Continued Regulatory Actions Affecting the Use of Erythropoiesis-Stimulating Agents

By Karen Hagerty, MD

On July 30, 2008, the US Food and Drug Administration (FDA) sent a Complete Response and Safety Labeling Change Order to the sponsors of erythropoiesis-stimulating agents (ESAs), ordering changes to the ESA package inserts, referred to as labels. The FDA had been in discussions with the sponsors since April regarding changes to the ESA labels, but the two parties were unable to agree about certain specific wording. Consequently, the FDA invoked for the first time its authority under section 505(o)(4)(E) of the 2007 Food, Drug, and Cosmetic Act to order a sponsor to make revisions to a product label. These revisions became effective August 2008.

The changes to the label are described in Table 1. In summary, the major change is that ESAs are now "not indicated" for patients receiving myelosuppressive therapy when the anticipated outcome is cure. Additional changes affect hemoglobin levels at which ESAs should be initiated and maintained.

In addition to the wording changes on the prescription label itself, the FDA used its authority under 21CFR208 to require the development of a patient Medication Guide, which will replace the existing patient package insert. Like the prescription label, the Medication Guide must be approved by the FDA.

Here we attempt to clarify the meaning of the changes described above—and how they could impact oncologists and their patients—based on the pertinent FDA regulations, statements from FDA's Office of Oncologic Drug Products, and publicly available communications from the FDA to the sponsor.

ESAs Not Indicated in the Curative Setting

The August revisions to the ESA labels contained the following language (Table 1 summarizes label changes since November 2007): "Aranesp/Epogen/Procrit is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure." Two phrases in this sentence have caused confusion in the oncology community. First, although the statements that a drug or biologic product is "indicated" or "contraindicated" are clear and unambiguous, there has been less certainty about how to interpret the phrase "not indicated." Second, oncologists have expressed uncertainty about the interpretation of the phrase, "when the anticipated outcome is cure." Although it seems that understanding of this latter phrase should be straightforward, all is not black and white in the treatment of cancer, given that each patient is unique and no two patients present under identical clinical circumstances.

Before the August 2008 label change, there had been no distinction in the FDA-approved ESA labels between patients in a palliative setting and patients in whom the anticipated outcome is cure. At the May 2007 Oncology Drug Advisory Committee meeting, the Advisory Committee, responding to a question posed by the FDA, voted in favor of restricting ESA use to a noncurative setting. The reasoning that the FDA uses for restricting the use of ESAs to the noncurative setting is described in the following passages of the order sent from the FDA to the sponsors [italics added]:

"Your proposed wording . . . is misleading because it suggests that you have been granted an indication for treatment of anemia in patients receiving myelosuppressive chemotherapy for cancers in which cure is anticipated. Clinical studies *supporting the approval of* [*ESAs*] *were conducted in patients with metastatic disease without the potential for cure.* You have not submitted data establishing a favorable risk-benefit ratio

Table 1. Summary of FDA ESA Label Changes: November 2007 to August 2008

Label Change	Impact of Change on Labeled Indication(s)
November 2007	
Added text to state that symptoms of anemia, fatigue, quality of life, or patient well-being have not been shown to improve in patients with cancer who are treated with ESAs	ESAs were never approved by the FDA for these indications in cancer patients; the added language was meant to clarify this position
ESAs should not be used in patients with cancer unless they are receiving myelosuppressive chemotherapy	Any use other than this indication, including for "anemia of cancer," is an off-label indication
ESAs should be discontinued once the patient's chemotherapy course has been completed	ESAs are not indicated beyond active chemotherapy treatment
ESAs caused tumor growth and shortened survival in patients with advanced breast, head and neck, lymphoid, and non–small-cell lung cancer when they received a dose that attempted to achieve a hemoglobin level of 12 g/dL or greater; no clinical data are available to determine whether there is a similar risk of shortened survival or increased tumor growth for patients with cancer who receive an ESA dose that attempts to achieve a hemoglobin level of < 12 g/dL	This statement did not change any indications, but made explicit the lack of prospective, controlled data on survival and tumor progression in patients whose hemoglobin levels are kept < 12 g/dL with ESA use
March 2008	
Revised Boxed Warnings and Warnings Section to change "advanced breast cancer" to "breast cancer" and to add "cervical cancer" to the following sentence: ESAs shortened overall survival and/or time-to-tumor progression in clinical studies in patients with breast, non–small-cell lung, head and neck, lymphoid, and cervical cancers when dosed to target a hemoglobin of ≥ 12 g/dL.	This statement did not change any indications, but added non-advanced breast and cervical cancer to the list of malignancies where studies had shown shortened overall survival and/or time to tumor progression when ESAs were dosed to target a hemoglobin > 12 g/dL
August 2008	
ESAs are no longer indicated if anticipated treatment outcome is cure	ESAs are no longer indicated in any patient, regardless of receipt of myelosuppressive chemotherapy and subsequent possible anemia, if the anticipated treatment outcome for that patient is cure ESAs are still indicated for patients receiving myelosuppressive chemotherapy when the goal of chemotherapy is palliation, not cure
ESAs should not be initiated at hemoglobin levels ≥ 10 g/dL	There is no approved use for beginning ESA therapy in any patient with a hemoglobin of 10 g/dL or higher
Removes ". . . or exceeds 12 g/dL" as an upper range for ESA use	Clarifies that 12 g/dL is not a goal or upper range for target hemoglobin; rather, the lowest hemoglobin level needed to avoid transfusion should be the goal
Removes language that allowed earlier initiation of ESAs or treatment to higher hemoglobin targets if the patient cannot tolerate anemia because of a comorbid condition	There is no approved use for beginning ESAs in patients with hemoglobin levels ≥ 10 g/dL, despite any comorbid conditions
Boxed Warning no longer focuses on studies with hemoglobin targets > 12 g/dL	This statement did not change any approved uses, but removes the emphasis on results from studies with hemoglobin targets > 12 g/dL

Abbreviations: FDA, Federal Drug Administration; ESA, erythropoeisis-stimulating agents.

in patients receiving myelosuppressive chemotherapy for cancers in which cure is anticipated."

The FDA states in the same order, "Further, the language ordered by FDA does not prevent or prohibit healthcare providers from prescribing [ESAs] in the setting where the anticipated outcome is cure under the practice of medicine."

In an interview with *Cancer Letter*,[1] Richard Pazdur, MD, head of the FDA's Office of Oncologic Drug Products, stated

the following regarding this change [italics added]: "Most medical oncologists *have a clear understanding of when they are treating for cure versus palliation*. If there is a question or uncertainty in people's minds, then *they should treat conservatively and not use the drug.*"

In the same interview, Pazdur also confirmed that the label wording "neither prohibits nor prevents a health care provider from prescribing the drug for patients with curative intent," or with different dosing regimens that are not in the label. "This would fall under the rubric of practice of medicine or off-label use," Pazdur said. "When we say the drug is not indicated, that is not the same thing as a contraindication. A contraindication is where risk clearly outweighs benefit. *When we are saying a drug is not indicated, we are stating a favorable risk-benefit* relationship has not been demonstrated." [italics added]

Hemoglobin Levels

The new label also contains changes to hemoglobin levels at which ESAs should be initiated or maintained. The new wording states that ESAs should not be initiated if a patient's hemoglobin is ≥ 10 g/dL; removes "or exceeds 12 g/dL" as an "upper range" for ESA use; and removes language that allowed earlier initiation (ie, hemoglobin > 10 g/dL) of ESAs, or treatment to higher hemoglobin targets, if the patient cannot tolerate anemia because he or she has a comorbid condition.

Although the previous label stated that ESAs should be initiated when the patient's hemoglobin reaches a level at which transfusion might be required, the new label states specifically that ESAs should not be initiated if a patient's hemoglobin is ≥ 10 g/dL. Furthermore, the phrase "or exceeds 12 g/dL" as an upper "safety range" for ESA use has been removed, and the revised label now reads, "[T]he dose should be adjusted for each patient to maintain the lowest hemoglobin level sufficient to avoid RBC transfusion." Finally, the new label removes previous language that allowed earlier initiation of ESAs, or treatment to higher hemoglobin targets, if the patient cannot tolerate anemia due to a comorbid condition.

These changes are also addressed in the order sent to the sponsors from the FDA. The order states, "You have not identified comorbid conditions in which maintenance of hemoglobin levels of 10.0 to 12.0 g/dL results in improved survival or decreased serious morbidity . . . You have not provided evidence from studies in patients with specified comorbid conditions, who are also receiving myelosuppressive therapy, that demonstrate that the benefits outweigh the risks for an alternate treatment strategy in which Aranesp is initiated at a hemoglobin level of 10 g/dL or higher and maintained at a higher hemoglobin level above that needed to avoid transfusions. The absence of these qualifying statements does not prohibit or prevent a healthcare provider from prescribing an alternate dosing regimen under the practice of medicine."

The updated label no longer includes any mention of the 12 g/dL of hemoglobin as an upper limit for cancer uses. Citing a lack of data on the safety of administering ESAs to patients with hemoglobin levels between 10 and 12 g/dL, Pazdur[1] said the FDA's direction is that "the lowest dose should be used to avoid transfusion. This generally is in the range of 9 to 10 g[/dL] of hemoglobin."

Patient Medication Guide

Under section 21CFR208, FDA may require sponsors of certain drugs or biologics that it deems particular risky or dangerous to provide a Medication Guide to patients receiving the agent. This Medication Guide must be provided by the manufacturer to packers and distributors, who in turn must ensure it is contained within the drug packaging. In a "Dear Health Care Professional" letter dated August 7, 2008, the sponsor of Aranesp stated that, "The Medication Guide must be distributed to all patients who are dispensed/administered these products." In addition, the "Precautions: Information for Patients" section of the FDA-approved label was revised to read, "Patients should be instructed to read the [ESA] Medication Guide and Patient Instructions for Use and should be informed that the Medication Guide is not a disclosure of all possible side effects." The Medication Guide itself states, "Read this Medication Guide before you start Aranesp, each time you refill your prescription, and if you are told by your healthcare provider that there is new information about [ESAs]."

The Medication Guide for the ESAs is a revised version of the previous patient package insert for the ESAs. Under FDA regulations, a Medication Guide must be given to patients when the drug is dispensed, whereas a patient package insert is voluntarily distributed to patients. Usually, Medication Guides apply only to drugs dispensed for use outside the office or hospital, although FDA has said that in rare instances, it might require a Medication Guide to be given to all patients.

ASCO contacted the FDA for clarification of these points and was told that the FDA would issue a public communication regarding interpretation of these regulations. As of press time, no such guidance has been forthcoming. ASCO continues to monitor this situation closely in order to convey promptly any further information to its membership.

Summary

On the basis of the collective recent revisions to the ESA labels, **the only FDA-approved oncologic (nonrenal) use for ESAs is in cancer patients receiving myelosuppressive chemotherapy who meet the following criteria:**

For initiation of ESA use:

- The anticipated treatment outcome is not cure, AND
- Hemoglobin less than 10 g/dL

For continuation of ESA use:

- The anticipated treatment outcome is not cure, AND
- The patient has not yet attained a hemoglobin level sufficient to avoid RBC transfusion

Although the FDA-approved label assigns no specific hemoglobin value to the latter statement, Pazdur has stated that "this generally is in the range of 9 to 10 grams[/dL] of hemoglobin." Dose adjustments and/or discontinuation are necessary under certain circumstances, for example, for lack of response or vigorous response, or if transfusions are still required (see "Dosage and Administration" section of the full prescribing label).

Where Do the FDA Changes Intersect With Insurance Coverage?

Currently, the Medicare program and many private payors will not cover costs associated with administering ESAs to a cancer patient receiving myelosuppressive chemotherapy with a hemoglobin greater than 10 g/dL. Although the Centers for Medicare and Medicaid Services (CMS) at present does not make a distinction in its coverage policy between patients in curative and noncurative settings—that is, Medicare covers ESAs administered to patients regardless of anticipated outcome, cure, or palliation, as long as they meet CMS's other requirements—it is possible that CMS may soon reconsider their coverage policies based on the new restrictions to the FDA-approved indications for ESA use. Because coverage determinations at the local level cannot be more restrictive than CMS coverage, local carriers should continue to reimburse for costs associated with ESAs administered in the curative setting. However, providers are urged to monitor this situation and to check with their local carriers for specific guidance. Finally, coverage of ESA use in myelodysplastic syndromes, an off-label use, also continues to be determined at the local level, given that CMS omitted discussion of myelodysplastic syndromes from the final version of the National Coverage Determination.

Private insurers may institute revisions to their coverage policies based on the new FDA-approved restrictions on ESA use. Physicians should check with individual health plans regarding any changes in policy.

Other Issues

In October 2007, ASCO and the American Society of Hematology (ASH) jointly published a clinical practice guideline on the use of ESAs in patients with cancer.[2] The ASCO/ASH guideline does not include discussion on the clinical issues raised by the FDA's recent label changes such as curative intent and the imposition of an upper hemoglobin limit of 10 g/dL. The ASCO/ASH guideline panel continues to monitor developments in the scientific literature closely and will update the guideline as new data become available.

Additional Information

FDA Web site on ESAs (includes links to the FDA-approved Medication Guides and updated FDA labels for ESAs): http://www.fda.gov/cder/drug/infopage/RHE/default.htm.

Medicare National Coverage Determination on ESAs for Cancer and Related Neoplastic Conditions: http://www.cms.hhs.gov/mcd/viewncd.asp?ncd_id=110.21&ncd_version=1&basket=ncd%3A110%2E21%3A1%3AErythropoiesis+Stimulating+Agents%28ESAs%29+in+Cancer+and+Related+Neoplastic+Conditions

ASCO/ASH Clinical Practice Guideline on Use of Epoetin and Darbepoetin in Cancer: http://jco.ascopubs.org/cgi/reprint/JCO.2007.14.3396v2.pdf

DOI: 10.1200/JOP.0863501

References

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