

## FOLLOW UP ON QUESTIONS ABOUT ESAs

Several questions were raised during recent meetings with Congressional staff on October 23, and with Administrator Weems on October 24, 2007. In response, ASH and ASCO provide additional clarification below.

**Q: Is the NCD in agreement with the “black box” warning from the FDA?**

**A:** The NCD is in partial agreement with the “black box” warning. The NCD varies from the warning in that the FDA warning does not advise against providing ESAs to patients with hemoglobins within the 10-12mg/dL range. The NCD and the black box warning are consistent in their language against ESA usage in treatment of anemic patients not receiving chemotherapy and in warning against targeting a range of greater than 12 g/dL.

**Q: Is there proof that the harms which led to this warning will not occur in patients receiving chemotherapy and whose hemoglobin is maintained between 10-12?**

**A:** Science cannot prove a negative, but there is good evidence showing harms are not increased. Two recent meta-analyses form the basis for many of the recommendations in the 2007 update of the ASCO-ASH ESA guideline:

1) Seidenfeld J, Piper M, Bohlius J, et al.: Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment. Comparative Effectiveness Review No. 3. (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-02-0026.) Rockville, MD: Agency for Healthcare Research and Quality. May 2006. Available at:

<http://effectivehealthcare.ahrq.gov/reports/topic.cfm?topic=2&sid=33&rType=4&sType=2>

2) Bohlius J, Wilson J, Seidenfeld J, et al.: Erythropoietin or Darbepoetin for patients with cancer. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD003407. DOI: 10.1002/14651858.CD003407.pub4. Available at:

<http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD003407/frame.html>

The AHRQ meta-analysis did not show worsened survival or tumor progression in studies where ESAs were discontinued when the hemoglobin reached 13. The Cochrane review, which analyzed subgroups based on starting hemoglobin, did not show worsened survival or tumor progression in patients whose hemoglobin was below 10, or between 10 and 12.

We refer you particularly to pages 71 through 92 of the AHRQ publication, with the associated figures and tables. Tables 27 and 28 may be specifically of interest.

We also refer you to pages 97-98 and pages 191-223 of the Cochrane review.

**Q: Do the expert panel members have a conflict of interest in terms of receiving funding from Amgen or Johnson & Johnson?**

**A:** The guideline panel received no support or funding from any outside entity.

Both ASH and ASCO follow rigorous conflicts of interest standards. Disclosures of potential panel members are reviewed prior to seating them on the panel to manage and avoid any potential conflicts that arise.

The EPO guideline panel had 13 members. Eight of the panel members indicated no conflicts. The remaining members either received honoraria from, or served in a consultant role to, companies that make ESAs. These relationships are identified in the published guideline document.

**Q: Can a guideline panel be assembled that has no conflict of interest?**

**A:** Clinical practice guidelines are expert advice to guide best quality of care. Our societies solicit national and international experts to distill scientific evidence and provide appropriate recommendations. The individuals who are most invaluable in research on a given topic have the greatest knowledge about all aspects of that topic. Multiple institutions or companies may seek advice from the same individuals as they develop research priorities or trial designs. Such experts may also be important to developing the best guideline. While they may be invited to participate in a guideline panel, such panel members are not the majority of the group, must disclose all relationships, and—depending on the nature of the conflict—may be excluded from voting on the final recommendations. The balance of the panel, by design, includes patient representatives or advocates, community physicians, and other healthcare professionals as required by the guideline content.

It should be noted that the work of the ESA panel members is then extensively reviewed by independent peer reviews solicited by both professional societies (ASCO and ASH) and their journals before content and publication is approved. (See attached).

**Q: How often does a cancer patient on chemotherapy need to get an ESA?**

**A:** The initiation and dosing of ESAs depends on individual patient circumstances, including type of chemotherapy, symptoms, functional impairment, and other medical conditions that need to be considered. A patient's hemoglobin falling below 10 g/dL is the signal for the physician to fully evaluate the patient's symptoms of anemia. It is not necessarily a trigger to start ESA treatment. Once a decision is made to use ESAs, the guideline calls for dosing which parallels that described in the FDA-approved label.

**Q: Does the CMS NCD put patients with cancer at risk for needing more blood transfusions?**

**A:** If patients experience symptoms of anemia (e.g., shortness of breath, chest pain, difficulty with normal activities of daily living, etc.) at hemoglobin levels above those CMS allows for initiation of ESAs, blood transfusions would be the alternative intervention.

We have no current data to show the extent to which this is currently happening under the new policy.

Because ESAs function by increasing hemoglobin production, they may take weeks before impact is seen. In contrast, transfusions have a much faster response. As a result, ESAs are best initiated before the patient's hemoglobin is low enough to require transfusion.

A blood transfusion is not without risk. In most cases, blood units provided to chemotherapy patients must first be irradiated in order to reduce the risk of graft versus host reactions. For patients where a bone marrow transplant may be a future treatment option, the blood may be screened to avoid cytomegalovirus. Second, because of the kind of monitoring, time and special treatment given for patients receiving blood transfusions, most blood is administered in the hospital, not the office, setting. This requires much greater investment of time and travel for patients who are generally compromised and feeling quite sick.

**Q: What hemoglobin level would a person have to drop to in order to impact his or her health?**

**A:** As noted above, the decision to intervene in developing/progressive anemia depends on a number of often interrelated factors, including the person's age, medical condition, symptoms, and chemotherapy regimen. This medical judgment rests on a full evaluation of the patient, not on one number such as hemoglobin concentration.

**Q: The FDA's letter to Representative Stark does not say that ESAs raise a patient's QOL. Do FDA labels for other drugs address quality of life issues?**

**A:** FDA labels are typically focused on the specific effects and use proposed by the manufacturer. Occasionally studies, which are the underpinning of any FDA label, have identified some quality of life benefit for the drug under review. In that case, the label may include such information. As an example, in 1996 the FDA approved gemcitabine for treatment of advanced pancreatic cancer based in part on two multi-center trials that reported improvement in clinical benefit (considered a surrogate for quality of life) for patients with locally advanced or metastatic pancreatic cancer treated with gemcitabine.

**Q: Should Congress be intervening in a discussion on a scientific issue? Isn't that the purview of FDA/CMS?**

**A:** Medicare coverage policy should be grounded in the best scientific information. Differences of opinion on interpretation of available evidence should be resolved in the course of open, professional dialogue. When the policy appears to depart from scientific evidence, and recommendations of experts in the field, there is a greater likelihood that some will seek alternate means for establishing that dialogue.

**PEER REVIEW OF ESA GUIDELINE**

<b>ORIGINAL 2002 GUIDELINE</b>	
<b>Type of Review</b>	<b>Number of Reviewers</b>
Panel	14
ASCO External reviewers	3
ASCO Health Services Committee	24
ASH Optimization Committee	14
ASCO Board	19
ASH Executive Committee	13
<i>Blood</i> (ASH Journal)	2
<b>TOTAL</b>	<b>89</b>
<b>2007 GUIDELINE UPDATE</b>	
<b>Type of Review</b>	<b>Number of Reviewers</b>
Panel	13
ASCO Health Services Committee	23 (During the voting 8 people recused themselves)
ASH Practice Committee	19
ASH Quality of Care Committee	8
ASCO Board	18
ASH Executive Committee	13
<i>Blood</i>	2
<b>TOTAL</b>	<b>96</b>