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From the Department of Pharmacy

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Update: Erythropoiesis-Stimulating Agents

Part 2: Centers for Medicaid and Medicare Services National Coverage Determination for Erythropoiesis-Stimulating Agents in Oncology

by Ambar Khan, Pharm.D., BCOP

Please see Pharmacotherapy Update Volume X, No. V, September/October 2007 for Part I, which focuses on a drug use evaluation (DUE) on erythropoiesis-stimulating agents (ESAs).

Over the past year, several important events have influenced the prescribing practices of ESAs, including epoetin alfa and darbepoetin alfa, in the cancer patient population. Emerging data regarding safety concerns of the use of ESAs in this patient population have sparked a great deal of debate amongst the oncology community. As a result of preliminary data released in several ongoing studies early in 2007, the safety of ESAs was reviewed for the oncology patient population.

The use of ESAs in cancer- and chemotherapy-related anemia has historically been to decrease transfusion requirements as well as to improve the quality of life for these patients. The current studies indicated that ESA therapy at recommended doses in cancer patients **not** receiving chemotherapy was linked to an increase risk for mortality with **no** reduction in transfusion requirements. While other ongoing studies indicated that the adjustment of ESA doses to a target hemoglobin >12 g/dl in head and neck cancer patients receiving radiation therapy resulted in accelerated tumor growth.

Both the Federal Drug Administration (FDA) and Centers for Medicaid and Medicare Services (CMS) have been heavily involved with the review of the clinical evidence related to the use of ESAs for the safe and effective treatment of anemia for patients receiving chemotherapy. As a result of the scientific data, the FDA worked with the manufacturers of both epoetin alfa and darbepoetin alfa to change the full prescribing information for both products and CMS chose to implement a stringent new policy regarding the coverage of ESAs in Medicare cancer patients (See Tables 1 and 2).

Several prominent oncology associations have been in communication with CMS regarding their interpretation of the safety data as well as disconnect between the CMS rule and clinical practice, national guidelines, and FDA-approved labels. However, at this time the current CMS ruling has been upheld. At the Cleveland Clinic, a treatment algorithm is being developed for ESAs in cancer patients receiving chemotherapy.

Table 1: Timeline of Events

- In March 2007, the FDA revised the labeling for both epoetin alfa and darbepoetin alfa to include a "black box" warning regarding the increased risk of death and other serious adverse events with the use of ESAs in certain patients with cancer and chronic kidney disease.

- In May 2007, the FDA convened with ODAC (Oncology Division Advisory Committee) to clarify the appropriate recommendations for the use of ESAs in the cancer patient population. ODAC recommended several safety initiatives for the appropriate use of ESAs in cancer patients, including a "baseline" hemoglobin level at which to initiate treatment as well as restrictions on the use of ESAs in certain malignancies.

- On, July 30, 2007, CMS released their national coverage determination (NCD) for the use of ESAs in cancer and related neoplastic conditions for Medicare patients. For important definitions and key points included in the policy see Table 2.

- In September 2007, the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) and the Drug Safety and Risk Management Advisory Committee (DSRMAC) met and recommended additional changes to product labeling (see Tables 3 and 4).

- In November 2007, the FDA published final revisions of product labeling changes for ESAs. These changes incorporate the recommendations and discussions from the May and September Advisory Committee meetings.

Table 2: Eligibility, Dosing, and Other Important Points for NCD of ESAs for Cancer Patients

Eligibility for ESAs:

- A patient on myelosuppressive chemotherapy is "eligible" for ESA therapy starting with the first dose of chemotherapy within a given course of chemotherapy.
- Eligibility for ESA coverage ends at 8 weeks following administration of the last dose of chemotherapy within a course of chemotherapy.
- Initiation phase:
    - Begins with the first dose of ESA within a course of chemotherapy and lasts 4 weeks from the first dose of ESA.
    - A patient's Hgb level must be < 10 g/dl to initiate ESA treatment.
- Maintenance phase:
    - Begins at week 5 after the first dose of ESA in a course of chemotherapy and continues until 8 weeks after the last dose of chemotherapy in the course.

Dosing and Dose Escalation:

- A patient's Hgb level must be < 10 g/dl to initiate ESA therapy.
- During the initiation phase (first 4 weeks after first dose of ESA), the Hgb may go above 10 g/dl and CMS will provide coverage for the ESA therapy.
- For every single dose of an ESA given after the first 4 weeks, there must be a documented Hgb level < 10 g/dl immediately preceding that dose.
- The CMS rule will cover only one dose escalation by 25% at the 5^{th} week of ESA treatment if the Hgb rise is less than 1 g/dl from baseline during the first 4 weeks after initial dose.
- CMS does not consider additional rounds of ESAs within the same course of chemotherapy "reasonable and necessary" if the Hgb rise is < 1 g/dl from baseline.

Other Important Points:

- In the ruling, CMS stated that ESAs given for the diagnosis of anemia of cancer will no longer be covered for Medicare patients. The patient must currently be receiving chemotherapy (or have received it within 8 weeks) in order to be eligible for ESA treatment.
- The CMS ruling did not affect Medicare patients with the diagnosis of myelodysplastic syndrome (MDS). These patients will continue to receive treatment according to nationally recommended guidelines.

Part 3: CMS National Coverage Determination for ESAs in Nephrology
by Julie Barnes, Pharm.D., BCPS

Recent trials have highlighted concerns regarding the use of ESAs for the treatment of anemia in patients with chronic kidney disease (CKD). These trials found that patients who were given ESAs to target higher versus lower hemoglobin (Hgb) had increased risks of death and cardiovascular events. One of these trials was the CHOIR trial (Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease). The CHOIR trial had two groups: a high-hemoglobin group (Hgb 13.5 g.dL) and a low-hemoglobin group (Hgb 11.3 g/dL). The primary endpoint was a composite of death, myocardial infarction, hospitalization for congestive heart failure and stroke. There were 222 composite events: 125 events in the high-hemoglobin group and 97 in the low-hemoglobin group. This difference was statistically significant.

As a result of this and other data, the FDA in concert with the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) has issued the following guidelines regarding the use of ESAs in chronic kidney failure (See Tables 3 and 4).

These changes in labeling reflect current knowledge regarding ESAs in chronic kidney failure and attempt to give clinicians clear guidelines for their use. At the Cleveland Clinic, there is continued work to optimize the use of ESAs in this patient population. The Department of Nephrology continues to refine its anemia management protocols to comply with CMS guidelines.

Table 3: Guidelines for Use of ESAs in Chronic Kidney Failure

- ESAs should be administered to maintain a target Hgb between 10 and 12 g/dL.
- Patients who receive ESA doses that maintain Hgb levels > 12 g/dl are at increased risk for death, heart attack, stroke, and heart failure.
- Patients who have an insufficient Hgb response to ESA therapy may have a greater risk for cardiovascular events and mortality than other patients.
- Patients who achieved a Hgb of 11 g/dl with ESA therapy had improved exercise tolerance and physical functioning.

Table 4: Dosing Guidelines for the Use of ESAs in CKD

- Doses should be titrated to maintain Hgb levels between 10 to 12 g/dl.
- If the Hgb increases > 1 g/dl in any 2-week period, the ESA dose should be reduced by 25%.
- As the Hgb approaches 12 g/dl, the ESA dose should be reduced by 25% to avoid overcorrection of Hgb.
- If the Hgb increases less than 1 g/dl over 4 weeks despite adequate iron stores, then the ESA dose should be increased by 25%.
- For patients whose Hgb does not reach 10 to 12 g/dl despite appropriate dose titrations over a 12-week period:
    - Do not administer higher ESA doses and use the lowest dose that will maintain a Hgb level sufficient to avoid the need for RBC transfusion.
    - Evaluate and treat for other causes of anemia.
    - ESA therapy should be discontinued if responsiveness does not improve and the patient requires recurrent RBC transfusion.

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Medication Safety

1. **Myfortic and Cellcept:** As of November 2007, the pregnancy ratings for both mycophenolic acid (Myfortic®; Novartis) and mycophenolate mofetil (Cellcept®; Roche) have been changed from Category C (risk of fetal harm cannot be ruled out) to Category D (positive evidence of fetal risk). This change is a result of post-marketing data from the United States National Transplantation Pregnancy Registry along with additional data collected in women exposed to these agents systemically during pregnancy. These agents have been associated with an increased risk of first trimester pregnancy loss and increased risk of congenital malformations. Females of childbearing potential must 1) be informed of these risks associated with the use of Myfortic® and Cellcept® during pregnancy, 2) receive contraceptive counseling and use effective contraception, and 3) be advised against using Myfortic® or Cellcept® if planning a pregnancy. For additional information please see: http://www.fda.gov/medwatch/safety/2007/safety07.htm#CellCept2 and/or http://www.fda.gov/medwatch/safety/2007/safety07.htm#Myfortic.
2. **Nonprescription Cough and Cold Medications:** The Food and Drug Administration (FDA) has completed its review of information regarding the safety of over-the-counter (OTC) cough and cold preparations in infants and children under the age of 2 years and is recommending that these agents not be used in this patient population due to serious and potentially life-threatening side effects. The FDA has not completed its review regarding the safety of these agents in children aged 2-11 years. Additional information can be reviewed at: http://www.fda.gov/cder/drug/advisory/cough_cold_2008.htm.
3. **Ortho Evra®:** Labeling for the birth control patch, Ortho Evra® (Ortho McNeil), has been changed to include results of a recent study that found patients to be at an increased risk of developing venous thromboembolism compared to women using birth control pills. Additional information can be reviewed at: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01781.html or www.orthoevra.com

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