Safety Concerns of Erythropoiesis Stimulating Agents (ESAs)

I. **What's the Issue?** The FDA has strengthened safety information for ESAs to include a boxed warning and product labeling changes.

II. **Summary of Alerts Leading to Strengthened Safety Information**

In November 2006, the FDA, prompted by a published clinical trial (n=715), issued an alert about a significant increase in the risk for serious and life-threatening cardiovascular (CV) complications associated with normalization of hemoglobin (Hgb) levels in chronic kidney disease patients receiving epoetin alfa (HR 1.3; 95% CI 1.03, 1.74; p=0.03). A VA PBM and MedSAFE safety bulletin was sent out to VA clinicians to update them about these safety concerns. [1]

In February 2007, the FDA issued a safety alert regarding results of an unpublished study (n=989) which showed that darbepoetin alfa was not only ineffective in reducing red blood cell transfusions or fatigue in anemic cancer patients not receiving concurrent chemotherapy, but also resulted in higher mortality than the placebo group (HR 1.25; 95% CI 1.04, 1.51).[2,3]

Previously, in a 2004 briefing of the Oncology Drug Advisory Committee, the FDA also noted numerous reports that raised concern regarding the safety and outcome of ESA therapy.[4,5]

III. **New Boxed Warning**

In light of the numerous alerts regarding ESAs, the FDA has strengthened the safety information for ESAs. Full prescribing information, including updated changes is available for darbepoetin alfa at http://www.fda.gov/cder/foi/label/2007/103951s5139lbl.pdf and for Epogen/Procrit at http://www.fda.gov/cder/foi/label/2007/103234s5122lbl.pdf. The following summarizes the new boxed warning:

- Use the lowest dose of ESA to gradually increase Hgb to the lowest level needed to avoid red blood cell transfusion.
- ESAs increased the risk for death and for serious cardiovascular events when administered to target a Hgb of greater than 12 g/dL.
- In patients not on prophylactic anticoagulation and receiving ESAs pre-operatively for reduction of allogeneic red blood cell transfusions (unapproved indication), a higher incidence of deep venous thrombosis was documented.
- In cancer patients, the use of ESAs:
    i. shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy when dosed to target a Hgb >12 g/dL.
    ii. shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when dosed to target a Hgb >12 g/dL.
    iii. increased the risk of death when dosed to target a Hgb of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy (unapproved indication). **NOTE**: *As of March 9, 2007, the Centers for Medicare & Medicaid Services (CMS) has prohibited Medicare coverage of ESAs for this unapproved indication.*

IV. VA MedSAFE Recommendation

- Avoid dosing ESAs to target Hgb levels above 12 g/dL.
- **For Cancer patients not on chemotherapy:** Treatment with ESA is not recommended. Findings show no benefit and possibly increased serious harm.
- **For Chronic Renal Failure, oncology, zidovudine-treated HIV and HCV treatment-related anemia:**

i. measure Hgb at least once every 2 weeks after initiating treatment, and then every 4-6 weeks after Hgb has stabilized. More frequent monitoring has been recommended during initiation; however, the effect of dosage adjustments may not be appreciated in a timeframe shorter than 2 weeks.
ii. if Hgb increases > 1 g/dL in any 2-week period, or exceeds 12 g/dL, decrease dose of ESA.
iii. if the Hgb exceeds 13 g/dL, hold ESA and resume at lower dose.

- **For patients with a history of cardiovascular disease or hypertension:** check blood pressure at initiation and each visit to ensure adequate blood pressure control.

V. **More Updates to Come**

- The FDA, Amgen, and Ortho Biotech will convene at an Oncologic Drugs Advisory Committee meeting scheduled for *May 10th, 2007* to review the use of ESAs in the treatment of cancer-related anemia. Amgen will report on an ongoing trial, Aranesp 145, involving patients with previously untreated small cell lung cancer.
- VA MedSAFE and PBM will track results and provide an update to VA clinicians.

1. http://www.pbm.va.gov/vamedsafe/National%20PBM%20Bulletin%20ESA%20Final.pdf
2. http://www.fda.gov/medwatch/safety/2007/safety07.htm#Aranesp
3. http://www.fda.gov/medwatch/safety/2007/Aranesp_DHCP_012707.htm Letter
4. http://www.fda.gov/ohrms/dockets/ac/04/briefing/4037b2.htm
5. http://www.fda.gov/ohrms/dockets/ac/cder04.html#Oncologic