Use of Darbepoetin and Epoetin in Non-Nephrology Patients – Adult/Pediatric – Inpatient/Ambulatory Clinical Practice Guideline

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CPG Contact for Changes:
Name: Philip Trapskin, PharmD, BCPS, Manager, DPP
Phone Number: 608-263-1328
Email address: PTrapskin@uwhealth.org

CPG Contact for Content:
Name: Jason Bergsbaken, PharmD
Phone Number: 608-265-0341
Email address: JBergsbaken@uwhealth.org
Guideline Authors:
Jason Bergsbaken, PharmD

Coordinating Team Members:
Monica Bogenschulz, PharmD
Cindy Gaston, PharmD, BCPS
Jennifer Nguyen, PharmD
Meghann Voegeli, PharmD, MS

Review Individuals/Bodies:
Sharon Bartosh, MD
Kenneth DeSantes, MD
Scott Hagen, MD
Mark Juckett, MD
Walter Longo, MD
Michael Lucey, MD
Dan Mulkerin, MD
Allison Redpath Mahon, MD
Aaron Wightman, MD
Eliot Williams, MD

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Executive Summary
Guideline Overview
Recommendations for the appropriate indications, dosage, administration and monitoring parameters for the use of darbepoetin alfa and epoetin alfa in adult and pediatric non-nephrology patients in the ambulatory and inpatient setting

Key Practice Recommendations
General Recommendations
1. Darbepoetin is the least costly, generally best-reimbursed, and most cost-effective agent for anemia management (compared to conventional epoetin) and the preferred agent
2. Epoetin is significantly more costly and is generally not as well reimbursed as darbepoetin, and therefore should be restricted to use under the following circumstances listed in this guideline

Adult Use
1. Darbepoetin Indications and Dosing
   a. Anemia due to chemotherapy in patients with non-myeloid malignancies (see Appendix A)
      i. Goal is to maintain a stable hemoglobin (Hgb) concentration; lowest dose necessary should be used to avoid transfusions\(^1,2\) (Class I, Level of Evidence A)
      ii. Targeted Hgb concentrations greater than 10 g/dL in oncology patients are not recommended\(^1,2\) (Class III, Level of Evidence A)
      iii. Recommended starting dose and schedule\(^1\) (Class I, Level of Evidence A):
         1. Darbepoetin 2.25 mcg/kg subcutaneously every week until completion of chemotherapy course OR
         2. Darbepoetin 500 mcg subcutaneously every three weeks until completion of chemotherapy course
      iv. Recommended dose adjustments are listed in Table 1\(^1\) (Class I, Level of Evidence A)
      v. Supplemental IV or oral iron supplementation should be administered when serum ferritin is <30 ng/mL and transferrin saturation is < 20%; supplemental IV or oral iron supplementation should be considered when serum ferritin is 30-800 ng/mL and transferrin saturation is 20-50% \(^2\) (Class I, Level of Evidence A)
      vi. For patients receiving chemotherapy, darbepoetin should be discontinued following completion of a chemotherapy course\(^1,3\) (Class I, Level of Evidence A)
   b. Myelodysplastic syndrome (MDS) (see Appendix B)
      i. Use of darbepoetin should be considered in patients who meet requirements for initiation\(^3-12\) (Class I, Level of Evidence A)
1. Documented diagnosis of both low grade MDS and anemia
2. Low risk myelodysplasia with less than 5% blasts
3. Pretreatment erythropoietin levels ≤500 mU/mL
4. Hgb concentration < 10 g/dL
   ii. The starting dose of 150 to 300 mcg subcutaneously weekly is recommended³ (Class I, Level of Evidence A)
   iii. Two months after initiating erythropoiesis-stimulating agent (ESA) therapy, a therapeutic response defined as an increase in clinically significant Hgb levels or a decrease in transfusion requirements must be documented to continue ESA treatment

2. Epoetin Indications and Dosing
   a. Anemia due to chemotherapy in patients with non-myeloid malignancies
      i. Darbepoetin therapy is preferred due to cost¹⁷ (see General Recommendations) (Class I, Level of Evidence A)
   b. Myelodysplastic syndrome (MDS)³⁻¹²,¹⁸
      i. Darbepoetin therapy is preferred due to cost¹⁹ (see General Recommendations) (Class I, Level of Evidence A)
   c. Anemia due to zidovudine in HIV-infected patients
      i. Therapy should be considered if measured endogenous serum erythropoietin levels ≤ 500 mUnits/mL and receiving zidovudine doses of 4,200 mg or less per week²,³,¹⁹ (Class I, Level of Evidence A)
      ii. The starting dose of 100 units/kg subcutaneously three times weekly is recommended¹⁹ (Class I, Level of Evidence A)
   d. Religious beliefs prohibiting blood transfusions²⁵ (Class IIb, Level of Evidence C)
      i. Time to start of treatment, dosages, route of administration and treatment duration varied widely among case reports; thus if clinically indicated a standardized dosing regimen may be considered²⁵ (Class IIb, Level of Evidence C)

3. Monitoring Parameters
   a. Iron Status
      i. Evaluate iron status in all patients before and during treatment and maintain iron repletion¹,²,¹⁹ (Class I, Level of Evidence A)
ii. Goals of therapy for ESAs should include serum ferritin ≥ 100 ng/mL and transferrin saturation is ≥ 20% saturation\(^1\) (Class I, Level of Evidence A)

b. Blood Pressure
i. Blood pressure should be controlled prior to initiating ESA therapy and monitor periodically during therapy\(^1,19\) (Class I, Level of Evidence A)

c. Hemoglobin
i. Hgb should be monitored weekly until it has stabilized and maintenance dose has been established\(^1,19\) (Class I, Level of Evidence A)

ii. After an adjustment in dose, Hgb should be monitored weekly for at least four weeks until stabilized; following stabilization Hgb may be monitored monthly\(^1,19\) (Class I, Level of Evidence A)

4. Warnings/Cautions
a. ESAs increase the risk for death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence, particularly when administered to target a Hgb of >12 g/dL; it is recommended to use the lowest dose of ESA to increase the Hgb concentration to the lowest level sufficient to avoid the need for RBC transfusion\(^1,19,26-28\) (Class I, Level of Evidence A)

5. Eligibility Period
a. For patients receiving chemotherapy, ESAs should be discontinued following completion of a chemotherapy course\(^1-3,19\) (Class I, Level of Evidence A)

6. Special Considerations for Oncology Indication\(^1,19\)

a. Prescribing of ESAs for patients with chemotherapy-induced anemia is restricted to UW Heath prescribers who have completed training and are currently enrolled in the ESA APPRISE Oncology Program\(^1,19,29\) (Class I, Level of Evidence A)

b. Approved prescribers must counsel each patient regarding risks of ESA therapy prior to new course\(^1,19,29\) (Class I, Level of Evidence A)

c. Prescriber and patient must sign approved ESA APPRISE acknowledgement form (available from website) prior to initiation and administration of ESAs; a copy of the signed acknowledgement form must be made available in patient’s medical record and given to patient\(^1,19,29\) (Class I, Level of Evidence A)

d. Prior to each administration of an ESA, a medication guide should be distributed to the patient per product labeling\(^1,19,29\) (Class I, Level of Evidence A)

**Pediatric Use**

1. Darbepoetin Indications and Dosing
a. Use of darbepoetin in pediatric patients is not indicated as safety and effectiveness have not been established\textsuperscript{19} (Class III, Level of Evidence A)

2. Epoetin Indications and Dosing
   a. Treatment of anemia in patients 5 to 18 years old due to concomitant myelosuppressive chemotherapy\textsuperscript{19} (Class I, Level of Evidence A)
      i. The starting dose of epoetin 600 units/kg intravenously weekly until completion of a chemotherapy course is recommended\textsuperscript{19} (Class I, Level of Evidence A)
   b. Anemia due to zidovudine in HIV-infected pediatric patients\textsuperscript{19} (Class I, Level of Evidence A)
      i. The starting dose of epoetin 50 to 400 units/kg subcutaneously or intravenously 2 to 3 times per week is recommended\textsuperscript{19} (Class I, Level of Evidence A)
   c. Reduction of blood transfusions in pediatric patients with acute kidney injury\textsuperscript{30-32} (Class IIb, Level of Evidence C)
      i. Use may be considered but effectiveness is not well established\textsuperscript{30-32} (Class IIb, Level of Evidence C)
      ii. Initiation of therapy may be considered if Hgb is less than 10 g/dL\textsuperscript{30-32} (Class IIb, Level of Evidence C)
      iii. No specific pediatric dosing recommendations are present with acute kidney injury; initial dosing strategies and dose adjustments may be based on anemia in chronic kidney disease\textsuperscript{17,30-32} (Class IIb, Level of Evidence C)

3. See adult section for monitoring parameters, warnings/cautions and documentation requirements

\textbf{Companion Documents}

Anemia Management in Chronic Kidney Disease – Adult – Inpatient/Ambulatory Clinical Practice Guideline
Scope
Disease/Condition(s): Adult or pediatric non-nephrology patients requiring darbepoetin alfa or epoetin alfa

Clinical Specialty: Hematology, Oncology, Hepatology, HIV, Pediatrics

Intended Users: Physicians, Physician Assistants, Advanced Practice Nurses, Pharmacists

CPG objective(s): To standardize and provide recommendations for the appropriate indications, use and monitoring for darbepoetin alfa and epoetin alfa for adult and pediatric patients across UW Health

Target Population: Adult or pediatric inpatient or ambulatory patients with indication for darbepoetin alfa or epoetin alfa therapy

Interventions and Practices Considered:
This guideline provides management recommendations for non-nephrology adult and pediatric patients requiring darbepoetin alfa or epoetin alfa in order to help standardize care in the inpatient and ambulatory setting

Methodology
Methods Used to Collect/Select the Evidence:
Searches of electronic databases (e.g., national and international guidelines for darbepoetin and epoetin use and cancer and chemotherapy induced anemia)

Methods Used to Assess the Quality and Strength of the Evidence:
Weighting according to rating scheme (scheme given below)

Rating Scheme for the Strength of the Evidence:
A rating scheme must be used to indicate the strength of the evidence. Recommended rating systems include the GRADE system or the United States Preventive Services Task Force (USPSTF) grading system.

Rating Scheme for the Strength of the Recommendations:
A modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) developed by the American Heart Association and American College of Cardiology (Figure 1) have been used to assess the Quality and Strength of the Evidence in this Clinical Practice Guideline

Figure 1: Quality of Evidence and Strength of Recommendation Grading Matrix*

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Contact: CCKM@uwhealth.org
Last Revised: 07/2015
Methods Used to Analyze the Evidence:
National Guideline Reviews, Systemic Reviews, Expert Opinion

Methods Used to Formulate the Recommendations:
See the “Rating Scheme for the Strength of Evidence.”

Definitions (optional):
1. Erythropoiesis-stimulating agent (ESA): Medications used to stimulate the production of red blood cells such as epoetin alfa (epoetin) and darbepoetin alfa (darbepoetin)

Introduction
Darbepoetin alfa (also referred to as darbepoetin) and erythropoietin alfa (also referred to as epoetin alfa or epoetin) are both synthetic, recombinant forms of the glycoprotein hormone erythropoietin and are hematopoietic agents that principally affect erythropoiesis (erythropoiesis-stimulating agents or ESAs). Unlike transfusion which immediately boosts the hemoglobin level, ESAs can take weeks to elicit a response, but they are effective in maintaining a target hemoglobin level with repeated administration. Darbepoetin differs structurally from the endogenous hormone and epoetin by the addition of two carbohydrate chains. This structural modification results in a longer terminal half-life allowing darbepoetin to be less frequently administered. Possible benefits of ESAs include avoidance of blood transfusion; however risks in some disease states include thromboembolism, hypertension/seizures and possible increased mortality.
This guideline is intended to define the appropriate indications for use of ESAs at UWHC for non-nephrology patients, taking into consideration available clinical data on efficacy, cost to UWHC and reimbursement by third-party payers. A separate guideline is available that addresses the use of these two products in nephrology patients.

Recommendations

General Recommendations
1. Darbepoetin is the least costly, generally best-reimbursed, and most cost-effective agent for anemia management (compared to conventional epoetin) and the preferred agent
2. Epoetin is significantly more costly and is generally not as well reimbursed as darbepoetin, and therefore should be restricted to use under the following circumstances listed in this guideline

Adult Use
1. Darbepoetin Indications
   a. Anemia due to chemotherapy in patients with non-myeloid malignancies\textsuperscript{1,2} (see Appendix A)
      i. The goal of ESA therapy for anemic cancer patients receiving concurrent chemotherapy is to reduce transfusion requirements and benefit should be weighed with the risk profile, including an increased incidence of thromboembolic reactions\textsuperscript{33,34} (Class IIa, Level of Evidence A)
      ii. Treatment goal is to maintain a stable Hgb concentration; lowest dose necessary should be used to avoid transfusions; a minimum of two additional months of planned chemotherapy is required\textsuperscript{1,2} (Class I, Level of Evidence A)
      iii. ESA therapy should not be prescribed for an improvement in quality of life (QOL) or improved cancer outcomes as available evidence does not support this\textsuperscript{1} (Class III, Level of Evidence A)
      iv. ESAs should not be used when anticipated outcome is cure as ESAs may promote tumor growth in an off-target manner\textsuperscript{2} (Class III, Level of Evidence A)
   b. Myelodysplastic syndrome (MDS)\textsuperscript{4-12} (see Appendix B)
i. ESAs may be considered for symptomatic patients with symptomatic anemia, as studies suggest ESAs may provide clinical benefit to patients with low-risk myelodysplastic syndrome\(^3\) (Class IIb, Level of Evidence A)

1. Coexisting causes of anemia should be treated first, including replacement of iron, folate, vitamin B\(_{12}\) if needed; current standard of care for symptomatic patients is red blood cell (RBC) transfusion support\(^3\) (Class I, Level of Evidence A)

ii. Use of darbepoetin should be considered in patients who meet requirements for initiation\(^3\) (Class I, Level of Evidence A) (see Appendix B):

1. Documented diagnosis of both low grade MDS and anemia
2. Low risk myelodysplasia with less than 5% blasts
3. Pretreatment erythropoietin levels ≤500 mU/mL
4. Hgb concentration < 10 g/dL

c. Severe autoimmune hemolytic anemia due to cold agglutinins

i. Darbepoetin may be considered as some patients benefit from modest doses to support an increased rate of bone marrow RBC production\(^13\) (Class IIb, Level of Evidence C)

d. Ribavirin-induced anemia

i. Darbepoetin may be considered to avoid ribavirin dose adjustments that compromise antiviral activity, however no evidence exists ESAs improve sustained viral response\(^14-16\) (Class IIb, Class of Evidence C)

e. Limitations of use

i. Darbepoetin is not indicated for use:\(^1\) (Class III, Level of Evidence A)

1. In patients with cancer receiving hormonal agents, biological products, or radiotherapy; unless receiving concomitant myelosuppressive chemotherapy
2. In patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure
3. As a substitute for RBC transfusions in patients who require immediate correction of anemia
4. For reduction of RBC transfusion in patients scheduled for surgical procedures

2. Darbepoetin Dosing and Administration

a. Anemia due to chemotherapy in patients with non-myeloid malignancies

i. Targeted Hgb concentrations greater than 10 g/dL in oncology patients are not recommended\(^1,2\) (Class III, Level of Evidence A)

ii. The lowest dose necessary should be used to avoid transfusions\(^1\) (Class I, Level of Evidence A)

iii. Recommended starting dose and schedule\(^1\) (Class I, Level of Evidence A):
1. Darbepoetin 2.25 mcg/kg subcutaneously every week until completion of chemotherapy course OR
2. Darbepoetin 500 mcg subcutaneously every three weeks until completion of chemotherapy course

iv. Recommended dose adjustments are listed in Table 1

(Class I, Level of Evidence A)

Table 1: Darbepoetin Dose Adjustments for chemotherapy-associated anemia

<table>
<thead>
<tr>
<th>Dose Adjustment</th>
<th>Weekly Schedule</th>
<th>Every 3 Week Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>If Hgb increases greater than 1 g/dL in any 2-week period OR</td>
<td>Reduce dose by 40%</td>
<td>Reduce dose by 40%</td>
</tr>
<tr>
<td>If Hgb reaches a level needed to avoid RBC transfusion</td>
<td>Withhold dose until Hgb approaches a level where RBC transfusions may be required</td>
<td>Withhold dose until Hgb approaches a level where RBC transfusions may be required</td>
</tr>
<tr>
<td></td>
<td>Reinitiate at a dose 40% below the previous dose</td>
<td>Reinitiate at a dose 40% below the previous dose</td>
</tr>
<tr>
<td>If Hgb exceeds a level needed to avoid RBC transfusion</td>
<td>Increase dose to 4.5 mcg/kg/week</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>If Hgb increases by less than 1 g/dL and remains below 10 g/dL after 6 weeks of therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discontinue darbepoetin</td>
<td>Discontinue darbepoetin</td>
</tr>
<tr>
<td>• If there is no response as measured by Hgb levels or if RBC transfusions are still required after 8 weeks of therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Following completion of a chemotherapy course</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

b. Myelodysplastic syndrome
i. The starting dose of 150 to 300 mcg subcutaneously weekly is recommended (Class I, Level of Evidence A)
ii. Two months after initiating ESA therapy, a therapeutic response defined as an increase in clinically significant Hgb levels or a decrease in transfusion requirements must be documented to continue ESA treatment

c. Ribavirin-induced anemia
i. Darbepoetin may be considered to avoid ribavirin dose adjustments that compromise antiviral activity, however no
evidence exists ESAs improve sustained viral response\textsuperscript{14-16}
(Class IIb, Class of Evidence C)

1. During the first two weeks of ribavirin treatment, darbepoetin may be used for hemoglobin declines of > 2 g/dL or for hemoglobin < 10 g/dL, before ribavirin dose adjustment is attempted.

2. Between weeks 2 and 12 of ribavirin treatment, darbepoetin may be used for hemoglobin < 10 g/dL before ribavirin dose adjustment is attempted.

3. After 12 weeks of ribavirin therapy, ribavirin dose adjustment should be attempted as an initial response to hemoglobin value < 10 g/dL; if hemoglobin values do not respond to a ribavirin dose adjustment and hemoglobin remains < 10 g/dL, darbepoetin should be initiated.

4. Cardiac patients may require earlier darbepoetin initiation or more aggressive darbepoetin dosing.

3. Epoetin Indications

a. Anemia due to chemotherapy in patients with non-myeloid malignancies

i. Epoetin is indicated in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, however darbepoetin therapy is preferred due to cost\textsuperscript{17} (see General Recommendations) (Class I, Level of Evidence A)

b. Myelodysplastic syndrome\textsuperscript{3-12,18}

i. Epoetin is indicated in patients with low risk MDS, however darbepoetin therapy is preferred due to cost\textsuperscript{17} (see General Recommendations) (Class I, Level of Evidence A)

c. Anemia due to zidovudine in HIV-infected patients

i. Epoetin therapy is only recommended for HIV-infected patients with measured endogenous serum erythropoietin levels ≤ 500 mUnits/mL and receiving zidovudine doses of 4,200 mg or less per week; at initiation of therapy, Hgb concentration must be less than 10 g/dL\textsuperscript{2,3,19} (Class I, Level of Evidence A)

d. Religious beliefs prohibiting blood transfusions (Class IIb, Level of Evidence C)

i. Elective surgical patients who decline blood-derived products because of religious beliefs, epoetin may be used if clinically indicated (i.e., anticipated blood loss, etc.) as several cases have been reported where recombinant human erythropoietin has been successfully administered to critically ill Jehovah’s Witnesses; however time to start of treatment, dosages, route of administration and treatment duration varied widely among case reports; thus if clinically indicated a standardized dosing regimen may be considered\textsuperscript{25} (Class IIb, Level of Evidence C)\textsuperscript{25}

4. Epoetin Dosing and Administration
a. Zidovudine-treated HIV-infected patients
   i. The starting dose of 100 units/kg subcutaneously three times weekly is recommended\(^1\) (Class I, Level of Evidence A)
   ii. Prior to starting epoetin therapy, an endogenous serum erythropoietin level should be drawn as patients with levels > 500 mUnits/mL are unlikely to respond to epoetin therapy\(^3\) (Class I, Level of Evidence A)
   iii. Dose Adjustments
      1. If Hgb does not increase after 8 weeks of therapy, recommend increasing epoetin dose by approximately 50 to 100 Units/kg at 4 to 8 week intervals until Hgb reaches a level needed to avoid RBC transfusions or 300 Units/kg\(^1\) (Class I, Level of Evidence A)
      2. Withholding epoetin if Hgb exceeds 12 g/dL is indicated; recommend resuming therapy at a dose 25% below the previous dose when Hgb declines to less than 11 g/dL\(^1\) (Class I, Level of Evidence A)
      3. No added clinical benefit has been demonstrated if epoetin doses exceed 300 units/kg three times weekly; epoetin should be discontinued if an increase in Hgb is not achieved at a dose of 300 units/kg three times weekly for 8 weeks\(^1\) (Class I, Level of Evidence A)

5. Monitoring Parameters
   a. Iron Status
      i. Evaluate iron status in all patients before and during treatment and maintain iron repletion\(^1,2,19\) (Class I, Level of Evidence A)
      ii. Goals of therapy for ESAs include serum ferritin ≥ 100 ng/mL and transferrin saturation is ≥ 20% saturation\(^1\) (Class I, Level of Evidence A)
   b. Blood Pressure
      i. Blood pressure should be controlled prior to initiating ESA therapy and monitor periodically during therapy\(^1,19\) (Class I, Level of Evidence A)
   c. Hemoglobin
      i. Hemoglobin should be monitored weekly until it has stabilized and maintenance dose has been established\(^1,19\) (Class I, Level of Evidence A)
      ii. After an adjustment in dose, Hgb should be monitored weekly for at least four weeks until stabilized; following stabilization Hgb may be monitored monthly\(^1,19\) (Class I, Level of Evidence A)
      iii. Targeted Hgb concentrations should not exceed 10 g/dL in oncology patients as adverse outcomes have been noted in trials when Hgb concentrations exceed 12 g/dL; clinical trial data evaluating patients with head and neck cancer documented accelerated tumor progression with ESA therapy compared to placebo\(^3\) and a subsequent trial
evaluating metastatic breast cancer patients receiving chemotherapy noted an increase in mortality due to disease progression and decreased overall survival (Class III, Level of Evidence A)

iv. Lack or loss of hemoglobin response
   1. Initiate a search for causative factors causing refractoriness prior to increasing dose, including: infection, inflammatory processes, occult blood loss, hemolysis or severe aluminum toxicity (Class I, Level of Evidence A)
   2. In absence of another etiology, the patient should be evaluated for evidence of pure red cell aplasia and serum should be tested for the presence of antibody to recombinant erythropoietins (Class I, Level of Evidence A)

6. Warnings/Cautions
   a. ESAs increase the risk for death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence, particularly when administered to target a Hgb of >12 g/dL thus it is recommended to use the lowest dose of ESA that will gradually increase the Hgb concentration to the lowest level sufficient to avoid the need for RBC transfusion (Class I, Level of Evidence A)
   b. Given use of ESAs in cancer patients has shortened overall survival and/or increased risk of tumor progression in patients with advanced head and neck, breast, non-small cell lung, and cervical cancers when administered to target a Hgb of >12 g/dL, ESAs should not be used for the treatment of anemia in cancer patients other than those with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy (Class I, Level of Evidence A)
   c. ESAs are contraindicated in patients with uncontrolled hypertension as approximately 40% of patients required initiation or intensification of antihypertensive therapy during early phase of treatment and hypertensive encephalopathy and seizures have been reported; ESAs may need to be reduced or withheld if blood pressure is difficult to control and patients should be advised regarding importance of compliance with antihypertensive therapy (Class I, Level of Evidence A)

7. Eligibility Period
   a. For patients receiving chemotherapy, ESAs should be discontinued following completion of a chemotherapy course (Class I, Level of Evidence A)

8. Special Considerations for Oncology Indication
   a. Prescribing of ESAs for patients with chemotherapy-induced anemia is restricted to UW Health prescribers who have completed training and are currently enrolled in the ESA APPRISE Oncology Program (Class I, Level of Evidence A)
b. Approved prescribers must counsel each patient regarding risks of ESA therapy prior to new course\textsuperscript{1,19,29} (Class I, Level of Evidence A)

c. Prescriber and patient must sign approved ESA APPRISE acknowledgement form (available from website) prior to initiation and administration of ESAs; a copy of the signed acknowledgement form must be made available in patient’s medical record and given to patient\textsuperscript{1,19,29} (Class I, Level of Evidence A)

d. Prior to each administration of an ESA, a medication guide should be distributed to the patient per product labeling\textsuperscript{1,19,29} (Class I, Level of Evidence A)

\textbf{Pediatric Use}

1. Darbepoetin Indications
   a. Use of darbepoetin in pediatric patients is not indicated as safety and effectiveness have not been established\textsuperscript{19} (Class III, Level of Evidence A)

2. Epoetin Indications
   a. Treatment of anemia in patients 5 to 18 years old due to concomitant myelosuppressive chemotherapy\textsuperscript{19} (Class I, Level of Evidence A)

   b. Anemia due to zidovudine in HIV-infected pediatric patients based off increases in Hgb levels and decreases in blood transfusions\textsuperscript{19} (Class I, Level of Evidence A)

   c. Reduction of blood transfusions in pediatric patients with acute kidney injury\textsuperscript{30-32} (Class IIb, Level of Evidence C)
      i. Pediatric nephrology service should be consulted for use in this population\textsuperscript{30-32} (Class I, Level of Evidence A)
      ii. Use may be considered but effectiveness is not well established\textsuperscript{30-32} (Class IIb, Level of Evidence C)
      iii. Continuation of therapy after resolution of renal insufficiency is not recommended as it exposes the patient to unnecessary risks of drug adverse effects and increases the cost of therapy\textsuperscript{30-32} (Class III, Level of Evidence C)
      iv. Patients should be evaluated for the need for epoetin on a daily basis and upon hospital discharge based on Hgb, serum creatinine, urine output and renal function\textsuperscript{30-32} (Class I, Level of Evidence A)

3. Epoetin Dosing and Administration
   a. Pediatric cancer patients (5 to 18 years) receiving chemotherapy
      i. The starting dose of epoetin 600 units/kg intravenously weekly until completion of a chemotherapy course is recommended\textsuperscript{19} (Class I, Level of Evidence A)
      ii. The following dose adjustments are recommended\textsuperscript{17} (Class I, Level of Evidence A)
         1. If Hgb does not increase by >1 g/dL and remains <10 g/dL after initial 4 weeks; increase to 900 units/kg/dose (maximum dose: 60,000 units)
2. If Hgb exceeds a level needed to avoid RBC transfusion: Withhold dose; resume treatment with a 25% dose reduction when Hgb approaches a level where transfusions may be required

3. If Hgb increases >1 g/dL in any 2-week period or Hgb reaches a level sufficient to avoid RBC transfusion; reduce dose by 25%

4. Discontinue after 8 weeks of treatment if RBC transfusions are still required or there is no Hgb response

b. Pediatric patients with HIV infection receiving zidovudine
   i. The starting dose of epoetin 50 to 400 units/kg subcutaneously or intravenously 2 to 3 times per week is recommended\(^\text{19}\) (Class I, Level of Evidence A)
   ii. The following dose adjustments are recommended\(^\text{17}\) (Class I, Level of Evidence A)
      1. Withhold dose if Hgb exceeds 12 g/dL, may resume treatment with a 25% dose reduction once Hgb <11 g/dL; titrate to minimum effective dose to maintain a Hgb sufficient to avoid RBC transfusions

C. Reduction of blood transfusions in patients with acute kidney injury
   i. Initiation of therapy may be considered if Hgb is less than 10 g/dL\(^\text{30-32}\) (Class IIb, Level of Evidence C)
   ii. No specific pediatric dosing recommendations are present with acute kidney injury; initial dosing strategies and dose adjustments may be based on anemia in chronic kidney disease; reduce or interrupt treatment if Hgb approaches or exceeds 11 g/dL\(^\text{17,30-32}\) (Class IIb, Level of Evidence C)
   iii. It is not recommended to continue epoetin beyond resolution of renal insufficiency or in admitted patients with Hgb >12 g/dL regardless of renal function\(^\text{30-32}\) (Class III, Level of Evidence C)
   iv. Epoetin alfa may be discontinued once acute kidney injury has resolved and renal function has returned to baseline\(^\text{30-32}\) (Class IIb, Level of Evidence C)

4. See adult section for monitoring parameters, warnings/cautions and documentation requirements
Appendix A: ESA Algorithm: Treatment of Anemia in Adult Cancer Patients
Modified from NCCN Cancer- and Chemotherapy-Induced Anemia Guidelines V.2.2015

Appendix A: ESA Algorithm for the Treatment of Anemia in Cancer Patients

Cancer Patient
Hgb ≤ 10 g/dL or ≥2 g/dL below baseline

- Initiate anemia evaluation (CBC with indices, peripheral smear, etc.)
- Evaluate for other sources of anemia (bleeding, hemolysis, iron deficiency, renal involvement etc.) and treat as indicated
- No Cause Identified
- Consider anemia of chronic inflammation or due to myelosuppressive chemotherapy

Not receiving chemotherapy or receiving chemotherapy with curative intent

- Titrate ESA dose to maintain lowest Hb level sufficient to avoid transfusion (see Dosing and Administration)
- Measure Hbg at least weekly until it has stabilized and maintenance dose established

Targeted hemoglobin concentrations should not exceed 10 g/dL in oncology patients and 12 g/dL for all other indications

Iron Stores - Achieve and maintain
- Ferritin ≥ 100 ng/mL
- Transferrin Saturation ≥ 20%

Observe

Asymptomatic without significant comorbidities

ESAs are not approved and are not recommended for use in this patient population

Clinical trials have demonstrated that ESAs negatively impact cancer treatment outcomes and have been shown to increase mortality in this patient population

Targeted hemoglobin concentrations should not exceed 10 g/dL in oncology patients and 12 g/dL for all other indications

Symptomatic (sustained tachycardia, tachypnea, chest pain, syncope, severe fatigue preventing work and usual activity)

Red blood cell transfusion per guidelines

Transfusion goal Hb ≥ 10 g/dL

Acute coronary symptoms or acute MI

Transfusion goal Hb 7-9 g/dL for asymptomatic hemodynamically stable cancer patients without acute coronary syndrome

Symptomatic anemia (tachycardia, tachypnea)

Transfusion goal Hb 8-10 g/dL as needed to prevent symptoms

ESAs Therapy: Risk - benefit consideration:
May be considered for patient on an active chemotherapy regimen or within 8 weeks of completing chemotherapy for a non-myeloid malignancy for non-curative intent

Transfusion goal Hb ≥ 10 g/dL

Periodic re-valuation (interval dependent upon myelosuppressive potential and other patient specific characteristics)
MDS with symptomatic anemia

Treat coexisting causes, replace iron, folate, vitamin B₁₂ if necessary. Red blood cell transfusion support (standard of care)

< 15% ringed sideroblasts and serum EPO ≤ 500 mU/mL

Epoetin 40,000 - 60,000 units 1-3x per week subcutaneously
OR
Darbepoetin 150-300 mcg/week subcutaneously

Response
Continue ESA, decrease dose to tolerance
No response despite adequate iron stores
Consider adding G-CSF 1-2 mcg/kg 1-3x per week subcutaneously

≥ 15% ringed sideroblasts and serum EPO ≤ 500 mU/mL

Epoetin 40,000 - 60,000 units 1-3x per week subcutaneously plus G-CSF 1-2 mcg/kg 1-3x per week subcutaneously
OR
Darbepoetin 150-300 mcg/week subcutaneously plus G-CSF 1-2 mcg/kg 1-3x per week subcutaneously

Decrease dose to tolerance
Refer to NCCN guidelines for MDS Low INT-1 (MDS-10)

Appendix B: Algorithm for the Treatment of Symptomatic Anemia in Adult Patients with Myelodysplastic Syndrome
Modified from NCCN MDS Guidelines V. 2.2015

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Contact: CCKM@uwhealth.org Last Revised: 07/2015
**UW Health Implementation**

**Potential Benefits:**
This guideline has been developed based on best evidence based recommendations. By implementing the parameters set forth in the guideline, non-nephrology adult and pediatric patients will receive ESAs appropriately and safely.

**Potential Harms:**
Side effects and adverse events associated with various medical/drug treatments.

**Implementation Tools/Plan**
1. Guideline will be housed on UConnect in a dedicated folder for Clinical Practice Guidelines.
2. Links to this guideline will be created in appropriate HealthLink or equivalent tools.
3. Pharmacists will be educated about these guidelines via department inservices.

**Disclaimer**
CPGs are described to assist clinicians by providing a framework for the evaluation and treatment of patients. This Clinical Practice Guideline outlines the preferred approach for most patients. It is not intended to replace a clinician’s judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

**References**