Information for Healthcare Professionals

Erythropoiesis Stimulating Agents (ESA)

[*Aranesp (darbepoetin), Epogen (epoetin alfa), and Procrit (epoetin alfa)*]

This is no longer current information. The FDA has new information about this safety issue at http://www.fda.gov/cder/drug/infopage/RHE/default.htm.

FDA ALERT [11/16/2006]: FDA is issuing this alert to advise you of a newly published clinical study showing that patients treated with an erythropoiesis-stimulating agent (ESA) and dosed to a target hemoglobin concentration of 13.5 g/dL are at a significantly increased risk for serious and life threatening cardiovascular complications, as compared to use of the ESA to target a hemoglobin concentration of 11.3 g/dL. The "Correction of Hemoglobin and Outcomes in Renal Insufficiency" (CHOIR) study, published November 16, 2006 in the New England Journal of Medicine, reports the adverse cardiovascular complications as a composite of the occurrence of one of the following events: death, myocardial infarction, hospitalization for congestive heart failure, or stroke.

The CHOIR study findings underscore the importance of following the currently approved prescribing information for Procrit, Epogen, and Aranesp, including the dosing recommendation that the target hemoglobin not exceed 12 g/dL.

This information reflects FDA's current analysis of data available to FDA concerning these drugs. FDA intends to update this sheet when additional information or analyses become available.

To report any serious adverse events associated with the use of these drugs, please contact the FDA MedWatch program using the contact information at the bottom of this sheet.

Considerations

Physicians and other healthcare professionals should consider the following when using erythropoiesis stimulating agents:

- **For all patients:**
  - Adhere to dosing to maintain the recommended target hemoglobin range of 10 to12 g/dL.
  - Measure hemoglobin twice a week for 2 to 6 weeks after any dosage adjustment to ensure that hemoglobin has stabilized in response to the dose change.
  - Decrease the dose of the ESA if the hemoglobin increase exceeds 1g/dL in any 2 week period.

- **For chronic renal failure (CRF) patients**: Measure hemoglobin twice a week after initiating treatment until hemoglobin has stabilized
- **For cancer patients and zidovudine-treated HIV patients:** Measure hemoglobin once a week after initiating treatment until hemoglobin has stabilized

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- **For patients with a history of cardiovascular disease or hypertension**: Closely monitor and control blood pressure

Information for the Patient

Physicians and other healthcare professionals should discuss the following with their patients:

- The goal of treatment with erythropoiesis stimulating agents (ESA) is to increase the number of red blood cells which can help them in treating their anemia.
- Treatment with an ESA can be harmful if not closely monitored.
- The importance of keeping their appointments for their blood tests
- The need to monitor their blood pressure every day (if appropriate) and call you if there are any changes outside of the range established for the patient.
- To call you if they experience any of the following symptoms:
    - Pain and/or swelling in the legs
    - Worsening in shortness of breath
    - Increases in blood pressures
    - Dizziness or loss of consciousness
    - Extreme tiredness
    - Blood clots in hemodialysis vascular access ports

Data Summary

Safety concerns related to the use of erythropoiesis-stimulating agents in the treatment of the anemia of chronic renal failure (CRF) is the topic of two clinical studies and an editorial published in *The New England Journal of Medicine* on November, 16, 2006. The 1,432 subject CHOIR study demonstrated increases in serious and potentially life threatening cardiovascular events when epoetin alfa (Procrit) is administered to reach higher target hemoglobin levels than lower target hemoglobin levels. The 603 subject CREATE study showed a trend toward more cardiovascular events in a pattern similar to the CHOIR study, thus supporting the findings of the CHOIR study. The CREATE study examined the use of epoetin beta, a product not approved in the USA.

- The CHOIR study was a randomized, open label design in which anemic chronic kidney disease (CKD) subjects were randomized to be dosed to either a higher average target hemoglobin (13.5 g/dL) or a lower average target hemoglobin (11.3 g/dL). All subjects received Procrit. The primary endpoint was a time to event analysis for a composite

cardiovascular endpoint (all cause mortality, congestive heart failure (CHF) hospitalization, non-fatal MI, or non-fatal stroke).

- Procrit was administered as 10,000 Units SC weekly and titration allowed to a maximum dose of 20,000 Units weekly.
- Overall, 715 subjects were randomized to the high target hemoglobin (13.5 g/dL) and 717 randomized to the low target hemoglobin (11.3 g/dL). At the end of the study, the average hemoglobin was 12.6 g/dL for the high group and 11.3 g/dL for the low group.
- The composite cardiovascular endpoint was statistically worse in the higher target hemoglobin group with a hazard ratio of 1.3 [95% CI 1.03, 1.74] (p = 0.03 by log rank test).
- The rates for the individual components of the composite primary endpoint were (high target vs. low):

Death:	7.3% vs 5.0% (p = 0.07)
CHF hosp:	9.0% vs 6.6% (p = 0.07)
Non-fatal MI:	2.5% vs 2.8%
Non-fatal stroke:	1.7% vs 1.7%

- The analyses for this study found no correlation between rate of rise of hemoglobin and adverse cardiovascular events. However, the relationship between seizures and the rate of rise of hemoglobin as reported in the labeling for all three products remains a concern.

The CHOIR and CREATE study findings underscore the importance of the existing warnings regarding cardiovascular risks that include thrombotic events and increased mortality observed in hemodialysis patients with cardiac disease targeted to higher hemoglobin levels (~14 g/dL), and recommendations not to exceed hemoglobin levels of 12 g/dL in approved labeling for Procrit, Epogen, and Aranesp. Please refer to the full prescribing information for additional information. Internet links to the full prescribing information for all approved ESA products may be found at the FDA page for this alert.