingent upon additional trials;
- labeling should specifically state that ESAs are not indicated for use in specific tumor types that may include breast cancer, head and neck cancer, and non small-cell lung cancer (NSCLC);
- the current evidence is insufficient to determine a lower limit different from the current level of 10 g/dl;
- the current evidence is insufficient to determine an upper limit different from the current level of 12 g/dl; and
- product labeling should recommend discontinuation of the ESA following completion of a chemotherapy regimen and re-evaluation of the degree of anemia with subsequent chemotherapy regimen.

CMS Final Decision

- Noncover specific off label indications
- Restrict the coverage of ESAs beyond specified duration and intensity
- Removed MDS from the scope of the NCD

Noncoverage

- any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis;
- the anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML), or erythroid cancers;
- the anemia of cancer not related to cancer treatment;
- any anemia associated only with radiotherapy;
- prophylactic use to prevent chemotherapy-induced anemia;
- prophylactic use to reduce tumor hypoxia;
- patients with erythropoietin-type resistance due to neutralizing antibodies; and
- anemia due to cancer treatment if patients have uncontrolled hypertension.

Restricted Coverage

(in solid tumors, multiple myeloma, lymphoma and lymphocytic leukemia)

- The hemoglobin level immediately prior to initiation or maintenance of ESA treatment is < 10 g/dL (or the hematocrit is < 30%).
- The starting dose for ESA treatment is the recommended FDA label starting dose, no more than 150 U/kg/three times weekly for epoetin and 2.25 mcg/kg/weekly for darbepoetin alpha. Equivalent doses may be given over other approved time periods.
- Maintenance of ESA therapy is the starting dose if the hemoglobin level remains below 10 g/dL (or hematocrit is < 30%) 4 weeks after initiation of therapy and the rise in hemoglobin is $\geq$ 1g/dL (hematocrit $\geq$ 3%).
- For patients whose hemoglobin rises <1 g/dl (hematocrit rise <3%) compared to pretreatment baseline over 4 weeks of treatment and whose hemoglobin level remains <10 g/dL after the 4 weeks of treatment (or the hematocrit is <30%), the recommended FDA label starting dose may be increased once by 25%. Continued use of the drug is not reasonable and necessary if the hemoglobin rises <1 g/dl (hematocrit rise <3 %) compared to pretreatment baseline by 8 weeks of treatment.
- Continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin > 1 g/dl (hematocrit > 3%) over 2 weeks of treatment unless the hemoglobin remains below or subsequently falls to < 10 g/dL (or the hematocrit is < 30%). Continuation and reinstitution of ESA therapy must include a dose reduction of 25% from the previously administered dose.
- ESA treatment duration for each course of chemotherapy includes the 8 weeks following the final dose of myelosuppressive chemotherapy in a chemotherapy regimen.