



American Society of Clinical Oncology

Important Information for Physicians about Changes Affecting the FDA-Approved Use of Erythropoiesis Stimulating Agents (ESAs)

On July 30, 2008, the U.S. Food and Drug Administration (FDA) sent a “Complete Response and Safety Labeling Change Order” to the sponsors of the ESAs, ordering changes to the ESA package inserts (“labels”). For the first time, the FDA used its statutory authority to order a sponsor to make revisions to a product label.

This document is intended to provide oncologists with an overview of the FDA label changes, which are effective as of August 2008, explain the practical implications of these changes, and discuss how these changes relate to other guidance to physicians on the use of ESAs. We expect that the FDA may issue additional guidance or requirements related to the use of ESAs in the coming weeks and will provide updates to this document as more information becomes available.

Summary of July/August Changes to the ESA Labels

The July 30 mandate changes the ESA labels in three important ways. Details on each of these changes follow.

- 1) **ESAs are now “not indicated” for patients receiving myelosuppressive therapy when the anticipated outcome is cure.**
- 2) **The new label includes changes to the hemoglobin levels at which ESAs should be initiated and maintained.**
- 3) **The FDA has required that manufacturers replace the patient package insert with an FDA-approved patient “Medication Guide”.**

These changes follow other revisions to the ESA labels made over the past year. A complete summary of recent changes to the ESA labels is included in the Appendix.

Summary of FDA-Approved Uses for ESAs

Based on the collective recent revisions to the ESA labels, **the only FDA-approved oncologic (non-renal) 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 <10 g/dL

For continuation of ESA use:

- the anticipated treatment outcome is not cure AND
- patient has not yet attained a hemoglobin level sufficient to avoid RBC transfusion¹

Dose adjustments and/or discontinuation are necessary under certain circumstances, e.g., for lack of response or vigorous response or if transfusions are still required (see “Dosage and Administration” section of the labels).

ESAs “Not Indicated” in the Curative Setting

The FDA has mandated the following label change regarding curative intent.

“[Aranesp/Epogen/Procrit] is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure. . . .”

Interpretation of “Not Indicated”

While the statements that a drug/biologic product is “indicated” or “contraindicated” are clear, there is less certainty over how to interpret the phrase “not indicated.”

Dr. Richard Pazdur, head of the FDA’s Office of Oncologic Drug Products, stated in an interview [Cancer Letter²] 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 contra-indication. A contra-indication 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]

Interpretation of “Curative”

Oncologists have also expressed uncertainty over the interpretation of the phrase, “when the anticipated outcome is cure.” Prior to 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.

In the same interview, Dr. Pazdur stated the following [italics added]: “The major change is that ESAs are not indicated in patients receiving chemotherapy when the anticipated outcome is cure. We heard comments that some people may need greater clarity on this concept. Most medical

¹ While the FDA-approved label assigns no specific hemoglobin value to this statement, Dr. Richard Pazdur, head of the FDA’s Office of Oncologic Drug Products, has stated that “this generally is in the range of 9 to 10 grams of hemoglobin.” The Cancer Letter, Volume 34, No. 31., August 8, 2008.

² The Cancer Letter, Volume 34, No. 31., August 8, 2008.

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.*”

Off-Label Use of ESAs

As with other FDA-approved drugs or biological agents, ESAs may be used “off-label” for conditions for which they are not approved. The FDA has stated that none of the new provisions in the label “prevent or prohibit” a healthcare provider from prescribing ESAs for conditions for which they are not approved. In other words, it is permissible for a physician to prescribe ESAs in the curative setting, initiate ESA when the patient’s hemoglobin is above 10 g/dL, etc. Insurance coverage of off-label uses will vary.

Changes to Hemoglobin Levels at Which ESAs Should Be Initiated or Maintained

The new labels:

- 1) State that ESAs should not be initiated if a patient’s hemoglobin is ≥ 10 g/dL;
- 2) Remove “...or exceeds 12 g/dL” as an “upper range” for ESA use, leaving the upper limit as the “level needed to avoid transfusion”; and
- 3) Remove language that allowed earlier initiation (i.e., hemoglobin above 10 g/dL) of ESAs, or treatment to higher hemoglobin targets, if the patient cannot tolerate anemia due to a co-morbid condition.

In an interview [Cancer Letter], Dr. Pazdur commented that the FDA had “removed all references to 12 grams of hemoglobin from the label” with respect to use in cancer patients. Citing a lack of data on the safety of administering ESAs to patients with a hemoglobin between 10 and 12, Dr. Pazdur 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 grams of hemoglobin.”

Distribution of FDA-Approved Medication Guide

The FDA is authorized to require sponsors of certain drugs or biologics that it deems particular risky or dangerous to provide an approved Medication Guide to patients receiving the agent. 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 has contacted the FDA to clarify whether physicians are required to distribute the Medication Guide to all patients receiving ESAs, regardless of the setting in which the drug is administered. The FDA told ASCO that the agency is working internally to address this question, but has not issued public guidance yet. ASCO will provide updates as they become available from the FDA.

Implications of the ESA Label Changes on Medicare Coverage of ESAs in Cancer

The Centers for Medicare & Medicaid Services (CMS) has ruled that Medicare will not cover ESAs for patients who have a hemoglobin level over 10 g/dL, as stated in the July 2007 National Coverage Determination on the ESAs in Cancer and Related Neoplastic Conditions.

CMS does not currently make a distinction in its coverage policy between patients in the curative and non-curative settings. Medicare covers ESAs administered to patients regardless of anticipated outcome, cure or palliation, as long as other coverage criteria are met. It is possible that CMS may propose a revised coverage policy based on the new restrictions to the FDA-approved indications for ESA use.

Implications of the ESA Label Changes on Private Health Plan Coverage of ESAs in Cancer

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.

ASCO/ASH Guideline on Use of Epoetin and Darbepoetin in Patients with Cancer

The American Society of Clinical Oncology/American Society of Hematology clinical practice guideline on the use of ESAs in patients with cancer 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 will continue to look at evidence related to the use of ESAs and will update the guidelines as warranted.

Additional Information

FDA Website 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>

Appendix

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 other use outside 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
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 above
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 due to a co-morbid condition	There is no approved use for beginning ESAs in patients with hemoglobin levels ≥ 10 g/dL, despite any co-morbid 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