Amid Health Concerns, FDA Reviews Safety of Several Heavily Used Anemia Drugs

By Rabiya S. Tuma

For the second time in 3 years, the U.S. Food and Drug Administration is reviewing the safety of a class of widely used anemia drugs. Earlier this year, the agency added the highest level of warning, a so-called black box, to the label of all three erythropoiesis-stimulating agents (ESAs). At the request of the agency, the Oncologic Drug Advisory Committee (ODAC) met last week to evaluate the drug’s safety and dosing.

The new wave of concern was triggered by the release of data from several randomized controlled trials, which showed that patients taking ESAs might be at higher risk of heart attacks or death if their target hemoglobin was above a certain level. Three of the trials were shut down early because of concerns about the health risks. This added to results from two previous studies that also suggested there were problems.

Three ESAs, all forms of the human hormone erythropoietin, are currently approved in the U.S. for anemia in chronic renal failure patients and cancer patients treated with chemotherapy (but not for anemia caused by the cancer itself). The original label for these drugs specified that the target range for hemoglobin was between 10 and 12 g/dL in both kidney failure and cancer patients. Although anemia in women is defined as a hemoglobin level below 12 g/dL, clinicians say that it is not clear if a patient’s quality of life would improve by raising his hemoglobin above 12 g/dL. The recently reported trials were aimed at increasing the target hemoglobin above 12 g/dL. The data from both old and new trials suggest that the use of ESAs to elevate a patient’s hemoglobin above 12 g/dL is associated with an increased risk of death or serious cardiac and thrombotic events in both chronic renal failure and cancer patients. Surprisingly, cancer patients who received ESAs to increase their levels to 12 g/dL or higher had a shorter time to disease progression, lower overall survival, and higher mortality than those given a placebo.

The agency went ahead with the labeling revisions before the ODAC meeting because the emerging data “had a consistent theme, which was that targeting the higher hemoglobin was associated with harm,” said Patricia Keegan, M.D., director of the division of biologic oncology products at the FDA, during a press conference announcing the new warnings.

The updated label stresses that the drugs are approved only to reduce the need for blood transfusions in renal failure patients on dialysis and cancer patients with chemotherapy-induced anemia. Also, it points out that physicians should use the lowest dose possible to raise their patients’ hemoglobin to a level between 10 and 11 g/dL.

“For oncology patients, these products have not been shown to improve or relieve symptoms of anemia or to improve the quality of life in patients with cancer,” said Richard Pazdur, M.D., director of the office of oncology drug products in the Center for Drug Evaluation and Research at the FDA, during the press conference. There is limited evidence that the drugs may improve the quality of life for renal failure patients. However, the agency is reviewing all of those data, because methods to assess quality of life and patient reported outcomes have improved substantially since the initial ESA trials were conducted and the approaches used in those studies no longer fit the agency’s standard.

Amgen, which manufactures all of the approved agents, does not doubt the quality or value of the drugs. “It is our strong belief based on the data that we have that, when ESAs are used in the appropriate indication and according to the labeled indication, the drugs are safe and effective,” said Roy Baynes, M.D., Ph.D., vice president of oncology supportive care development at Amgen, which sells darbepoetin alfa (Aranesp) and epoetin alfa (Epogen). The third ESA approved in the U.S., also epoetin alfa, is sold by Johnson & Johnson under the name Procrit.

While it is true that all the new danger signs come from trials in which the hemoglobin target was above the approved target of 10–12 g/dL, there has been considerable off-label use of the drugs in both kidney patients on dialysis and cancer patients. More than half of the kidney dialysis patients who receive the drug have a hemoglobin level above 12 g/dL when they are treated, said Daniel Coyne, M.D., professor of medicine and director of renal outpatient clinics at Washington University in St. Louis. Also, oncologists have regularly been using the drugs to treat anemia in cancer patients who are not currently undergoing treatment.

There are several likely reasons for giving patients the drug when the patients are already above the suggested treatment levels. First, dialysis centers are reimbursed at a higher rate than it costs them to buy the drug, so many of the centers have been using the drug to boost their profits.
said. And the fraction of the centers’ patients with a hemoglobin level above 11—in the higher half of the approved range—has been used as a measure of quality for the facility.

Second, and more relevant for oncology, there is a general sense among physicians that patients with a higher hemoglobin level feel better and live longer than those with a lower level. “There are certain things clinically that I think are self-evident: If indeed you have a drug that reduces the need for transfusion, it would seem to be very logical to conclude that it must be doing something to the signs and symptoms of anemia,” Baynes said.

However, that assumption isn’t based on clinical trial results. The effects of the drug may be getting confused with the benefit of being healthier in general. This supposition is particularly true because healthier patients are more likely to make more hemoglobin in response to ESA treatment than less healthy ones, Coyne said. “So the observational data that the people with highest hemoglobin have best quality of life is very flawed. Of the randomized trials that have looked at quality of life, some have shown benefits, but the benefits are relatively limited and don’t last very long. Other trials show no benefit at all.” Moreover, evidence from as early as 1998 shows that when hemoglobin is increased with ESAs, the risk of deep vein thrombosis also increases. This finding suggests a cost that needs to be weighed into the risk–benefit equation.

Until now, there has been considerable off-label use because of a feeling among doctors that these drugs are relatively benign, especially compared with many oncology drugs, said Mark Heaney, M.D., who specializes in blood cancers at Memorial Sloan-Kettering Cancer Center in New York and has helped set the center’s policy on ESA use. The black box warning will probably affect patients as doctors hold back on giving borderline patients the drug. “We are restricting their use to more closely follow the accepted indications. We are basically preventing people from using them for off-label things like anemia of cancer,” Heaney said. “We are also a little bit more stringent about the cutoffs at which we recommend holding doses, and we’re putting things in place to check the hemoglobin closer to the time the drugs are administered.”

The ODAC meeting is likely to be only the beginning of an ongoing discussion around these drugs. “We look at this whole issue as a process of reevaluating this class of agents,” Pazdur said. This task will include ESAs approved only in other countries and agents that might be currently under regulatory review. Although the specific questions that will be discussed at the meeting were not available at press time, Pazdur noted that the issues will include dosing of ESAs in oncology patients, the indications for its use, and off-label use in a “real-world” oncology setting. Also, the agency will have more complete data for discussion at the meeting than they did when the label changes and warning were announced. Amgen recently released new results from a 600-patient randomized trial using darbepoetin alfa in small-cell lung cancer patients undergoing chemotherapy treatment. There was no difference in overall survival between the two arms, which was a primary endpoint. The results did show an increase in hemoglobin in the ESA treated arm, compared to placebo, which was also an endpoint. More detailed data, including the secondary quality of life endpoint, should be provided for ODAC. The quality-of-life data were obtained using the Functional Assessment of Cancer Therapy questionnaire, a patient reporting tool, so it may provide some of the best quality-of-life data available for these agents.

Significantly, at the time of the original FDA approval of the drugs, Amgen committed to evaluate ESAs’ effect on survival and tumor progression after the agents went on the market, FDA’s Keegan said.

continued on page 753
This process sped the drug’s approval at the time. Although it is not yet clear how ESAs might lead to cancer progression, the new data add to a growing pattern of such effects in head and neck, lung, and metastatic breast cancer. One possibility is that the tumor cells have epoetin receptors on their surface, and the growth hormone stimulates cell proliferation when it binds to the surface. Another hypothesis is that the drugs alter the vascular system in a way that benefits the tumor.

Many of the issues discussed at last week’s ODAC meeting, including the drug’s effect on tumor growth, were discussed at the 2004 meeting. With that in mind, Pazdur sees the issues as cutting across all antianemia drugs and not as a problem with individual drugs. Any restrictions or changes will therefore apply to all the ESAs currently approved, as well as any currently under regulatory review.

“This is more than just one ODAC meeting,” Pazdur said. “I’m emphasizing that this is process that we’re undertaking here. There is a lot of emerging information that had just come out in the past quarter here.”