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DEPARTMENT OF VETERANS AFFAIRS VETERANS HEALTH ADMINISTRATION
PHARMACY BENEFITS MANAGEMENT STRATEGIC HEALTHCARE GROUP,
MEDICAL ADVISORY PANEL, RENAL FIELD ADVISORY COMMITTEE, ONCOLOGY FIELD ADVISORY
COMMITTEE, HEPATITIS C WORKGROUP, AND
CENTER FOR MEDICATION SAFETY (VA MEDSAFE)

FDA - Erythropoiesis Stimulating Agents (ESA) Safety Alert

- I. **ISSUE** – A recent clinical trial publication has prompted the Food and Drug Administration (FDA)¹ to warn providers about a significant increase in the risk for serious and life-threatening cardiovascular (CV) complications associated with normalization of hemoglobin (Hgb) levels in patients receiving erythropoiesis stimulating agents (ESA).²
- II. **BACKGROUND** – Based on a review of randomized controlled trials comparing different Hgb targets and their effects on clinical outcomes in different populations of patients with chronic kidney disease (CKD), the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines previously recommended a lower limit of Hgb ≥ 11 g/dL, with an upper limit of < 13 g/dL. The guidelines stated that there was insufficient evidence to recommend routinely maintaining Hgb levels at or above 13 g/dL since previous reports had shown that patients with CKD treated to higher target Hgb levels experienced an increase in clinical events.³

The recently published Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial compared dosing epoetin alfa to two different target levels in over 1400 patients not on dialysis. The study found that patients in the higher Hgb target group (13 – 13.5 g/dl) had a shorter time to the primary endpoint (the composite outcome of death, myocardial infarction, hospitalization for congestive heart failure, or stroke) compared to patients in the lower Hgb target group (10.5 – 11 g/dl) (hazard ratio of 1.3; 95% CI 1.03, 1.74; $p=0.03$). The average Hgb at the end of the study was 12.6 g/dL for the high Hgb group and 11.3 g/dL for the low Hgb group.²

Results of a separate Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) found that treatment to a target Hgb 13 – 15 g/dL did not significantly reduce CV events compared to a target of 10.5 – 11.5 g/dL. Approximately 93% of patients enrolled had preexisting CV disease.⁴

Although the two studies were conducted in patients with CKD not on dialysis and involved different ESAs (epoetin beta used in CREATE is not approved for use in the U.S.), the FDA has issued an alert to include the use of all ESAs for the normalization of Hgb levels without specification given to the etiology of anemia.¹

There are three ESA products available in the U.S.: Procrit™, Epogen™, and Aranesp™. The package inserts, consistent with the FDA, recommend that the target Hgb level not exceed 12 g/dL. The major areas where ESAs are utilized within VA are oncology, renal disease, and infectious disease (hepatitis C and zidovudine-treated HIV).

- III. **DISCUSSION** – Neither of the two cited open-label studies in patients with CKD indicated that normalization of Hgb levels reduces the risk of cardiovascular events. Based on the available clinical trial data, there is no demonstrable benefit on mortality or cardiovascular outcomes when exceeding a target hemoglobin of 12.0 g/dl. More importantly, recent clinical trials suggest there may be harm in targeting higher hemoglobin levels in the CKD population. While the optimal target range for Hgb correction remains to be clearly defined, a target Hgb range of 11-12 g/dL is commonly accepted, although this needs to be applied in the context of each patient's overall therapy.³ In addition, it should be

noted that the lower limit for the target Hgb has not been studied in clinical trials, and a 1 g/dL range may be too narrow to maintain due to normal biologic variation in Hgb.

IV. VA MEDSAFE RECOMMENDATIONS

1. **Hgb limits:** Avoid dosing ESAs to target Hgb levels above 12 g/dL; a target of 12 g/dL is recommended.
2. **Monitoring**
 - a. **Frequency:** For chronic renal failure (CRF), oncology, zidovudine-treated HIV and HCV treatment-related anemia patients, 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 treatment initiation; however, the effect of dosage adjustments may not be appreciated in a timeframe shorter than 2 weeks.
 - b. **Adjustments:**
 - If Hgb increases > 1 g/dL in any 2-week period, or exceeds 12 g/dL, decrease dose of ESA.
 - If the Hgb exceeds 13 g/dL, hold ESA and resume at lower dose.
3. **Precautions:** For patients with a history of cardiovascular disease or hypertension, check blood pressure at initiation and each visit to ensure adequate blood pressure control.
4. **Safety Initiatives:** Local VAMCs should have initiatives in place to address this safety issue, if not already implemented.

V. REFERENCES

1. Food and Drug Administration (FDA) Alert. 11/16/06.
http://www.fda.gov/cder/drug/InfoSheets/HCP/RHE_HCP.pdf
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<http://www.kidney.org/professionals/KDOQI/guidelines.anemia/cpr21.htm>. Accessed December 8, 2006.
4. Druke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med 2006;355:2071-84.