

NATIONAL PBM COMMUNICATION · August 9, 2011

Erythropoiesis-Stimulating Agents (ESAs) in Chronic Kidney Disease (CKD) and New Dosing Recommendations

- On June 24, 2011, the FDA released revised dosing recommendations for erythropoiesis-stimulating agents (ESAs) in the treatment of anemia in patients with chronic kidney disease (CKD), after review of additional data on increased risk of cardiovascular (CV) events with higher hemoglobin (Hgb) targets with these agents. The product information for the ESAs darbepoetin alfa (Aranesp) and epoetin alfa (Epogen, Procrit) has recently been updated to reflect these recommendations.
- A previous FDA Alert (11/16/2006) reinforced manufacturer recommendations for dosing ESAs to not exceed Hgb levels > 12 g/dL after review of results from the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial that reported an increase in the risk of composite death, myocardial infarction, hospitalization for congestive heart failure, and stroke in patients treated with epoetin alfa to a target Hgb of 13.5 g/dL (mean achieved Hgb 12.6 g/dL) vs. 11.3 g/dL. (For previous National PBM Communication on the FDA recommendations and adverse cardiac events associated with ESAs, see: <http://www.pbm.va.gov/vamedsafe/National%20PBM%20Bulletin%20ESA%20Final.pdf>). In 2007, the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) updated their recommendations for Hgb target in patients with CKD on ESAs to generally be within the range of 11 to 12 g/dL.
- The more recent FDA Drug Safety Communication (6/24/2011) for dosing ESAs in patients with CKD is based on review of clinical trials including data from the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), in which a total of 4038 patient with CKD, diabetes, and anemia (Hgb ≤ 11 g/dl) were randomized to treatment with darbepoetin alfa to a target Hgb of 13 g/dL (median 12.5 g/dL), or placebo with rescue darbepoetin alfa therapy for Hgb < 9 g/dL (median 10.6 g/dL). There was no significant difference in the primary endpoints of death or CV events and of death or end-stage renal disease between treatment groups; however, there was a significant increase in fatal or nonfatal stroke (HR 1.92; 95% CI 1.38 to 2.68; P<0.001) in patients treated with an ESA in the higher Hgb target group.
- **For patients with CKD and anemia, FDA and current product labeling recommends:**
 - *Not on dialysis: Consider initiating (i.e., administer first dose) treatment with an ESA in a patient with a Hgb < 10 g/dl if the rate of decrease in Hgb reflects the potential for requiring red blood cell (RBC) transfusion and it is a goal to reduce the risks associated with RBC transfusions. If Hgb is > 10 g/dL, decrease or interrupt therapy and to use the lowest effective dose to decrease the need for RBC transfusions.*
 - *Dialysis: Initiate (i.e., administer first dose) treatment with an ESA in a patient with a Hgb < 10 g/dl. If the Hgb increases to near or over 11 g/dL, decrease or interrupt therapy.*
 - **FDA further clarifies that initiate means to administer a first dose of an ESA, and that these recommendations do not define how far below a Hgb of 10 g/dL is appropriate to initiate treatment with an ESA nor is it a recommendation to achieve a Hgb of 10 g/dL or 11 g/dL as a treatment goal. FDA recommends that dosing of the ESAs needs to be individualized so as to use the lowest effective dose to prevent the need for RBC transfusions.**
 - *The previous recommendation to dose ESAs to a target Hgb of 10 to 12 g/dL in patients with CKD is no longer part of the manufacturer labeling. The revised product information includes a warning that treatment with an ESA to a Hgb level > 11 g/dL has been associated with an increase in the risk for death, serious CV events, and stroke in controlled clinical trials. Data are currently not available on the optimal dosing or Hgb target to avoid these events.*
 - *Advise patients on the risk vs. benefit of using ESAs and that treatment can increase the risk for stroke, heart attack, heart failure, blood clots, and death.*
 - *The manufacturer labeling recommends evaluation of iron status before and during treatment with an ESA and to maintain iron repletion. Other causes of anemia (e.g., vitamin deficiency, metabolic or chronic inflammatory conditions, bleeding, etc.) should be excluded or corrected before initiating an ESA. In addition, it is recommended that the Hgb rate of rise, rate of decline, ESA responsiveness and Hgb variability be considered when adjusting therapy; noting that a single deviation in Hgb may not require a change in dose.*
- As the above FDA recommendations could be perceived to require maintaining patients within a tight Hgb range, it is important to reiterate that the goal is to use the lowest effective dose of ESA to prevent the need for RBC transfusions, and to individualize therapy. In addition, as noted by the NKF KDOQI anemia guidelines, it is important to distinguish between target and achieved Hgb, as there can be significant fluctuations in patients over a given period of time.
- Providers should continue to report any adverse reactions with the use of ESAs by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800-FDA 0178, online at <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>, or by mail).

REFERENCES

FDA Drug Safety Communication: Modified dosing recommendation to improve the safe use of Erythropoiesis-Stimulating Agents (ESAs) in chronic kidney disease.

<http://www.fda.gov/Drugs/DrugSafety/ucm259639.htm> (Accessed June 27, 2011)

Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355:2085-98.

National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. http://www.kidney.org/professionals/KDOQI/guidelines_anemiaUP/index.htm

Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009;361:2019-32.

ACTIONS

- **Facility Director (or physician designee):** Forward this document to the Facility Chief of Staff (COS).
- **Facility COS and Chief Nurse Executives:** Forward this document to all appropriate providers who prescribe these medications (e.g., nephrologists, primary care providers and clinic staff, including contract providers, etc.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.
- **ACOS for R&D:** Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).