

2007-2008 BOARD

PRESIDENT

Nancy E. Davidson, MD

IMMEDIATE PAST PRESIDENT

Gabriel N. Hortobagyi, MD

PRESIDENT-ELECT

Richard L. Schilsky, MD

TREASURER

Bruce J. Roth, MD

**EXECUTIVE VICE PRESIDENT
AND CHIEF EXECUTIVE OFFICER**

Allen S. Lichter, MD

DIRECTORS

Dean F. Bajorin, MD

Howard A. Burris, III, MD

Alexander M. Eggermont, MD, PhD

Waun Ki Hong, MD

Thomas A. Marsland, MD

Barbara L. McAneny, MD

Robert S. Miller, MD

Martin J. Piccart-Gebhart, MD, PhD

Kathleen I. Pritchard, MD

Gregory H. Reaman, MD

Deborah Schrag, MD, MPH

George W. Sledge, Jr., MD

Joel E. Tepper, MD

Jamie Hayden Von Roenn, MD

August 30, 2007

Steve E. Phurrough, MD, MPA
Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services
Mail Stop C1-09-06
7500 Security Boulevard
Baltimore, MD 21244

RE: Recommended Language Changes To CMS “Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N)”

Dear Dr. Phurrough,

As requested by CMS in our conference call on August 20, 2007, below are specific language modifications ASCO requests for the National Coverage Decision:

Page 1, Para 1

ORIGINAL:

Though we continue to be interested in these specific issues, this final decision does not differentiate ESA coverage by the erythropoietin receptor status of the underlying disease, and we have narrowed the scope of this final decision to make no national coverage determination (NCD) at this time on the use of ESAs in MDS.

NEW:

Though we continue to be interested in these specific issues, this final decision does not differentiate ESA coverage by the erythropoietin receptor status of the underlying disease. CMS will continue to provide coverage for ESA therapy in patients with MDS who have a hemoglobin level <12 g/dL.

Page 2 (the below numbered items run together as one list in the original document)

ORIGINAL:

We have also determined that ESA treatment for the anemia secondary to myelosuppressive anticancer chemotherapy in solid tumors, multiple myeloma, lymphoma and lymphocytic leukemia is only reasonable and necessary under the following specified conditions:

1. The hemoglobin level immediately prior to initiation or maintenance of ESA treatment is < 10 g/dL (or the hematocrit is < 30%).

2008 Annual Meeting
May 30-June 3, 2008
Chicago, Illinois

For more information
about ASCO Meetings
Phone: (703) 631-6200
Fax: (703) 818-6425
Website: www.asco.org

NEW:

We have also determined that ESA treatment for the anemia secondary to an anticancer drug or biologic agent known to cause anemia in solid tumors, multiple myeloma, lymphoma and lymphocytic leukemia is only reasonable and necessary under the following specified conditions.

1. The hemoglobin level immediately prior to initiation of ESA treatment is < 10 g/dL (or the hematocrit is $< 30\%$) or between 10 g/dL and 12 g/dL when accompanied by moderate to severe anemia symptoms (e.g., shortness of breath or impaired exercise capacity), or certain clinical circumstances (e.g., limited cardiopulmonary reserve or underlying coronary artery disease).

ORIGINAL:

2. The starting dose for ESA treatment is the recommended FDA label starting dose, no more than 150 U/kg/three times weekly for epoetin and 2.25 mcg/kg/weekly for darbepoetin alpha. Equivalent doses may be given over other approved time periods.

NEW:

2. The starting dose for ESA treatment is the recommended FDA label starting dose, no more than 150 U/kg/three times weekly for epoetin and 2.25 mcg/kg/weekly for darbepoetin alpha or comparable fixed dosing schedules. Equivalent doses may be given over other approved time periods.

ORIGINAL:

3. Maintenance of ESA therapy is the starting dose if the hemoglobin level remains below 10 g/dL (or hematocrit is $< 30\%$) 4 weeks after initiation of therapy and the rise in hemoglobin is ≥ 1 g/dL (hematocrit $\geq 3\%$).

NEW:

3. Maintenance of epoetin therapy is the starting dose if the hemoglobin is not approaching 12 g/dL 4-6 weeks after initiation of epoetin therapy, and the rise in hemoglobin is ≥ 1 g/dL (hematocrit $\geq 3\%$). If the hemoglobin level approaches 12 g/dL (or hematocrit approaches 36%) at any point during epoetin therapy, decrease epoetin dose by 25%. Maintenance of darbepoetin therapy is the starting dose if the hemoglobin is not above 11 g/dL (hematocrit 33%) 4-6 weeks after initiation of darbepoetin therapy, and the rise in hemoglobin is ≥ 1 g/dL (hematocrit $\geq 3\%$). If the hemoglobin level goes above 11 g/dL (hematocrit 33%) at any point during darbepoetin therapy, decrease darbepoetin dose by 40%.

ORIGINAL:

4. For patients whose hemoglobin rises < 1 g/dl (hematocrit rise $< 3\%$) compared to pretreatment baseline over 4 weeks of treatment and whose hemoglobin level remains < 10 g/dL after the 4 weeks of treatment (or the hematocrit is $< 30\%$), the recommended FDA label starting dose may

be increased once by 25%. Continued use of the drug is not reasonable and necessary if the hemoglobin rises <1 g/dl (hematocrit rise <3 %) compared to pretreatment baseline by 8 weeks of treatment.

NEW:

4. For patients whose hemoglobin rises <1 g/dl (hematocrit rise <3%) compared to pretreatment baseline over 4-6 weeks of treatment , the recommended FDA label starting dose may be increased by up to 50% for fixed-dosing schedules and up to 100% for weight-based dosing schedules. Continued use of the drug is not reasonable and necessary if the hemoglobin rises <1 g/dl (hematocrit rise <3 %) compared to pretreatment baseline by 8 weeks of treatment, assuming appropriate dose increase has been attempted.

ORIGINAL:

5. Continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin > 1 g/dl (hematocrit > 3%) over 2 weeks of treatment unless the hemoglobin remains below or subsequently falls to < 10 g/dL (or the hematocrit is < 30%). Continuation and reinstatement of ESA therapy must include a dose reduction of 25% from the previously administered dose.

NEW:

5. If there is a rapid rise in hemoglobin > 1 g/dl (hematocrit > 3%) over 2 weeks of treatment, the epoetin dose should be reduced by 25%. Continuation of epoetin therapy must include a dose reduction of 25% from the previously administered dose. If there is a rapid rise in hemoglobin > 1 g/dl (hematocrit > 3%) over 2 weeks of treatment, the darbepoetin dose should be reduced by 40%. Continuation of epoetin therapy must include a dose reduction of 40% from the previously administered dose.

ORIGINAL:

6. ESA treatment duration for each course of chemotherapy includes the 8 weeks following the final dose of myelosuppressive chemotherapy in a chemotherapy regimen.

NEW:

We made no change to #6.

Page 29 (Proposed Noncovered Indication #2: Anemia of myelodysplasia (MDS))

ORIGINAL:

Summary

MDS is not an oncologic disease; it is a premalignant condition. Thus, we believe it appropriate to not include this indication in this decision.

NEW:

Summary

MDS is not an oncologic disease; it is a premalignant condition. Thus, we believe it appropriate to not include this indication in this decision, and ESA therapy for patients with MDS and hemoglobin <12 will be covered.

Page 47 (Proposed Restrictions)(Note that the language in bold represents the *proposed* restrictions that came out originally; the language following the bolded sections is CMS' current position, and is where we made our changes.)

ORIGINAL:

1. The hemoglobin/hematocrit levels immediately prior to initiation of dosing for the month should be < 9 g/dl (hematocrit < 27%) in patients.

However, we do agree that a starting level of 9 g/dL has the potential to result in more hemoglobins dropping to transfusion levels and will thus modify our proposed decision and find that the use of ESAs is reasonable and necessary in beneficiaries with cancer undergoing myelosuppressive therapy when their hemoglobin levels immediately prior to initiation or maintenance of ESA treatment are < 10 g/dL (or the hematocrit < 30%).

NEW:

However, we do agree that a starting level of 9 g/dL has the potential to result in more hemoglobins dropping to transfusion levels and will thus modify our proposed decision and find that the use of ESAs is reasonable and necessary in beneficiaries with cancer undergoing myelosuppressive therapy when their hemoglobin levels immediately prior to initiation of ESA treatment are < 10 g/dL (or the hematocrit < 30%).

ORIGINAL:

3. The maximum covered 4 week treatment dose is 126,000 units for erythropoietin and 630 µg for darbepoetin alpha.

Summary

We have determined that the starting dose for ESA treatment is the recommended FDA label starting dose, no more than 150 U/kg/three times weekly for epoetin and 2.25 mcg/kg/weekly for darbepoetin alpha. Equivalent doses may be given over other approved time periods. Maintenance of ESA therapy is the starting dose if the hemoglobin level remains below 10 g/dL (or hematocrit is < 30%) 4 weeks after initiation of therapy and the rise in hemoglobin is \geq 1g/dL (hematocrit \geq 3%).

NEW:

Summary

We have determined that the starting dose for ESA treatment is the recommended FDA label starting dose, no more than 150 U/kg/three times weekly for epoetin and 2.25 mcg/kg/weekly for darbepoetin

alpha. Equivalent doses may be given over other approved time periods. Maintenance of ESA therapy is the starting dose if the rise in hemoglobin is ≥ 1 g/dL (hematocrit $\geq 3\%$) and the hemoglobin is not approaching 12 g/dL (epoetin) or above 11 g/dL (darbepoetin) 4-6 weeks after initiation of therapy.

ORIGINAL:

4. Continued use of the drug is not reasonable and necessary if there is evidence of poor drug response (hemoglobin/hematocrit rise < 1 g/dl/ $< 3\%$) after 4 weeks of treatment.

Summary

We have determined that it is reasonable and necessary to increase the covered dose once by 25% in patients whose hemoglobin rise is < 1 g/dl (hematocrit rise $< 3\%$) compared to pretreatment baseline over 4 weeks of treatment and the hemoglobin level has remained < 10 g/dL (hematocrit $< 30\%$) after the 4 weeks of treatment. Continued use of the drug is not reasonable and necessary if the hemoglobin rise is < 1 g/dl (hematocrit rise $< 3\%$) compared to pretreatment baseline after 8 weeks of treatment.

NEW:

Summary

We have determined that it is reasonable and necessary to increase the covered dose by up to 100%, in accordance with the FDA-approved label, in patients whose hemoglobin rise is < 1 g/dl (hematocrit rise $< 3\%$) compared to pretreatment baseline over 4-6 weeks of treatment. Continued use of the drug is not reasonable and necessary if the hemoglobin rise is < 1 g/dl (hematocrit rise $< 3\%$) compared to pretreatment baseline after 8 weeks of treatment, assuming appropriate dose increase has been attempted.

ORIGINAL:

6. Continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin/hematocrit > 1 g/dl/ $> 3\%$ after 2 weeks of treatment.

Summary

We have determined that continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin > 1 g/dl (hematocrit $> 3\%$) in 2 weeks of treatment unless the hemoglobin remains below or subsequently falls to < 10 g/dL (or the hematocrit is $< 30\%$) and there has been a dose reduction of 25% from the previously administered dose.

NEW:

Summary

We have determined that the dose of ESAs should be decreased by 25% (epoetin) or 40% (darbepoetin) if there is a rapid rise in hemoglobin > 1 g/dl (hematocrit $> 3\%$) in 2 weeks of treatment.

End of Document

ORIGINAL:

Summary of restrictions for covered indications:



For patients with anemia secondary to anticancer chemotherapy, ESAs are appropriate when the hemoglobin is < 10g/dL (hematocrit < 30%). The maximum dose for the first 4 weeks is 1800 U/kg for epoetin and 9 mcg/kg for darbepoetin alpha. If after the first 4 weeks the hemoglobin is > 10g/dL (hematocrit > 30%), ESA treatment is not covered. ESA treatment may resume if the hemoglobin again drops below 10g/dL (hematocrit below 30%). If after any 4 week ESA treatment cycle, the hemoglobin remains below 10 g/dL (hematocrit below 30%), ESA treatment may continue at the same dose. If after the first 4 week ESA treatment cycle, the hemoglobin rise is less than 1 g/dL (hematocrit < 3%) and the hemoglobin level remains < 10 g/dL (hematocrit < 30%), the dose may be increased by 25% one time. If the rise in hemoglobin is < 1g/dL (hematocrit < 3%) for 8 weeks in spite of a 25% increase in dose, ESA treatment should be discontinued. If after any 2 week period of time, the hemoglobin rise is > 1g/dL (hematocrit > 3%), then ESA treatment should be discontinued unless the hemoglobin is < 10 g/dL (hematocrit <3 0%) at which time ESA treatment may be reinstated at a dose reduction of 25%. ESA treatment meeting the above requirements may be continued for 8 weeks following the completion of the final dose of myelosuppressive chemotherapy in a chemotherapy regimen.

NEW:

For patients with anemia secondary to anticancer drugs or biologic agents, initiation of ESAs is appropriate when the hemoglobin is < 10g/dL (hematocrit < 30%), or when the hemoglobin is between 10 g/dL and 12 g/dL in patients with certain symptoms and/or comorbid conditions. The maximum dose for the first 4 weeks is 1800 U/kg for epoetin and 9 mcg/kg for darbepoetin alpha. If after the first 4-6 week ESA treatment cycle, the hemoglobin is not approaching 12 g/dL (hematocrit below 36%)(epoetin) OR is below 11 g/dL (darbepoetin), and hemoglobin increase is \geq 1g/dL (hematocrit \geq 3%), ESA treatment may continue at the same dose. If after the first 4-6 week ESA treatment cycle, the hemoglobin rise is less than 1 g/dL (hematocrit < 3%), the dose may be increased by up to 100%. If the rise in hemoglobin is < 1g/dL (hematocrit < 3%) for 8 weeks in spite of appropriate dose escalation, ESA treatment should be discontinued. If after any 2 week period of time, the hemoglobin rise is > 1g/dL (hematocrit > 3%), then ESA dose should be decreased by 25% (epoetin) or 40% (darbepoetin). ESA treatment meeting the above requirements may be continued for 8 weeks following the completion of the final dose of myelosuppressive chemotherapy in a chemotherapy regimen.

Sincerely,

A handwritten signature in black ink that reads "Joseph S. Bailes". The signature is written in a cursive, flowing style.

Joseph S. Bailes, MD
Chair, Government Relations Council