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Quick Pulse

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FDA Issues Public Health Advisory on Erythropoiesis-Stimulating Agents (ESAs)

On March 9, 2007, the FDA put a black box warning on all currently approved erythropoiesis-stimulating agents (ESAs) – Amgen's Aranesp (darbepoetin alfa), Amgen's Epogen (epoetin alfa), and Johnson & Johnson's Procrit (epoetin alfa), all of which are manufactured by Amgen. The Agency also revised the product labels for these drugs, with updated warnings and modifications to the dosing instructions, and it warned physicians to use as little of them as possible.

The FDA action comes after studies found an increased risk of death, blood clots, strokes, and heart attacks in patients with chronic kidney failure when ESAs were given at higher than recommended doses ***and*** after studies which found more rapid tumor growth in patients with head and neck cancer who received these higher doses.

ESAs are FDA-approved to reduce blood transfusions, and they are labeled for treatment of anemia to reduce the number of blood transfusions. FDA officials could not estimate how many Americans take an ESA, but Medicare spends more on Epogen than any other single separately billed drug – $2 billion in 2005.

What exactly is the FDA warning in the black box? **Prescribe the *lowest* dose of ESA to the *lowest* level to avoid blood transfusions.**

Basically, the FDA is warning that using too much of an ESA can affect survival and increase serious side effects, and the Agency is strongly suggesting that ESAs should be used on-label, not off-label. The FDA has modified the labels for Aranesp, Epogen, and Procrit. Dr. Richard Pazdur, Director of the FDA's Office of Oncology Drug Products, Center for Drug Evaluation and Research (CDER), said, "In some cases, ESAs can increase the risk of death and the potential for the growth of tumors…The FDA reminds physicians that ESAs are approved for reduction in red cell transfusions. For oncology patients, these products have ***not been shown*** to improve symptoms of anemia or quality of life…Physicians should discuss the above information with all patients receiving this class of agents…We are asking people to look at the lowest dose of this class of agents that ***gradually*** increases to the lowest level to avoid blood transfusions. That would require discussion on the part of the physician, based on each particular clinical situation."

FDA officials did not come out and say it directly, but the inference was clear that the Agency is encouraging on-label use of ESAs. Dr. Karen Weiss, deputy director of the FDA's Office of Oncology Drug Products in CDER, said, "Those strategies that (use) a higher than recommended dose are the bulk of the data that has raised concerns…and that is in the renal and the cancer populations – and tumor-related outcomes specific to the cancer population."

Dr. Pazdur said the FDA has four messages for patients and physicians:

1. Use the lowest dose of ESA that will gradually increase hemoglobin (Hgb) concentrations to the lowest level sufficient to avoid blood transfusions.
2. ESAs increase the risk for death and serious cardiovascular events when administered to target Hgb >12 g/dL.
3. A higher incidence of DVT (deep vein thrombosis) has been documented in patients receiving epoetin alfa prior to blood transfusions who did not receive prior anticoagulation therapy.
4. For cancer patients, an ESA:
   a. When administered to head & neck cancer patients getting radiation, shortened the time to progression when Hgb was targeted >12 g/dL.
   b. Shortened overall survival and increased death attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy, when administered to a target Hgb >12 g/dL.
   c. Increased mortality in cancer patients not receiving chemotherapy or radiotherapy when targeting Hgb >12 g/dL. He declared, "ESAs are ***not*** indicated for these patients."

On what is the FDA's decision based? **A review of 6 trials, some but not all of which are new.**

Dr. Pazdur said, "We recently got new safety information on ESAs." The six trials are:

1. **CHOIR** – a randomized clinical trial in anemic chronic renal failure patients which found that Hgb >13 increased the risk of heart attack, death, and stroke. As a reminder, the results of CHOIR were published in the ***New England Journal of Medicine*** in November 2006. This trial studied 1,432 pre-dialysis patients with chronic kidney disease (CKD) treated with Procrit to boost levels of hemoglobin in the blood. Half the patients were treated with a hemoglobin goal of 13.5 g/dL and the other with a target of 11.3 g/dL. This open-label study, sponsored by J&J, was stopped early in May 2005 by the data safety monitoring board (DSMB) because of an excess of cardiovascular adverse events. Researchers found that patients with the higher hemoglobin target had a 33.7% increased risk of death, myocardial infarction (MI), and stroke; and their "strong recommendation was to target hemoglobin of 11-12 in all CKD patients."
2. **BEST** – a randomized clinical trial of placebo vs. weekly epoetin alfa (with a goal of maintaining Hgb at 12-14 g/dL) in 939 metastatic breast cancer patients which was stopped early for higher mortality and more thrombolic events in the epoetin arm. BEST was published in ***Lancet*** in 2003 and later, in greater detail, in the ***Journal of Clinical Oncology***. The study, conducted in 20 countries, was stopped early by the DSMB because survival was worse in the ESA arm. An independent retrospective chart review of BEST found that the baseline performance status was worse in the ESA-treated group, and most of the excess deaths were believed to be due to early disease progression. Most of the excess deaths in the ESA arm occurred in the first 4 months of the trial.
3. **A Phase III randomized clinical trial** – in 989 patients with active malignant disease (cancer) who did ***not*** receive chemotherapy or radiation which found no statistically significant reduction in red blood cell transfusions in patients receiving Aranesp vs. placebo. And the absolute number of deaths was greater with Aranesp than placebo.
4. **DAHANKA** – a randomized clinical trial in head and neck cancer patients in Denmark that was stopped early after an analysis of the first 484 patients found a trend to worse survival with Aranesp vs. placebo.
5. **A trial in advanced lung cancer (NSCLC) patients** – an interim analysis of 70 patients in this randomized clinical trial comparing epoetin alfa targeting Hgb 12-14 g/dL vs. placebo found a significant decrease in median survival in the ESA arm.
6. **SPINE** – a randomized clinical trial of 681 patients undergoing spinal surgery in which a preliminary analysis showed a higher incidence of DVTs with epoetin alfa than standard-of-care (4.7% vs. 2.1%, or 12 patients vs. 7 patients). These patients did not get prophylactic anticoagulation therapy.

What does this mean for patients in ongoing clinical trials? **Patients need to be informed and re-consented. Institutional review boards (IRBs) also should be informed, and investigators should "re-evaluate if investigations should continue in light of this new safety data."**

Dr. Pazdur said, "Patients in clinical trials need to be re-consented in light of the new risks…After re-consent, if the trial is deemed appropriate to continue, those trials will continue…This does not mean that all clinical trials should be halted…but they should be re-evaluated for the risk:benefit relationship in light of this new data, and patients should be informed…This is not a blanket statement on cessation of clinical trials for this class of drugs." The FDA also will send a letter to all IND sponsors with its recommendations.

What is the recommended Hgb target? **The FDA is leaving that to physicians but emphasizing that "frequently patients are transfused to a level of 10 Hgb."**

Dr. Pazdur said, "We left (the target Hgb level) to the discretion of physicians…In general, however, most physicians would transfuse a patient up to 10 g/dL and not go to a higher level. There has been some creep here due to this not being an

exact science, to having a little higher level due to the variability of the response of the patient over time. I think we really need to re-evaluate this…And it will be a topic of discussion at advisory committees." (**NOTE**: *Notice that he said committees, plural.*)

Why is the FDA holding a meeting of the Oncology Drugs Advisory Committee (ODAC) on May 10, 2007? **To publicize its message as well as to evaluate the safety and dosing of ESAs in cancer patients. The FDA also indicated further labeling revisions may occur after that meeting.**

Dr. Pazdur said, "The reason we are taking this to panel is that we have top-line data, but not the full data of these trials." He said the panel will:

1. Take a look at the whole issue of use in the oncology patient population.
2. Discuss the oncology patient population, looking at indications and off-label use of these drugs, and discussing in a real-world situation how different the potential indications are.
3. Emphasize the importance of this new data in a public forum. Dr. Pazdur said this is the most important reason.

What future events are planned that will give visibility to this issue? **In addition to the FDA ODAC advisory panel scheduled for May 10, 2007, it is likely there will also be a Cardiovascular and Renal Drugs Advisory Committee meeting, and there may be additional ODAC meetings.**

While there currently is only one meeting of the Oncology Drugs Advisory Committee (ODAC) scheduled, Dr. Pazdur suggested that there may be additional ODAC meetings on this topic in the future, "We may need to discuss this at future meetings…This is an emerging problem…There is a lot of (new) data."

Dr. Pazdur said the FDA is currently reviewing all quality of life claims in the (oncology) labels, and, since that will take some time, there may be additional changes in the future. He said, "We believe they (the claims) should be consistent with current FDA standards on patient-reported outcomes…We are looking at the whole issue of quality of life claims for this class…Some of the claims in the product labels have been there for several years…We are reviewing that (advertising) in light of contemporary labeling claims of other classes of products. In addition to that, we are looking at the labeling issues and quality of life ***in other products*** where we allow these types of patient-reported outcomes…Patient-reported outcomes is a developing field…It was only in embryonic stage at the time (Epogen was approved for chronic renal failure)…Obviously, if we applied current standards for patient-reported outcomes, which has developed over the past 3-5 years, the issues of the oncology claims would not be supported at this time…There was also some feeling that the claims in renal could be (inappropriate)…So, basically we have an evolving field and an evolving interpretation by the Agency."

Thus, a meeting (or meetings) of the Cardio-Renal panel also appears likely since the FDA is reviewing the evidence for "vague" claims relating to fatigue in the Epogen label for chronic renal failure. Dr. Pazdur said, "We have asked the company (Amgen) to re-submit the primary data submitted to the FDA. They were submitted many years ago…We want to see if that data support marketing claims based on the current standard of patient-reported outcomes…There have been some vague claims on fatigue in the package insert which was removed (from the oncology labels)…We are looking at renal claims…They are still in the label, and we are looking at them …Much of the quality of life information was put in many years ago…We left it in the package insert on chronic renal failure because that needs to be reviewed, and there was at least a substantial body of evidence that needed to be examined."

Will this affect advertising by Amgen and J&J? **Absolutely. No more cancer fatigue ads.**

Why were quality of life ads ever allowed in the first place? FDA officials did not really have a good answer for that question, but they indicated advertising will be more carefully scrutinized in the future, and some current claims and implications will simply not be allowed any more. Dr. Pazdur said, "Any marketing claims will have to be in compliance with the label…substantiated by sufficient evidence, and related to the disease one is looking at." He said it would not be appropriate to claim an ESA improves energy during chemotherapy.

Why do ESAs fuel the growth of cancers/tumors? **Experts do not know.**

Dr. Pazdur said, "We have no explanation for the mechanism …It has been postulated that tumors contain receptors for erythropoiesis, and there might be direct tumor stimulation by these products. That is theory; it is not established yet. Perhaps, the vascular effects of erythropoiesis may be responsible, but again that is a theory. We do not know why yet, but we are concerned with the observation in large, well-controlled trials."

What does this mean for chronic renal failure patients? **The same message: Prescribe the *lowest* dose of ESA to the *lowest* level to avoid blood transfusions.**

Dr. Rafel Dwaine Rieves, acting director of the FDA's Division of Medical Imaging and Hematology Products in CDER, said, "The product (Epogen) has been used in chronic renal failure anemia for nearly 18 years, so there is extensive experience with that, and our revised labeling does emphasize the importance of using a minimum dose to raise the hemoglobin to a level to avoid blood transfusions, to minimize

risks, and that is our recommendation for physicians caring for chronic renal failure patients…The quality of life situation in chronic renal failure goes back to the original approval and was part of the original Epogen approval. We are revisiting those instruments and the tools used to support those claims. (Those claims) involved a series of questionnaires administered to patients…They are pretty lengthy. They talk about energy, sleep, health status, satisfaction with health, sex life, and happiness, etc. So, you can imagine there was quite a lengthy list of questions. And the sophistication in this field has really evolved in the past decade, and especially in the past 3-5 years for drugs used for symptomatic treatment. In that light we are re-examining these instruments, how they were utilized in those studies, and re-evaluating them to be sure these are robust claims." Dr. Pazdur said, "We have concerns regarding the drug ***in general*** (not just in oncology). That is why we are recommending the lowest dose be used to avoid transfusion. There are safety events that have been observed in the renal population…so this is not limited just to oncology."

What does this mean for other anemia drugs in the pipeline? **The FDA considers this to be a class effect, so expect the FDA to be tough about labeling claims and probably demand additional data for approval.**

Will the labels for Procrit and Epogen be close to the Aranesp label? **Similar but slightly different.**

Dr. Patricia Keegan, director of the FDA's Division of Biologic Oncology Products in CDER, said, "The warning, the boxed warning, and the spirit of the dosing recommendations are similar but not identical…These are different products. Epogen and Procrit have more claims than Aranesp…(But) most of the language is very similar if not identical." Dr. Pazdur said, "In looking at the product labels, there were claims of 'symptoms of anemia.' We felt that those claims needed to have a risk:benefit relationship and should come out of the label because we do not, at this time, feel they are supported…There was a re-look at the package insert to remove the claims regarding oncology…In the oncology population, we don't see a need for these drugs except to avoid transfusions."

What does this FDA action mean for Medicare reimbursement? **CMS has already cut reimbursment in oncology. Stay tuned for more from CMS.**

The FDA notified CMS about this health advisory, and CMS instructed Medicare carriers not to cover ESAs when used for the treatment of the anemia of cancer (ICD-9 code 285.22), ***effective immediately***. ESAs used for the treatment of anemia due to chemotherapy are not affected and will still be covered. A Medicare contractor predicted that all Medicare Part B carriers would quickly follow this CMS advice.

THE NEW LABELS

Epogen/Procrit – both IV and subcutaneous

Indications and usage

- Epogen is indicated for the treatment of anemia related to therapy with zidovudine in HIV-infected patients.
- Epogen is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients.
- Epogen is not indicated for the treatment of anemia in HIV-infected patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding, which should be managed appropriately.
- Epogen, at a dose of 100 Units/kg TIW, is effective in decreasing the transfusion requirement and increasing the red blood cell level of anemic, HIV-infected patients treated with zidovudine, when the endogenous serum erythropoietin level is 500 mUnits/mL and when patients are receiving a dose of zidovudine 4200 mg/week.

Treatment of anemia in cancer patients on chemotherapy

Epogen is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. Epogen is indicated to decrease the need for transfusions in patients who will be receiving concomitant chemotherapy for a minimum of 2 months. Epogen is not indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding, which should be managed appropriately.

Reduction of allogeneic blood transfusion in surgery patients

Epogen is indicated for:

- The treatment of anemic patients (Hgb >10 to 13 g/dL) scheduled to undergo elective, non-cardiac, non-vascular surgery to reduce the need for allogeneic blood transfusions.
- Patients at high risk for perioperative transfusions with significant, anticipated blood loss.

Epogen is ***not*** indicated for anemic patients who are willing to donate autologous blood.

Aranesp – both IV and subcutaneous

Indication

Aranesp is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis, and for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. ♦