

## Use of Epoetin and Darbepoetin in Patients with Cancer 2007 ASCO/ASH Guideline Update Table

*Special Announcement (Updated 08/05/08): Effective July 31, 2008, the US Food and Drug Administration (USA) FDA mandated the following changes to the labels for the erythropoiesis stimulating agents, epoetin alfa and darbepoetin: 1) ESAs are no longer indicated for patients receiving myelosuppressive chemotherapy if the anticipated treatment outcome is cure. They remain indicated when myelosuppressive chemotherapy is intended for palliation. 2) ESAs should not be initiated if the patient's hemoglobin is above 10 g/dL. Further, the label change: a.) specifies that ESA treatment should target the lowest hemoglobin concentration that will avoid transfusion, b.) removes "...or exceeds 12 g/dL" as an upper range for ESA use, and c.) 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.*

*The labels' Boxed Warnings now read: "ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers." The warning is no longer focused on studies with hemoglobin targets at or above 12 g/dL*

Type of change	Previous Recommendation (2002)	Current Recommendation (2007)
<b>Title</b>		
	Use of Epoetin in Patients with Cancer: Evidence-Based Clinical Practice Guidelines of the American Society of Clinical Oncology and the American Society of Hematology (JCO Vol 20, Issue 19 (Oct.) 2002)	American Society Of Clinical Oncology/American Society Of Hematology 2007 Clinical Practice Guideline Update on the Use of Epoetin And Darbepoetin
<b>I. General Recommendation</b>		
Modifications appear in italics.	As in any medical situation, it is essential to give consideration to other correctable causes of anemia before proceeding to therapy with stimulants of erythropoiesis. Therefore, it is advisable to conduct an appropriate history and physical and to consider relevant diagnostic testing aimed at identifying causes of anemia aside from chemotherapy or underlying hematopoietic malignancy. At a minimum, one should take a thorough drug exposure history, carefully review the peripheral blood smear (and in some cases, the bone marrow), consider iron, folate, and B12 deficiency where indicated, and assess for occult blood loss. Coomb's testing may be appropriate for patients with chronic lymphocytic leukemia; endogenous erythropoietin levels may predict response in patients with myelodysplasia.	I. As in any medical situation, it is essential to consider to other correctable causes of anemia before proceeding to therapy with stimulants of erythropoiesis. Therefore, it is advisable to conduct an appropriate history and physical and to consider relevant diagnostic testing aimed at identifying causes of anemia aside from chemotherapy or underlying hematopoietic malignancy. At a minimum, one should take a thorough drug exposure history, carefully review the peripheral blood smear (and in some cases, the bone marrow), consider iron, folate, and B12 deficiency where indicated, and assess for occult blood loss <i>and renal insufficiency</i> . Coomb's testing may be appropriate for patients with chronic lymphocytic leukemia, <i>non-Hodgkin's lymphoma, and for those with a history of auto-immune disease</i> ; endogenous erythropoietin levels may predict response in patients with myelodysplasia. <i>Consideration should be given to minimize use of ESAs in patients with high risk of thromboembolic events, as further discussed in Recommendation IV.</i>
<b>II. Special Commentary on the Comparative Effectiveness of Epoetin and Darbepoetin</b>		
New to 2007 guideline.		II. Based on a comprehensive systematic review comparing outcomes of epoetin and darbepoetin in patients with chemotherapy-induced anemia; and on identical indications, warnings, and cautions in the relevant FDA-approved package inserts, the Update Committee considers these agents to be equivalent with respect to effectiveness and safety.

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### IIIa. Chemotherapy-Induced Anemia: Threshold for Initiating ESA Therapy (Hemoglobin concentration approaching or < 10 g/dL)

<p>Recommendation is essentially unchanged from the 2002 guideline. Slight modifications to the recommendation appear in italics.</p>	<p>1. The use of epoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and a hemoglobin concentration that has declined to a level <math>\leq 10</math> g/dL. RBC transfusion is also an option depending upon the severity of anemia or clinical circumstances.</p>	<p>IIIa. The use of epoetin <i>or darbepoetin</i> is recommended as a treatment option for patients with chemotherapy-associated anemia and a hemoglobin concentration <i>that is approaching, or has fallen below, 10 g/dL, to increase hemoglobin and decrease transfusions</i>. Red blood cell (RBC) transfusion is also an option depending upon the severity of the anemia or clinical circumstances.</p>
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### IIIb. Chemotherapy-Induced Anemia: Initiation Threshold > 10 g/dL but < 12 g/dL

<p>Recommendation is essentially unchanged from the 2002 guideline. Slight modifications to the recommendation appear in italics.</p>	<p>2. For patients with declining hemoglobin levels but less severe anemia (those with hemoglobin concentration &lt; 12 g/dL, but who have never fallen below 10 g/dL), the decision of whether to use epoetin immediately or to wait until hemoglobin levels fall closer to 10 g/dL should be determined by clinical circumstances. RBC transfusion is also a therapeutic option when warranted by severe clinical conditions.</p>	<p>IIIb. For patients with declining hemoglobin levels but less severe anemia (those with hemoglobin concentration &lt; 12 g/dL, but who have never fallen <i>near 10 g/dL</i>), the decision of whether to use epoetin <i>or darbepoetin</i> immediately or to wait until the hemoglobin levels fall closer to 10 g/dL should be determined by clinical circumstances (<i>including but not limited to elderly individuals with limited cardiopulmonary reserve or those with underlying coronary artery disease or symptomatic angina, or substantially reduced exercise capability, or substantially reduced exercise capacity, energy, or ability to carry out activities of daily living [ADLs]</i>). RBC transfusion is also a clinical option when warranted by clinical conditions.</p>
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### IV. Thromboembolic Risk

<p>New to 2007 Guideline.</p>		<p>IV. <i>Clinicians should carefully weigh the risks of thromboembolism in patients for whom epoetin or darbepoetin are prescribed. Randomized clinical trials and systematic reviews of available randomized clinical trials demonstrate an increased risk of thromboembolism in patients receiving epoetin or darbepoetin. Specific risk factors for thromboembolism have not been defined in these trials; therefore, clinicians should use caution and clinical judgment when considering use of these agents. Established, general risk factors for thromboembolic events include previous history of thromboses, surgery, and prolonged periods of immobilization or limited activity. Patients with multiple myeloma who are being treated with thalidomide or lenalidomide and doxorubicin or corticosteroids are at increased risk. There are no data regarding concomitant use of anticoagulants or aspirin to modulate this risk.</i></p>
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### V. Starting and Escalating Doses

<p>Weekly starting dose for epoetin added which is equivalent to a three times</p>	<p>3. The recommendations are based on evidence from trials in which epoetin was administered subcutaneously thrice weekly. The recommended starting dose is 150 U/kg</p>	<p>V. The FDA-approved starting dose of epoetin is 150 U/kg TIW <i>or 40,000 U weekly subcutaneously. The FDA-approved starting dose of darbepoetin is 2.25 microgram/kg weekly or 500 micrograms every 3</i></p>
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weekly starting dose.	thrice weekly for a minimum of 4 weeks, with consideration given for dose escalation to 300 U/kg thrice weekly for an additional 4 to 8 weeks in those who do not respond to the initial dose. Although supported by less strong evidence, an alternative weekly dosing regimen (40,000 U/wk), based on common clinical practice, can be considered. Dose escalation of weekly regimens should be under similar circumstances to thrice weekly regimens.	<i>weeks subcutaneously. Alternative starting doses or dosing schedules have shown no consistent difference in effectiveness on outcomes including transfusion and hemoglobin response, although they may be considered to improve convenience. Dose escalation should follow FDA-approved labeling (Table 6); no convincing evidence exists to suggest differences in dose escalation schedules are associated with different effectiveness.</i>
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### VI. Discontinuing Therapy for No Response

Slight modifications appear in italics.	4. Continuing epoetin treatment beyond 6 to 8 weeks in the absence of response (eg, < 1-2 g/dL rise in hemoglobin), assuming appropriate dose increase has been attempted in nonresponders, does not appear to be beneficial. Patients who do not respond should be investigated for underlying tumor progression or iron deficiency. As with other failed individual therapeutic trials, consideration should be given to discontinuing the medication.	VI. Continuing epoetin or darbepoetin treatment beyond 6-8 weeks in the absence of response (e.g., < 1-2 g/dL rise in hemoglobin <i>or no diminution of transfusion requirements</i> ), assuming appropriate dose increase has been attempted in non-responders <i>as per FDA - approved labeling</i> , does not appear to be beneficial <i>and ESA therapy should be discontinued</i> . Patients who do not respond should be investigated for underlying tumor progression, iron deficiency, <i>or other etiologies for anemia</i> .
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### VII. Hemoglobin Target

Modifications appear in italics.	5. Hemoglobin levels can be raised to (or near) a concentration of 12 g/dL, at which time the dosage of epoetin should be titrated to maintain that level or restarted when the level falls to near 10 g/dL. Insufficient evidence to date supports the "normalization" of hemoglobin levels to above 12 g/dL.	VII. Hemoglobin levels can be raised to (or near) a concentration of 12 g/dL, at which time the dosage of epoetin or darbepoetin should be titrated to maintain that level. <i>Dose reduction and dose modification recommendations recorded in the package insert as of March 2007 and approved by the FDA can be found in Table 6 of the full text (and table 6A based on November 8, 2007 FDA label announcement) . Dose reductions are also recommended when hemoglobin rise exceeds 1 g/dL in any 2 week period or when the hemoglobin exceeds 11 g d/L. Risk of venous thromboembolism should also be considered when determining dose reduction schedules.</i>
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### VIII. Iron Monitoring and Supplementation

There is no change from the original guideline recommendation.	6. Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels and instituting iron repletion when indicated may be valuable in limiting the need for epoetin, maximizing symptomatic improvement for patients, and determining the reason for failure to respond adequately to epoetin. There is inadequate evidence to specify the optimal timing, periodicity, or testing regimen for such monitoring.	VIII. Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels and instituting iron repletion when indicated may be valuable in limiting the need for epoetin <i>or darbepoetin</i> , maximizing symptomatic improvement for patients, and determining the reason for failure to respond adequately to <i>ESA therapy</i> . There is inadequate evidence to specify the timing, periodicity, or testing regimen for such monitoring.
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### IX. Anemia in Patients Not Receiving Concurrent Chemotherapy

This recommendation has been strengthened.	7. There is evidence from one well-designed, placebo-controlled, randomized trial that supports the use of	IX. There is evidence that supports the use of epoetin <i>or darbepoetin</i> in patients with anemia associated with low-risk myelodysplasia.
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<p>Changes appear in italics.</p>	<p>epoetin in patients with anemia associated with low-risk myelodysplasia, but there are no published high-quality studies to support its use in anemic myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia patients in the absence of chemotherapy. Treatment with epoetin for myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia patients experiencing chemotherapy-associated anemia should follow the recommendations outlined above.</p>	<p>There are no published high-quality studies to support its <i>exclusive</i> use in anemic myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia patients in the absence of chemotherapy. <i>Analyses of primary data from Study 20010103 (as yet unpublished) submitted to the FDA in March of 2007, support a stronger recommendation against the use of ESAs to treat anemia associated with malignancy, or the anemia of cancer, among patients with either solid or non-myeloid hematological malignancies who are not receiving concurrent chemotherapy. This recommendation is consistent with the black-box warning that was added to the prescribing information for both epoetin alfa and darbepoetin in March of 2007, as follows: "Use of ESAs increased the risk of death when administered to a target hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated in this population."</i></p>
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### X. Treatment of Anemia in Patients with Non-Myeloid Hematological Malignancies Who Are Receiving Concurrent Chemotherapy

<p>Recommendation is essentially unchanged from the 2002 guideline. Slight modifications to the recommendation appear in italics.</p>	<p>8. Physicians caring for patients with myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia are advised to begin treatment with chemotherapy and/or corticosteroids and observe the hematologic outcomes achieved solely through tumor reduction before considering epoetin. If a rise in hemoglobin is not observed after chemotherapy, epoetin should be used in accordance with the criteria outlined above for chemotherapy-associated anemia if clinically indicated. Blood transfusion is also a therapeutic option.</p>	<p>X. Physicians caring for patients with myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia are advised to begin treatment with chemotherapy and/or corticosteroids and observe the hematologic outcomes achieved solely through tumor reduction before considering epoetin <i>or darbepoetin</i>. If a rise in hemoglobin is not observed following chemotherapy, treatment with epoetin <i>or darbepoetin for patients with myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia experiencing chemotherapy-associated anemia should follow the recommendations outlined above. Particular caution should be exercised in the use of epoetin or darbepoetin concomitant with chemotherapeutic agents and diseases where risk of thromboembolic complications is increased. (Refer to Recommendation IV.)</i> Blood transfusion is also a therapeutic option.</p>
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## Use of Epoetin and Darbepoetin in Patients with Cancer 2007 ASCO/ASH Guideline Update Table

**Table 6. ESA Dosing.** (The doses contained on the FDA label as of March 2007 [shown below] have been revised. The dosing from the November 8, 2007 FDA label is shown in Table 6A.)

Dose & Modifications	Epoetin alfa		Darbepoetin alfa	
	Initial Dose	150 U/kg SC TIW	40,000 U SC Weekly	2.25 mcg/kg SC Weekly
Dose Increases	Increase dose to 300 U/kg TIW if no reduction in transfusion requirements or rise in Hb after 8 weeks	Increase dose to 60,000 U SC weekly if no increase in Hb by $\geq 1$ g/dL after 4 weeks of therapy, in the absence of a RBC transfusion	Increase dose to 4.5 mcg/kg if there is $< 1$ g/dL increase in Hb after 6 weeks	N/A
Dose Reductions	Decrease dose by 25% when Hb approaches 12 g/dL or Hb increases $> 1$ g/dL in 2 weeks		Decrease dose by 40% of previous dose when Hb exceeds 11 g/dL or Hb increases $> 1$ g/dL in 2 weeks	
Dose Withholding	If Hb exceeds 12 g/dL, withhold dose until Hb $< 11$ g/dL; restart dose at 25% below previous dose		If Hb exceeds 12 g/dL, withhold dose until Hb $= 11$ g/dL; restart dose at 40% below previous dose	

Abbreviations: ESA, erythropoiesis-stimulating agent; FDA, US Food and Drug Administration; SC, subcutaneous; TIW, three times per week; Q3W, every 3 weeks; Hb, hemoglobin; wk, week.

**Table 6a. ESA Dosing.** (This table includes new doses contained in the FDA-approved label released by the FDA on November 8, 2007)

Dose and Modifications	Epoetin Alfa		Darbepoetin Alfa	
	Initial dose	150 U/kg SC TIW	40,000 U SC weekly	2.25 mcg/kg SC weekly
Dose increase	Increase dose to 300 U/kg TIW if no reduction in transfusion requirements or rise in Hb after 8 wks	Increase dose to 60,000 U SC weekly if no increase in Hb by $\geq 1$ g/dL after 4 wks of therapy, in the absence of a RBC transfusion	Increase dose to 4.5 mcg/kg if there is $< 1$ g/dL increase in Hb after 6 wks	-
Dose reductions	Decrease dose by 25% when Hb <b>reaches a level needed to avoid transfusion</b> or Hb increases $> 1$ g/dL in 2 wks		Decrease dose by 40% of previous dose when <b>Hb reaches a level needed to avoid transfusion</b> or Hb increases $> 1$ g/dL in 2 wks	
Dose withholding	If Hb exceeds 12 g/dL, withhold dose <b>until Hb approaches a level where transfusions may be required</b> ; restart dose at 25% below previous dose		If Hb exceeds 12 g/dL, withhold dose <b>until Hb approaches a level where transfusions may be required</b> ; restart dose at 40% below previous dose	

NOTE. New label text is shown in bold type.

Abbreviations: ESA, erythropoiesis-stimulating agent; FDA, US Food and Drug Administration; SC, subcutaneous; TIW, three times per week; Q3W, every 3 weeks; Hb, hemoglobin; wk, week.

<sup>1</sup>FDA Approved label for 11-08-07. Epoetin alfa: Available at <http://www.fda.gov/cder/foi/label/2007/103234s5158lbl.pdf>; accessed 11/12/07. Darbepoetin alfa: <http://www.fda.gov/cder/foi/label/2007/103951s5164lbl.pdf>; accessed 11/21/07.

This flow sheet is derived from recommendations in the Use Of Epoetin And Darbepoetin In Patients With Cancer: 2007 American Society of Clinical Oncology/American Society of Hematology Clinical Practice Guideline Update. This table is a practice tool based on ASCO® practice guidelines and is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients. This tool does not purport to suggest any particular course of medical treatment. Use of the practice guidelines and this resource are voluntary. The practice guidelines and additional information are available at <http://www.asco.org/guidelines/epo>. Copyright © 2007 by the American Society of Clinical Oncology. All rights reserved.