

# Revisions in the Prescribing Information for Epoetin alfa: Implications for Nephrology Nurses and Patients on Dialysis

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Epoetin alfa (EPOGEN®) revolutionized the treatment of anemia and has been used to treat patients with anemia due to chronic renal failure (CRF) over the past two decades. On November 8, 2007, the Food and Drug Administration (FDA) approved updated prescribing information for Epoetin alfa for use in the United States to reflect the most current data on the risks and benefits of Epoetin alfa therapy. These updates for patients with CRF included information on the Hb range, safety, health-related quality of life (HRQoL), and hyporesponse to therapy. This update in the prescribing information was based on a thorough review of safety and outcomes data conducted in September 2007 by a joint meeting of the FDA's Cardio-Renal Drug Advisory Committee (CRDAC) and Drug Safety and Risk Management Advisory Committee (DSRMAC). This article provides an overview of the changes in the Epoetin alfa prescribing information for patients with CRF, and the implications for nephrology nurses and patient care.

### FDA Joint Advisory Committees On Use of Epoetin alfa in Patients with CRF

The joint meeting of the CRDAC and DSRMAC convened to discuss

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*The prescribing information for Epoetin alfa administered to patients with chronic renal failure (CRF) or cancer was updated in November 2007. The revisions include revised safety information, new Epoetin alfa dosing recommendations, and revised information on health-related quality of life (HRQoL). The most significant changes included revision of the box warning, the reinstatement of a hemoglobin (Hb) range of 10 to 12 g/dL for patients with chronic renal failure, a new section on managing patients with hyporesponse to Epoetin alfa, and updated HRQoL data. These changes may necessitate revisions in anemia management protocols for patients with CRF, as well as changes in how nurses and other members of the nephrology team educate patients on the risks and benefits of Epoetin alfa therapy. Nurses will play a key role in assessing trends in laboratory values, predicting the course of Hb, and enacting appropriate physician-prescribed interventions to ensure adherence to the revised prescribing information.*

the risks and benefits of Epoetin alfa in the treatment of the anemia of CRF. This re-analysis of data was prompted by safety concerns arising from the results of clinical studies such as the Normal Hematocrit Cardiac Trial (NHCT) (Besarab et al., 1998) and the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study (Singh et al., 2006). The results of these trials suggested an increased risk for death and serious cardiovascular events when Epoetin alfa was administered to achieve higher target Hb levels of 13.5 and 14.0 g/dL (similar to the boxed warning), and raised concerns regarding both the target Hb level and the potential benefits of therapy in patients with CRF.

The interdisciplinary committees also reviewed the historical treatment of the anemia of CRF, including blood transfusions and androgens; the negative effect of these interventions; and the beneficial impact of Epoetin alfa in ameliorating both the anemia of CRF and the need for these therapies. Though not a primary focus of the meeting, the committee also expressed a great

deal of interest in research on the associations between Epoetin alfa, improved Hb, and HRQoL.

### Revised Epoetin alfa Prescribing Information

On November 8, 2007 the FDA issued the revised prescribing information for use of Epoetin alfa in the United States. These revisions were consistent with the recommendations of the joint CRDAC/DSRMAC committee, and addressed five major topics: (a) Hb range, (b) safety warnings, (c) benefits of Epoetin alfa therapy in patients with CRF, (d) dosing recommendations, and (e) how to define and manage hyporesponse to Epoetin alfa therapy.

### Hemoglobin Range

The revised prescribing information recommends that patients should achieve and maintain Hb levels within the range of 10 to 12 g/dL. This is a significant change from the March 2007 prescribing information revision that had stated that the lowest dose of Epoetin alfa should be used to gradually increase Hb to the

lowest level sufficient to avoid the need for blood transfusion (Amgen, 2007a). The reestablishment of a Hb range acknowledges both the recommendations of the joint committee, as well as the inevitable Hb fluctuations that occur when trying to maintain a Hb of 10 to 12 g/dL.

### Safety Warnings

The modified boxed warnings in the revised prescribing information provides disease-specific guidance safety information when Epoetin alfa is used to treat the anemia of CRF, cancer, or perisurgery. For patients with CRF, the revised warnings recognize the potential risks of higher Hb levels from the NHCT and CHOIR studies, and states that patients experienced greater risks for death and serious cardiovascular events when administered Epoetin alfa to target higher versus lower Hb levels in two clinical studies (i.e., 13.5 versus 11.3 g/dL in the CHOIR study and 14.0 versus 10.0 g/dL in the NHCT). Dosing should therefore be individualized to achieve and maintain Hb levels within the range of 10 to 12 g/dL (Amgen, 2007b). Additional information on the safety of Epoetin alfa in patients on dialysis has been discussed by Carter and Keen (2007).

### Health-Related Quality of Life Benefits of Epoetin alfa Therapy in Patients with CRF on Dialysis

The prescribing information language regarding patient reported outcomes (PROs) was updated to reflect data supported by double-blind, placebo-controlled studies that included both physician-assessed and patient-reported outcomes (in line with the draft PRO guidance that has been developed by the FDA). Of particular interest was the work of the Canadian Erythropoietin Study Group (Laupacis, 1990; Laupacis, Wong, & Churchill, 1991). This double-blind, randomized, placebo-controlled study evaluated objective outcomes measures, including exercise tolerance and

physical functioning, among 118 patients on hemodialysis. Patients were randomized to receive a placebo ( $n = 40$ , baseline Hb  $7.1 \pm \text{SD } 0.9$  g/dL) or Epoetin alfa to achieve a Hb of either 9.5 to 11.0 g/dL ( $n = 40$ , baseline Hb  $6.9 \pm 1$  g/dL) or 11.5 to 13.0 g/dL ( $n = 38$ , baseline Hb  $7.1 \pm 1.2$  g/dL). Exercise capacity was assessed using: (a) the 6-minute walk test, in which patients walked as far as possible on a flat surface during the allotted time, and (b) a treadmill stress test that was conducted in eleven 2-minute stages, with the speed and incline of the treadmill gradually increasing (modified Naughton protocol). Patient-reported HRQoL indicators were assessed at baseline, 2, 4, and 6 months and included the Sickness Impact Profile (SIP) and the Kidney Disease Questionnaire (KDQ) (Laupacis, 1990; Laupacis et al., 1991).

The original publication presented analyses based on data for patients who completed all assessments. Such "completers analyses" are known to have high potential for bias. Therefore, a reanalysis of the original study data was undertaken to determine the effect of Epoetin alfa treatment on exercise and PROs. This reanalysis used all patients enrolled in the study (i.e., the intent-to-treat cohort), and applied current statistical methods to account for missing data and the effects of conducting multiple statistical analyses. Patients randomized to the placebo group ( $n = 40$ ) achieved a non-significant 0.2 g/dL increase in mean Hb over the 6-month study period. The placebo group showed little change in the number of minutes walked during a modified Naughton protocol treadmill stress test (+ 1.3 minutes) or the number of meters walked in a 6-minute walk test (- 5.5 meters). In comparison, patients randomized to Epoetin alfa to a target Hb of 9.5 to 11.0 g/dL ( $n = 40$ ) had a 3.2 g/dL increase in mean Hb over the 6-month study period ( $P < 0.0001$ ), and improvements in the number of minutes walked in the treadmill stress test (+

3.1 minutes,  $P = 0.0001$ ) and the number of meters walked in 6 minutes (+ 24.6 meters,  $P = 0.05$ ). Similarly, patients randomized to achieve a target Hb of 11.5 to 13.0 g/dL ( $n = 38$ ) had a 4.6 g/dL increase in mean Hb over the 6-month study period and improvements in the number of minutes walked (+ 4.8 minutes) and the number of meters walked (+ 54.6 meters). The improvements over time between patients treated with placebo versus Epoetin alfa were statistically significant (Hb,  $P < 0.0001$ ; exercise stress,  $P < 0.001$ ; minutes walked,  $P < 0.05$ ) (Amgen, 2007c).

Improvements were also noted in patient-reported physical function. In the placebo group, there was essentially no change on the SIP physical function scale (2% improvement). In contrast, patients randomized to Epoetin alfa achieved a 61% improvement in SIP physical function in both Hb target groups. The improvements in patient-reported physical function over time between patients treated with placebo versus Epoetin alfa were statistically significant ( $P < 0.002$ ) (Amgen, 2007c).

On the basis of the Canadian Erythropoietin Study Group data, the HRQoL information in the Epoetin alfa prescribing information was modified to indicate that in patients with CRF who were treated with Epoetin alfa, average Hb increased to approximately 11 g/dL and remained unchanged in patients receiving placebo. Patients receiving Epoetin alfa experienced improvements in exercise tolerance and patient-reported physical functioning at month 2 and improvements were maintained throughout the study. The Epoetin alfa clinical experience section was revised to include additional study data that support the modified quality of life claim (Amgen, 2007b). A comparison of current and previous HRQoL statements for patients with CRF is provided in Table 1.

### Dosing Recommendations

The revised prescribing information no longer recommends that

**Table 1**  
**Changes in Epoetin alfa HRQoL Benefits for Patients with CRF**

New Label	Previous Label
In a 26-week, double-blind, placebo-controlled trial, 118 patients on dialysis with anemia with an average Hb of approximately 7 g/dL were randomized to either Epoetin alfa or placebo. By the end of the study, average Hb increased to approximately 11 g/dL in the Epoetin alfa-treated patients and remained unchanged in patients receiving placebo. Epoetin alfa-treated patients experienced improvements in exercise tolerance and patient-reported physical functioning at month 2 that was maintained throughout the study.	Once the target Hct of 32% to 38% was achieved, statistically significant improvements were demonstrated for most quality of life parameters measured, including energy and activity level, functional ability, sleep and eating behavior, health status, satisfaction with health, sex life, well-being, psychological effect, life satisfaction, and happiness. Patients also reported improvement in their disease symptoms. They showed a statistically significant increase in exercise capacity, energy, and strength, and a significant reduction in aching, dizziness, anxiety, shortness of breath, muscle weakness, and leg cramps.

**Note:** Adapted from Amgen, 2007a,b.

**Table 2**  
**Changes in Epoetin alfa Dosing Recommendations**

New Label	Previous Label
<p><b>Increase dose by 25% if:</b></p> <ul style="list-style-type: none"> <li>• Hb is below 10 g/dL and has not increased by 1 g/dL after 4 weeks of therapy, or</li> <li>• Hb decreases below 10 g/dL.</li> </ul> <p><b>Decrease dose by 25% if:</b></p> <ul style="list-style-type: none"> <li>• Hb approaches 12 g/dL, or</li> <li>• Hb increases by more than 1 g/dL in any 2-week period.</li> </ul>	<p><b>Increase dose if:</b></p> <ul style="list-style-type: none"> <li>• Hb does not increase by 2 g/dL after 8 weeks of therapy, and Hb remains at a level not sufficient to avoid the need for RBC transfusion.</li> </ul> <p><b>Decrease dose if:</b></p> <ul style="list-style-type: none"> <li>• Hb approaches 12 g/dL, or</li> <li>• Hb increases by more than 1 g/dL in any 2-week period.</li> </ul>

**Note:** Adapted from Amgen, 2007 a,b.

physicians use the lowest Epoetin alfa dose that will gradually increase the Hb concentration to the lowest level sufficient to avoid the need for RBC transfusion. This confusing language has been updated to provide more specific guidance for dose adjustments, including: (a) individually titrate Epoetin alfa doses to achieve and maintain Hb levels between 10 to 12 g/dL, (b) increase the dose by 25% if the Hb is below 10 g/dL and has not increased by 1 g/dL after 4 weeks of therapy or the Hb decreases below 10 g/dL, and (c) reduce the Epoetin alfa dose by 25%

when Hb approaches 12 g/dL or increases by more than 1 g/dL in any 2-week period (Amgen, 2007b). These revisions acknowledge the fact that Hb levels inevitably fluctuate when trying to maintain a Hb of 10 to 12 g/dL in patients with CRF, necessitating modifications in Epoetin alfa doses in response to changes in Hb status. In addition, the revised language encourages clinical interventions that will maintain Hb levels in the 10 to 12 g/dL range. A comparison of the current and previous dosing recommendations is provided in Table 2.

### Definition, Recommendations For Addressing Hyporesponse To Epoetin alfa Therapy

The new prescribing information contains a definition of hyporesponse to Epoetin alfa therapy. A hyporesponsive patient is an individual whose Hb does not attain the range of 10 to 12 g/dL despite the use of appropriate Epoetin alfa dose titrations over a 12-week period.

The revised prescribing information provides specific guidance on how to manage such patients. First, higher doses of Epoetin alfa should not be administered, and clinicians should use the lowest dose that will maintain a Hb level sufficient to avoid the need for recurrent RBC transfusions (the definition of an appropriate level of Hb to avoid a blood transfusion is left to the discretion of the physician) (Amgen, 2007b).

Second, patients should be evaluated for other causes of anemia, including iron deficiency. Prior to and during Epoetin alfa therapy, iron status should be evaluated, and transferrin saturation and ferritin should be maintained at least at 20% and 100 ng/mL, respectively. Other potential etiologies that may affect the response to Epoetin alfa and should be considered when a patient is being assessed for hyporesponse include infection, inflammation, malignant processes, occult blood loss, underlying hematologic diseases, vitamin deficiencies, hemolysis, aluminum intoxication, osteitis fibrosa cystica, and pure red cell aplasia. If detected, these conditions should be promptly corrected whenever possible (Amgen, 2007b).

Third, Hb should continue to be monitored and, if responsiveness improves, Epoetin alfa dose adjustments should be made as described in Table 2. Finally, if responsiveness does not improve and the patient requires recurrent RBC transfusions, Epoetin alfa should be discontinued. The revised prescribing information also cautions that patients with CRF and an insufficient Hb response to Epoetin alfa therapy may be at even

**Table 3**  
**Points to Discuss With Patients Regarding Epoetin alfa Therapy**

<b>Goal of Therapy:</b>	<ul style="list-style-type: none"> <li>• Achieve and maintain a Hb of 10 to 12 g/dL.</li> </ul>
<b>Expected Response to Therapy:</b>	<ul style="list-style-type: none"> <li>• At least 2 weeks of Epoetin alfa treatment is typically required before there is an increase in the number of RBC.</li> </ul>
<b>Dose Adjustments:</b>	<ul style="list-style-type: none"> <li>• Epoetin alfa doses may be adjusted periodically, but increases should not be made more often than once every 4 weeks.</li> </ul>
<b>Potential Benefits of Therapy:</b>	<ul style="list-style-type: none"> <li>• Amelioration of blood transfusions.</li> <li>• Improved exercise tolerance.</li> <li>• Improved physical functioning.</li> </ul>
<b>Safety:</b>	<ul style="list-style-type: none"> <li>• Epoetin alfa increases the chance of blood clots, and the risk of dying may be greater in certain circumstances.</li> <li>• Patients should be encouraged to keep appointments for blood tests so Hb levels can be monitored.</li> <li>• Patients should monitor their blood pressure and call the healthcare team if there are any changes outside the range that has been established for them.</li> <li>• Patients should be told to call the healthcare team if they experience any of the following symptoms:             <ul style="list-style-type: none"> <li>- Pain or swelling in the legs.</li> <li>- Worsening in shortness of breath.</li> <li>- Increases in blood pressure.</li> <li>- Dizziness or loss of consciousness.</li> <li>- Extreme tiredness.</li> <li>- Blood clots in hemodialysis access ports.</li> </ul> </li> </ul>

**Note:** Adapted from Food and Drug Administration, 2007.

greater risk for cardiovascular events and mortality than other patients (Amgen, 2007b).

### **Implications for Nurses and Patient Care**

For nurses caring for patients on dialysis, the changes in the Epoetin alfa prescribing information will necessitate working with physicians and other members of the team to ensure that anemia management protocols comply with the recommendations for Hb, Epoetin alfa dose adjustments, and the approach to hyporesponse. The renewed emphasis on maintaining Hb levels in the range of 10 to 12 g/dL will require increased and proactive vigilance in anemia management to ensure that patients have the best chance of achieving and maintaining

a Hb level in this range.

If Hb excursions outside the recommended range occur, the Epoetin alfa dose should be adjusted as recommended in the prescribing information. Fluctuations in Hb can sometimes occur quickly following dosing changes, and it is vital that Hb be monitored frequently to ensure that current data are used to guide appropriate interventions. Improved Hb stability can be encouraged by adhering to a physician-approved and guided protocol that includes: (a) longitudinal monitoring of the trends in Hb values that incorporates several months of values; (b) application of nursing critical thinking and assessment skills to analyze the trend and determine the risk of going below or over the desired Hb level; (c) prompt detection and correction of factors that may con-

tribute to hyporesponse; and (d) changes in Epoetin alfa doses, in accordance with prescribing information recommendations, to avoid Hb levels outside the range of 10 to 12 g/dL (Amgen, 2007b).

The changes in the Epoetin alfa prescribing information may also necessitate that dialysis facilities modify the educational information that is provided to patients. As part of a risk minimization plan, the FDA is currently developing a patient medication guide to better communicate the risks and benefits of Epoetin alfa use to patients. Physicians, nurses, and other healthcare professionals are encouraged to discuss Epoetin alfa therapy with their patients, including the goal of therapy, potential risks and benefits, dosing adjustments, laboratory monitoring, and symptoms that may be indicative of an adverse response (see Table 3) (Amgen, 2007b; FDA, 2007).

### **Conclusions**

Epoetin alfa therapy has allowed patients to achieve and maintain a Hb level of 10 to 12 g/dL while eliminating the need for transfusions and improving HRQoL. The revised prescribing information properly acknowledges the potential safety concerns associated with higher Hb levels, while simultaneously recognizing the potential benefits of therapy and providing improved guidance on how to maintain Hb at a level that will improve patient outcomes. Nurses will play a key role in assessing trends in laboratory values, predicting the course of Hb, and enacting appropriate physician-prescribed interventions to ensure that Hb is maintained in the recommended range.

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## References

- Amgen. (2007a). EPOGEN® (Epoetin alfa) prescribing information, March, 2007. Retrieved March 23, 2007, from <http://www.epogen.com>
- Amgen. (2007b). EPOGEN® (Epoetin alfa) prescribing information, November, 2007. Retrieved February 1, 2008, from [http://www.epogen.com/pdf/epogen\\_pi.pdf](http://www.epogen.com/pdf/epogen_pi.pdf)
- Amgen (2007c). Data on file. Epoetin alfa physician-assessed and patient-reported outcomes post-marketing commitment supplement addendum 2: Intent to treat analysis of study Ortho 86-004. August 27, 2007.
- Besarab, A., Bolton, W.K., Browne, J.K., Egrie, J.C., Nissenson, A.R., Okamoto, D.M. et al. (1998). The effects of normal compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *The New England Journal of Medicine*, 339(9), 584-590.
- Carter, B., & Keen, M. (2007). Safety of erythropoiesis stimulating agents in patients on dialysis: Current issues for nephrology nurses. *Nephrology Nursing Journal*, 34, 311-315.
- Food and Drug Administration (FDA). (2007). Information on erythropoiesis stimulating agents (ESA) (marketed as Procrit, Epogen, and Aranesp). Retrieved January 31, 2008, from [www.fda.gov/cder/drug/advisory/RHE2007.htm](http://www.fda.gov/cder/drug/advisory/RHE2007.htm)
- Laupacis, A. (1990). Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. *British Medical Journal*, 300, 573-578.
- Laupacis, A., Wong, C., & Churchill, D. (1991). The use of generic and specific quality-of-life measures in hemodialysis patients treated with erythropoietin. *Controlled Clinical Trials*, 12, 168S-179S.
- Singh, A.K., Szczech, L., Tang, K.L., Barnhart, H., Sapp, S., Wolfson, M. et al. (2006). Correction of anemia with Epoetin alfa in chronic kidney disease. *The New England Journal of Medicine*, 355(20), 2085-2098.