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Information for Healthcare Professionals Erythropoiesis Stimulating Agents (ESA)

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

The issues described in this Alert have been addressed in product labeling.

FDA ALERT [11/16/2006, Updated 2/16/2007 and 3/09/2007]: FDA is issuing this alert to provide new safety information for erythropoiesis-stimulating agents (ESAs) [Aranesp (darbepoetin alfa), Epogen (epoetin alfa), and Procrit (epoetin alfa)]. Analyses of four new studies in patients with cancer found a higher chance of serious and life-threatening side effects and/or death with the use of ESAs. These research studies were evaluating an unapproved dosing regimen, a patient population for which ESAs are not approved, or a new unapproved ESA. In another study, patients scheduled for orthopedic surgery had a higher rate of deep venous thrombosis when treated with Procrit at the approved dose. This new information is consistent with risks found in two clinical studies in patients with chronic renal failure treated with an unapproved regimen of an ESA that were reported in November 2006 and are summarized in the data section below.

All ESAs have the same mechanism of action. As a result, FDA believes these new concerns apply to all ESAs and is re-evaluating how to safely use this product class. FDA and Amgen, the manufacturer of Aranesp, Epogen and Procrit, have changed the full prescribing information for these drugs. The new product labeling includes a new boxed warning, updated warnings, and a change to the dosage and administration sections for all ESAs. These changes are summarized below.

This information reflects FDA's preliminary analysis of data concerning this drug. FDA is considering, but has not reached a final conclusion about, this information. 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

Changes to the prescribing information for the ESAs (Aranesp, Epogen and Procrit) are summarized here:

A New Boxed Warning providing the following information:

- Avoid serious cardiovascular and arterial and venous thromboembolic events by using the lowest dose of [Aranesp /EPOGEN/PROCRIT] that will gradually raise the hemoglobin concentration to the lowest level sufficient to avoid the need for blood transfusion
- [Aranesp /EPOGEN/PROCRIT] and other ESAs increased the risk for death and for serious cardiovascular events when dosed to achieve a target a hemoglobin of greater than 12 g/dL
- Use of ESAs to achieve a target hemoglobin of 12 g/dL or greater in cancer patients:
 - shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy;
 - shortened overall survival and increased deaths attributed to disease progression in patients with metastatic breast cancer receiving chemotherapy;
 - increased the risk of death in patients with active malignant disease not under treatment with chemotherapy or radiation therapy. ESAs are not indicated for this patient population.
- Patients treated before surgery with epoetin alfa to reduce allogenic red blood cell transfusions had a higher incidence of deep venous thrombosis. Aranesp is not approved for this indication.

Additional Warnings about increased mortality, cardiovascular events, tumor progression and uncontrolled hypertension

- *Increased Mortality and Cardiovascular Events* – the warnings now describes the results of new studies showing an increased incidence of thrombotic events in patients with chronic renal failure, cancer patients on chemotherapy, and surgical candidates.
- *Potential for Tumor Growth Progression* – A new subsection in Warnings describes the new data and emphasizes the evidence for increased rate of tumor progression.
- *Hypertension* - this subsection advises against the use of ESAs in patients with uncontrolled hypertension, and describes the risks to and guidance for managing controlled hypertensive patients.

Recommendations and Considerations

Physicians and other healthcare professionals should consider the following when using ESAs:

For all patients:

- Use the lowest dose possible to gradually increase the hemoglobin concentration to avoid the need for transfusion.
- 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.
- Withhold the dose of the ESA if the hemoglobin increase exceeds 12 g/dL or rises by 1g/dL in any 2 week period.

For cancer patients:

- Use of an ESA in anemic cancer patients who are not on chemotherapy offered no benefit and may shorten the time to death.

- ESAs are not FDA approved to treat anemia in cancer patients not receiving chemotherapy
- There is a potential risk of shortening the time to tumor progression or disease-free survival
- ESAs are administered only to avoid red blood cell transfusions in cancer patients. ESAs do not improve the outcome of cancer treatment and do not alleviate fatigue or increase energy.

Dosing and Monitoring Recommendations

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.

For patients with a history of cardiovascular disease or hypertension

- Closely monitor and control blood pressure.

Patient Counseling Information

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 to avoid blood transfusions.
- ESAs require at least 2-6 weeks of treatment before there is an increase in the number of red blood cells.
- The effects of treatment with an ESA can be harmful in certain circumstances.
- They should keep appointments for blood tests so they can be adequately monitored.
- They need to monitor blood pressure every day (if appropriate) and to call you if there are any changes outside of the range established for the patient.
- 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 pressure
 - Dizziness or loss of consciousness
 - Extreme tiredness
 - Blood clots in hemodialysis vascular access ports

Data Summary

Studies in cancer patients receiving radiotherapy

In December, 2006 Amgen informed FDA of the interim results of the Danish Head and Neck Cancer Study Group trial (DAHANCA 10). This open-label, randomized trial compared radiation therapy alone to radiation therapy plus Aranesp in the treatment of advanced head and neck cancer. The trial assessed whether treating anemia to maintain a hemoglobin concentration

of 14.0-15.5 g/dL during radiotherapy would improve loco-regional disease control. The DAHANCA 10 data monitoring committee found that 3-year loco-regional control in subjects treated with Aranesp was significantly worse than for those not receiving Aranesp ($p=0.01$).

Overall survival also favored those not treated with Aranesp, though this finding was not statistically significant ($p=0.08$). The data monitoring committee recommended the trial's termination on December 1, 2006. See <http://conman.au.dk/dahanca> for additional information on the DAHANCA 10 study. FDA will review and analyze the complete study results after they are submitted by Amgen.

This study is similar in design and in outcomes to that reported by Henke, et al. The data from the Henke study were presented at the May 4, 2004 meeting of the Oncologic Drugs Advisory Committee. The briefing information and transcript for the Advisory Committee is available at <http://www.fda.gov/ohrms/dockets/ac/cder04.html#Oncologic>. The increased rate of tumor progression and increased mortality reported in the Henke study were incorporated into product labeling (see: *Precautions, Tumor Growth Factor Potential*) in 2004.

Study in cancer patients not receiving chemotherapy

FDA was notified in January 2007 of the results of a 989 patient, multi-center, double-blind, randomized, placebo-controlled study of Aranesp (darbepoetin alfa) in anemic cancer patients who are not receiving chemotherapy. The target hemoglobin in the Aranesp treatment group was 12 g/dl. The study results provided to FDA show Aranesp did not reduce the need for red blood cell transfusions and showed an increase in mortality in patients receiving Aranesp compared to those receiving placebo (hazard ratio 1.25; 95% confidence interval: 1.04, 1.51). FDA will review and analyze the complete study results after they are submitted by Amgen. Additional information on the study is provided in a January 26th, 2007 Dear Health Care Professional letter sent by Amgen (see <http://www.fda.gov/medwatch/safety/2007/safety07.htm#Aranesp>).

FDA was notified in February 2007 of the final results of a double-blind, placebo controlled study to evaluate whether use of epoetin alfa in anemic non-small cell lung cancer patients not on chemotherapy improved their quality of life. The epoetin alfa dose was titrated to maintain a hemoglobin level of 12 to 14 g/dL; epoetin alfa was dosed at 40,000 IU every week. Though planned to enroll 300 patients, the study was closed to accrual in December 2003 after enrolling only 70 patients because its data monitoring committee found higher mortality in those treated with epoetin alfa. Median time to death in those treated with epoetin alfa was 68 days and significantly shorter than the median time to death of 131 days in those treated with placebo ($p = 0.04$), with the majority of deaths reported as disease progression. Also, treatment with epoetin alfa did not significantly reduce the need for red blood cell transfusion or improve quality of life. Prognostic factors and previous treatments were reported to be well balanced between the treatment groups. FDA will review and analyze the complete study results after they are submitted by Johnson & Johnson Pharmaceutical Research and Development.

Study in cancer patients with an investigational ESA

In February 2007 FDA was notified by Hoffmann-La Roche that it was suspending a study of a new ESA product because of safety concerns. The study was a multi-center, randomized, dose-finding assessment of a pegylated epoetin beta product in anemic patients with Stage IIIB or IV non-small cell lung cancer who were receiving first line chemotherapy. Three dosing regimens of the investigational drug were being compared to Aranesp (given according to an FDA-approved

dosing regimen). The dose of pegylated epoetin beta was titrated to maintain the hemoglobin level between 11 and 13 g/dL. An interim analysis, after randomization of 153 patients, demonstrated a numerical imbalance in the number of deaths across the four arms of the study. FDA has not yet received the complete study results, and will review and analyze the data after they are submitted by Hoffmann-La Roche.

Study in patients undergoing surgery

FDA was notified in February 2007 of the preliminary results of a 681 patient, multi-center, randomized, open-label, non-inferiority study of Procrit (Epoetin Alfa) compared to the standard of care in adult patients undergoing elective spinal surgery. Procrit was administered according to the dosage and administration section of the label for pretreatment hemoglobin values >10 and ≤ 13 g/dL. The frequency of deep venous thrombosis in patients treated with Procrit was 4.7 percent (16 patients), more than twice that of patients who received usual blood conservation care (frequency of 2.1 percent, seven patients). FDA will review and analyze the complete study results after they are submitted by Ortho Biotech, L.P.

Studies in patients with chronic renal failure

Two clinical studies and an editorial published in the New England Journal of Medicine in November, 2006 addressed safety concerns about the use of erythropoiesis stimulating agents in the treatment of anemia of chronic renal failure (CRF). The 1,400 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 600 subject CREATE study trended toward more cardiovascular events in a pattern similar to the CHOIR study, thus strengthening 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 target hemoglobin (13.5 g/dL) or a lower 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 U SC weekly and titration allowed to a maximum dose of 20,000 U weekly. Overall, 715 subjects were randomized to the high hemoglobin target (13.5 g/dL) and 717 randomized to the low target (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 primary endpoint, composite of death, and cardiovascular events was statistically significant worse outcome in the higher target hemoglobin group ($p = 0.03$ by log rank test) with a hazard ratio of 1.3 [95% CI 1.03, 1.74]. The rates for the individual components of the composite primary endpoint were (high target hemoglobin vs. low target hemoglobin):

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 published analyses for this study found no correlation between adverse cardiovascular

events and rate of rise of hemoglobin.

The published CHOIR and supportive CREATE study findings underscore the importance of the warnings in the labeling for Procrit, Epogen, and Aranesp 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 warning regarding the increased risk of death if ESAs are dosed to raise hemoglobin levels to >12 g/dL.

Report serious adverse events to
FDA's MedWatch reporting system by completing a form on line at
<http://www.fda.gov/medwatch/report.htm>, by faxing (1-800-FDA-0178),
by mail using the postage-paid address form provided online
(5600 Fishers Lane, Rockville, MD 20852-9787),
or by telephone (1-800-FDA-1088).

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