BACKGROUND INFORMATION

FOR

THE JOINT MEETING BETWEEN THE CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE & DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

11 September 2007

SAFETY AND EFFICACY OF ERYTHROPOIESIS-STIMULATING AGENTS (ESAs) IN CHRONIC RENAL FAILURE

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KEY POINTS:

Background:

- Anemia is one of the most common and debilitating complications of chronic renal failure (CRF) and is an independent risk factor for increased mortality and cardiovascular morbidity.
- Before the introduction of Epoetin alfa (the first licensed erythropoiesis-stimulating agent [ESA]) in 1989, correction of symptomatic anemia was considered a critical unmet medical need in the dialysis patient population. Treatment options were primarily restricted to androgen therapy and red blood cell transfusions, both of which were limited by safety and efficacy concerns.
- ESA therapy significantly improved the lives of patients with CRF.
- Amgen is the innovator and US license holder of Epoetin alfa and darbepoetin alfa, which are approved for the treatment of anemia associated with CRF.
    - Epoetin alfa is marketed under the trade names EPOGEN® by Amgen and PROCRIT® by Ortho Biotech Products, LP in the US, and EPREX® and other product names by affiliates of Johnson & Johnson outside the US.
    - Darbepoetin alfa is marketed under the trade name Aranesp® by Amgen.

Clinical Benefits of ESA Therapy in Patients With CRF

- In the original registration trials, Epoetin alfa therapy targeted to achieve a hematocrit of 32% to 38% (hemoglobin 10.7 to 12.7 g/dL) resulted in almost complete transfusion independence and improved physician-assessed and patient-reported outcomes for dialysis subjects.
- Double-blind, randomized, controlled clinical trials demonstrate that treatment of anemia with ESAs improves functional ability, energy, muscle weakness, shortness of breath, and exercise capacity for dialysis patients.
- Clinical trial data demonstrate that ESAs correct and maintain hemoglobin concentrations in nondialysis CRF patients. In addition, data also indicate that ESAs reduce transfusion requirements and improve physician-assessed and patient-reported outcomes in these patients.

Risks of ESA Therapy in Patients With CRF

- Risks of ESA therapy in patients with CRF include:
    - increased mortality and serious cardiovascular and thromboembolic events when targeting higher-than-approved hemoglobin concentrations
    - hypertension
    - seizure
    - serious allergic reactions
    - antibody-mediated pure red cell aplasia
- Each of these risks are prominently communicated, with the first risk included in a boxed Warning, in the current prescribing information for Epoetin alfa (EPOGEN®/PROCRIT®) and darbepoetin alfa (Aranesp®).

Clinical Considerations for ESA Therapy

- Clinical practice data suggest no evidence of harm as a result of ESA therapy, compared with no treatment, for anemia in CRF patients. Furthermore, the mortality risk appears to be lower for CRF patients treated with ESAs compared with those not receiving an ESA.
- Achieved hemoglobin concentrations between 11.0 to 13.0 g/dL are associated with the lowest clinical risk in CRF patients.
- The use of a hemoglobin target range is appropriate to guide clinical practice, maximizing benefit and minimizing risk in these patients.
    - Evidence supports 12.0 g/dL as the upper end of the target range to provide a safety margin against higher hemoglobin targets (> 13.0 g/dL).
    - The preponderance of available evidence supports 11.0 g/dL as the lower end of the target range. Given the lack of definitive data and limited feasibility to delineate between narrow hemoglobin targets, it may be reasonable to consider a lower boundary. Amgen and Johnson & Johnson Pharmaceutical Research & Development, LLC (J&JPRD) believe the lower boundary of the target should not be less than 10.0 g/dL.

Clinical Considerations for ESA Therapy (continued)

- The relationship between ESA dose and clinical outcomes is confounded because ESA dose is dependent on 2 key factors:
    - the targeted hemoglobin level, and
    - the ability of an individual patient to generate a hematopoietic response to ESA therapy.
- Patients with poor responsiveness to ESA therapy:
    - appear to have a greater underlying burden of illness and, therefore, a greater inherent risk of mortality and cardiovascular morbidity; and
    - require higher ESA doses to reach any given hemoglobin target.
- Because ESA responsiveness reflects underlying patient health status, it is a better indicator of clinical risk than ESA dose alone.
- Iron treatment is commonly used with ESA therapy. Because iron utilization has been associated with an increased risk of infection and cardiovascular events in dialysis patients, further consideration of iron and its impact on morbidity and mortality in ESA-treated patients is warranted.
- Amgen and J&JPRD believe that the area of hypo-responsiveness to ESAs warrants further evaluation. At the joint Advisory Committee meeting, Amgen and J&JPRD will present the results of ongoing analyses to facilitate discussion regarding an appropriate definition of hypo-responsiveness, as well as trial design options to evaluate appropriate ESA treatment for hypo-responsive patients.

Risk Management Plan

- Safety concerns regarding increased mortality and cardiovascular events were raised by 2 prospective clinical trials, Normal Hematocrit Cardiac Trial (NHCT) and Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR), each of which evaluated higher-than-approved hemoglobin targets in CRF patients.
    - Amgen and J&JPRD updated the product labelling and informed healthcare providers, investigators, clinical trial subjects, and data safety monitoring committees.
    - Amgen and J&JPRD will sponsor additional educational programs that specifically highlight the increased risk of mortality and cardiovascular/thromboembolic events when targeting higher-than-approved hemoglobin concentrations.
    - Amgen and J&JPRD recommend that the label should reflect the use of a hemoglobin target range to guide clinical practice.
- Exploratory analyses of observational and clinical trial data suggest a higher risk of cardiovascular morbidity and mortality in hypo-responsive patients.
    - Amgen and J&JPRD will provide draft concepts for precautionary ESA label language relating to the evaluation and management of hypo-responsive patients at the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) and Drug Safety and Risk Management Advisory Committee (DSRM AC) joint meeting on 11 September 2007. This language will be finalized in collaboration with the FDA using input received from the CRDAC and DSRM AC.
    - Amgen and J&JPRD will sponsor additional educational programs that specifically highlight the increased risk of mortality and cardiovascular events in hypo-responsive patients.
- Amgen and J&JPRD perform continuous postmarketing pharmacovigilance activities to monitor the safety of Epoetin alfa and darbepoietin alfa.

Risk Management Plan (continued)

- Ongoing clinical trials (eg, 'Trial to Reduce Cardiovascular Events With Aranesp® Therapy' [TREAT]) are addressing important unanswered questions that will further inform our understanding of the benefit: risk profile of ESA therapy. For example, the primary objective of TREAT, a randomized, placebo-controlled trial, is to evaluate the effect of anemia therapy with darbepoetin alfa on the composite event of all-cause mortality and nonfatal cardiovascular events in anemic, nondialysis CRF subjects with type 2 diabetes mellitus.
- Amgen and J&JPRD will present draft concepts for clinical trial designs to evaluate the appropriate dosing paradigm for hypo-responsive patients at the CRDAC and DSRM AC joint meeting on 11 September 2007.

Conclusions

- The benefit: risk profile of ESA therapy in CRF patients is favorable with appropriate guidance not to exceed a hemoglobin target of 12.0 g/dL.
- ESAs provide clear clinical benefit in CRF patients with regard to transfusion avoidance and improvements in physician-assessed and patient-reported outcomes.
- ESA use in CRF patients is associated with specific and well-described risks that are primarily cardiovascular or immunologic in origin. Importantly, an increased risk for mortality and cardiovascular morbidity has been observed in clinical trials targeting hemoglobin concentrations > 13.0 g/dL in CRF patients. These risks are prominently reflected in the product labeling.
- Amgen and J&JPRD believe that risk management through the following appropriately addresses the known safety concerns:
    - inclusion of hemoglobin target range in ESA product labeling;
    - precautionary ESA label language regarding hypo-responsiveness;
    - communication of overall risks of ESA use to healthcare providers;
    - continuous monitoring of ongoing clinical trials (eg, TREAT); and
    - a clinical trial to evaluate the appropriate dosing paradigm for hypo-responsive patients.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition/Explanation
CHF	congestive heart failure
CI	confidence interval
CKD	chronic kidney disease
CRF	chronic renal failure
CHOIR	study entitled 'Correction of Hemoglobin and Outcomes in Renal Insufficiency'
CRDAC	Cardiovascular and Renal Drugs Advisory Committee
CREATE	study entitled 'Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta'
DHCP	Dear Healthcare Provider
DSMC	data safety monitoring committee
DSRM AC	Drug Safety and Risk Management Advisory Committee
eGFR	estimated glomerular filtration rate
EPO	erythropoietin
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
FDA	Food & Drug Administration
FMC-NA	Fresenius Medical Care-North America
HCP	healthcare provider
J&J	Johnson & Johnson
J&JPRD	Johnson & Johnson Pharmaceutical Research & Development, LLC
KDQ	Kidney Disease Questionnaire
NHANES	National Health and Nutrition Examination Survey
NHCT	study entitled 'Normal Hematocrit Cardiac Trial'
NHP	Nottingham Health Profile
NKDKTS	National Kidney Dialysis and Kidney Transplantation Study
NKF-KDOQI™	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
PRCA	pure red cell aplasia
rHuEPO	recombinant human erythropoietin
SIP	Sickness Impact Profile
TREAT	study entitled 'Trial to Reduce Cardiovascular Events With Aranesp® Therapy'

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition/Explanation
US	United States
USPI	United States Prescribing Information
USRDS	United States Renal Data System

1. EXECUTIVE SUMMARY

The approval of the first recombinant erythropoiesis-stimulating agent (ESA), Epoetin alfa, in 1989 constituted an important scientific breakthrough in medicine and revolutionized the care of patients with anemia of chronic renal failure (CRF). Since their introduction, Epoetin alfa (EPOGEN®/ PROCRIT®/ EPREX®) and darbepoetin alfa (Aranesp®) have a combined postmarketing exposure of over 8 million person-years. This accumulated information from extensive clinical experience over nearly 2 decades strongly supports a favorable benefit: risk profile for these ESAs when used in accordance with their product labeling to treat anemia in patients with CRF.

Amgen, the United States (US) license holder of Epoetin alfa and darbepoetin alfa, created these products as chronic, supportive therapies to elevate and maintain hemoglobin concentrations in anemic patients with CRF, in whom the ability to produce endogenous erythropoietin is substantially compromised. In registration clinical trials that targeted a hematocrit range of 32% to 38% (hemoglobin 10.7 to 12.7 g/dL), chronic transfusion dependence was virtually eliminated and health-related quality of life was improved as a result of ESA therapy in dialysis patients. Accordingly, ESA therapy was rapidly adopted as the standard of care for anemia treatment in dialysis patients by offering an effective alternative to the significant risks and limitations of chronic transfusions. In anemic, nondialysis CRF patients, registration clinical trials demonstrated that ESA therapy effectively increased and maintained hemoglobin concentrations, thereby reducing the need for blood transfusion. Additional data from both registration and non-registration clinical studies have described a variety of other clinical benefits of ESA therapy in both dialysis and nondialysis CRF patients, including reduction in hospitalization and left ventricular hypertrophy.

Amgen and Johnson & Johnson Pharmaceutical Research & Development, LLC (J&JPRD) endorse appropriate risk communication and have collaborated with the Food and Drug Administration (FDA) to revise the ESA product labels to include emphasized and prominent warnings as safety information has become available through postmarketing surveillance and clinical trials. These include warnings on risks of increased mortality and serious cardiovascular and thromboembolic events when targeting hemoglobin concentrations > 12.0 g/dL; hypertension; seizure; allergic reactions; and antibody-mediated pure red cell aplasia (PRCA).

With respect to patients with CRF, safety concerns regarding increased mortality and cardiovascular events were primarily raised by 2 prospective, open-label, active-control clinical trials, Normal Hematocrit Cardiac Trial (NHCT) in dialysis subjects (Besarab et al, 1998) and Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) in nondialysis subjects (Singh et al, 2006), each of which evaluated higher-than-approved hemoglobin targets. NHCT compared the impact of a hemoglobin target of 14.0 ± 1.0 g/dL to a target of 10.0 ± 1.0 g/dL on the time to mortality or nonfatal myocardial infarction. CHOIR compared the impact of a hemoglobin target of 13.5 g/dL to a target of 11.3 g/dL on the time to mortality or composite cardiovascular event.

Based on the results of the NHCT, the Epoetin alfa United States Prescribing Information (USPI) was initially revised in 1996 to include the warnings on risks of increased mortality and serious cardiovascular and thromboembolic events when targeting hemoglobin concentrations > 12.0 g/dL. This information was also included in the Warnings section of the original USPI for darbepoetin alfa in 2001. In March 2007, the Warnings section of the USPIs for licensed ESAs was revised to include heightened communication regarding these risks based upon the results of the CHOIR study and other studies in cancer and peri-surgery patients. In addition, the previous product labeling specifying a target hemoglobin was replaced by guidance to use the lowest ESA dose to increase hemoglobin concentration to the lowest level sufficient to avoid the need for transfusion and to not exceed an *achieved* hemoglobin level of 12.0 g/dL. These changes have had the unintended consequence of removing the key clinical approach (hemoglobin target) utilized by physicians to guide ESA therapy. This has caused confusion for physicians and other healthcare providers regarding how to administer ESAs to patients with CRF (American Association of Kidney Patients, 2007; Hartwell, 2007; Renal Physicians Association, 2007). Subsequently, several important questions have been asked regarding the use of ESAs to treat anemia in patients with CRF:

- What is the clinical benefit of ESA therapy beyond transfusion avoidance?
- What are the clinical considerations for ESA dose optimization, specifically with respect to the following:
    - What hemoglobin target results in an optimal benefit: risk profile for ESAs?
    - Do higher ESA doses and/or poor ESA response cause adverse clinical outcomes, including mortality?

- How should ESA responsiveness be defined and how should hypo-responsive patients be managed?

Answers to these questions should be based on comprehensive analyses of all available and relevant data. Therefore, to address these questions in conjunction with the FDA, Amgen and J&JPRD conducted additional exploratory analyses of NHCT and CHOIR, pooled clinical trials, relevant observational data, and published literature regarding ESA therapy in patients with CRF. This briefing document provides a detailed assessment of the results of these analyses in preparation for the 11 September 2007 Cardiovascular and Renal Drugs Advisory Committee (CRDAC) & Drug Safety and Risk Management Advisory Committee (DSRM AC) joint meeting. Results from these exploratory analyses have been provided to the FDA. It is our intention that this briefing document will serve to facilitate robust, evidence-based discussions regarding the safety and benefits of ESA therapy, with particular attention directed towards benefits beyond transfusion avoidance (ie, physician assessments of overall health status and patient-reported outcomes). The totality of the evidence and the consistency of key results across these multiple analyses support the following conclusions in CRF patients:

- Since the approval of Epoetin alfa in 1989, ESAs have had a favorable benefit: risk profile in the treatment of anemia associated with CRF.
- Clinical benefits of Epoetin alfa therapy in CRF patients include transfusion avoidance and improvements in physician assessments of overall health status and patient-reported outcomes.
- Clinical practice data suggest no evidence of harm as a result of ESA therapy, compared with no treatment, for anemia in CRF patients. Furthermore, the mortality risk appears to be lower for CRF patients treated with ESAs compared with those not receiving an ESA.
- Achieved hemoglobin concentrations between 11.0 to 13.0 g/dL are associated with the lowest clinical risk in CRF patients.
- The use of a hemoglobin target range is appropriate to guide clinical practice, maximizing benefit and minimizing risk in these patients.
    - Evidence supports 12.0 g/dL as the upper end of the target range to provide a safety margin against higher hemoglobin targets (> 13.0 g/dL).

  - The preponderance of available evidence supports 11.0 g/dL as the lower end of the target range. Given the lack of definitive data and limited feasibility to delineate between narrow hemoglobin targets, it may be reasonable to consider a lower boundary. Amgen and J&JPRD believe the lower boundary of the target should not be less than 10.0 g/dL.

- The relationship between ESA dose and clinical outcomes is confounded because ESA dose is dependent on 2 key factors:
  - the targeted hemoglobin level, and
  - the ability of an individual patient to generate a hematopoietic response to ESA therapy.
- Patients with poor responsiveness to ESA therapy:
  - appear to have a greater underlying burden of illness and, therefore, a greater inherent risk of mortality and cardiovascular morbidity; and
  - require higher ESA doses to reach any given hemoglobin target.
- Because ESA responsiveness reflects underlying patient health status, it is a better indicator of clinical risk than ESA dose alone.
- Iron treatment is commonly used with ESA therapy. Because iron utilization has been associated with an increased risk of infection and cardiovascular events in dialysis patients, further consideration of iron and its impact on morbidity and mortality in ESA-treated patients is warranted.
- Amgen and J&JPRD believe that the area of hypo-responsiveness to ESAs warrants further evaluation. At the joint Advisory Committee meeting, Amgen and J&JPRD will present the results of ongoing analyses to facilitate discussion regarding an appropriate definition of hypo-responsiveness, as well as trial design options to evaluate appropriate ESA treatment for hypo-responsive patients.

Amgen and J&JPRD are committed to continuous postmarketing pharmacovigilance activities to monitor the safety of Epoetin alfa and darbepoietin alfa and to minimizing risks associated with the use of Epoetin alfa and darbepoetin alfa by strengthening the risk communication in ESA labeling. Ongoing clinical trials (eg, 'Trial to Reduce Cardiovascular Events With Aranesp® Therapy' [TREAT]) are addressing important unanswered questions that will further inform our understanding of the benefit: risk profile of ESA therapy. For example, the primary objective of TREAT, a randomized,

placebo-controlled trial, is to evaluate the effect of anemia therapy with darbepoetin alfa on the composite event of all-cause mortality and nonfatal cardiovascular events in anemic, nondialysis CRF subjects with type 2 diabetes mellitus. Furthermore, Amgen and J&JPRD believe that risk management through the following appropriately addresses the known safety concerns:

- inclusion of hemoglobin target range in ESA product labeling;
- precautionary ESA label language regarding hypo-responsiveness;
- communication of overall risks of ESA use to healthcare providers;
- continuous monitoring of ongoing clinical trials (eg, TREAT); and
- a clinical trial to evaluate the appropriate dosing paradigm for hypo-responsive patients.

2. BACKGROUND

2.1 Key Points

- Anemia is one of the most common and debilitating complications of CRF and is an independent risk factor for increased mortality and cardiovascular morbidity.
- Before the introduction of Epoetin alfa (the first licensed ESA) in 1989, correction of symptomatic anemia was considered a critical unmet medical need in the dialysis patient population. Treatment options were primarily restricted to androgen therapy and red blood cell transfusions, both of which were limited by safety and efficacy concerns.
- ESA therapy significantly improved the lives of patients with CRF.
- Amgen is the innovator and US license holder of Epoetin alfa and darbepoetin alfa, which are approved for the treatment of anemia associated with CRF.
    - Epoetin alfa is marketed under the trade names EPOGEN® by Amgen and PROCRIT® by Ortho Biotech Products, LP in the US, and EPREX® and other product names by affiliates of Johnson & Johnson (J&J) outside the US.
    - Darbepoetin alfa is marketed under the trade name Aranesp® by Amgen.

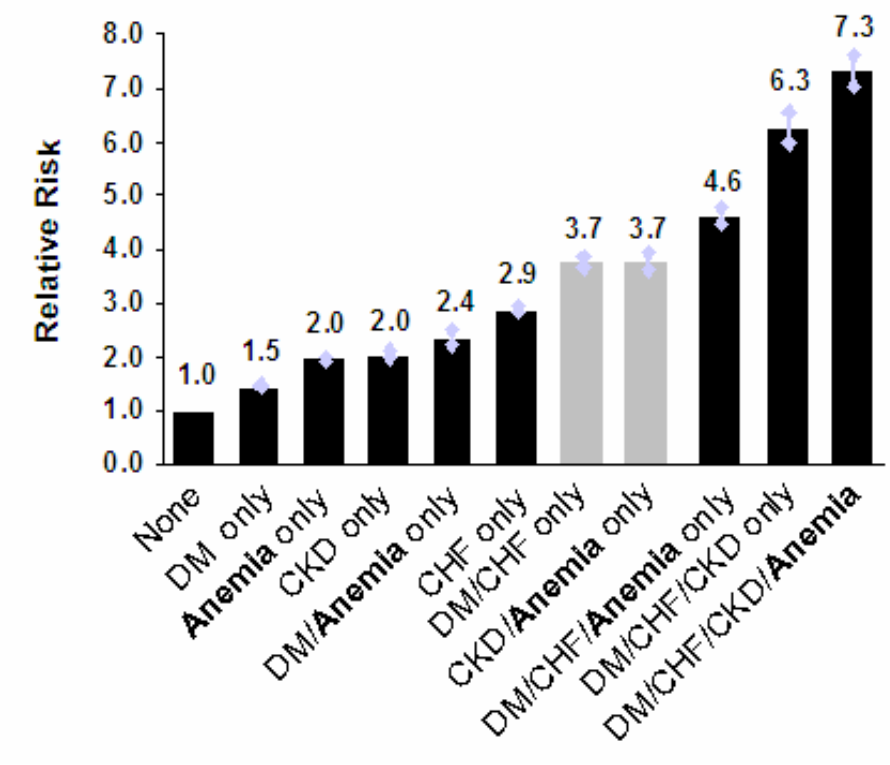
2.2 Anemia and Chronic Renal Failure

Chronic renal failure (CRF) is a common condition and a growing health concern (US Renal Data System [USRDS], 2006). At least 8 million people in the US have moderate to severe loss of kidney function (estimated glomerular filtration rate [eGFR] 15 to 60 mL/min/1.73 m^2) (Coresh et al, 2003). Over 470,000 patients have progressed to end-stage renal disease (ESRD) and require either dialysis or a kidney transplant for survival (USRDS, 2006).

Anemia is one of the most common and debilitating complications of CRF, resulting primarily from decreased production of erythropoietin by the kidney (Eschbach and Adamson, 1985). Anemia develops early in the course of renal disease and progresses with loss of renal function (Astor et al, 2002; Kazmi et al, 2001). An estimated 5% of patients with eGFR between 30 and 59 mL/min/1.73m^2 and 44% of patients with eGFR less than 30 mL/min/1.73m^2 are anemic (Astor et al, 2002). In patients who have progressed to ESRD, anemia is a ubiquitous comorbidity (USRDS, 2006).

Many clinical sequelae are associated with anemia, such as impaired oxygen delivery and utilization, decreased physical functioning and rehabilitation, increased cardiovascular complications, and shorter survival time (Appendix Table 1). Anemia has also been shown to be an independent predictor and risk multiplier for increased mortality in patients with CRF who have not progressed to ESRD (Astor et al, 2006; Collins, 2003; McClellan et al, 2002; Al-Ahmad et al, 2001). Importantly, patients diagnosed with CRF and anemia have a risk of death that is equivalent to that in patients diagnosed with both diabetes and congestive heart failure (Figure 1).

Figure 1. Relative Risk of Death Before ESRD During 2-Year Follow-up (US Medicare Patients)



International Classification of Disease (ICD)-9 diagnosis codes for anemia: 280.XX-285.XX
ESRD = end-stage renal disease; CHF = congestive heart failure; CKD = chronic kidney disease; DM = diabetes mellitus.
Source: adapted from Collins, 2003

2.3 Anemia Treatment in Patients with CRF Prior to the Introduction of ESA Therapy

Before ESA therapy was available, correction of symptomatic anemia was considered a critical unmet medical need in the dialysis patient population (Eschbach, 1989). Despite attempts by physicians to manage anemia through minimization of blood loss, regular

dialysis treatment, blood transfusions, iron supplementation, and androgen therapy, severe anemia was a significant issue in this patient population. Hemoglobin concentrations averaged approximately 8.0 g/dL, with some patients exhibiting concentrations as low as 4 g/dL (Winearls, 1998; Eschbach, 1989).

The most effective anemia treatments before ESAs were androgen therapy and blood transfusions (Eschbach and Adamson, 1985; Sexauer and Matson, 1981), although both had significant risks and limitations, which are still relevant today. Androgen therapy is rarely, if ever, used in CRF patients due to suboptimal hemoglobin response and adverse effects, including virilization, potential liver toxicity, and hepatocellular carcinoma (Watson, 1989). Transfusions are generally reserved for acute treatment of severe anemia in CRF patients. They are only transiently effective, with a progressive decrease in hemoglobin levels following the initial increase. Chronic transfusions also expose patients to significant risks, the foremost of which are the development of allo-antibodies (Vella et al, 1998; Scornik et al, 1984) and iron overload (Eschbach and Adamson, 1999). The development of antibodies directed against human leukocyte antigens (HLA) makes it difficult to find a match for kidney transplantation, thus, prolonging the time to transplantation (Lietz et al, 2003; Braun, 2002), and is associated with increased risk for poor graft function or graft failure (Colvin, 2007; Cardarelli et al, 2005; Nicol et al, 1993). In addition, the development of antibodies directed against red cell antigens can result in hemolysis.

Iron overload can occur early in transfusion-dependent CRF patients since each unit of red blood cells contains approximately 250 mg of iron and iron excretion capacity is extremely limited. The resulting iron accumulation in tissues can be responsible for liver cirrhosis with its associated risk of hepatocellular carcinoma, diabetes mellitus, and cardiac failure (O'Neil and Powell, 2005). In dialysis patients, studies performed before ESAs became available also suggested that iron overload increased the risk of bacterial infection (Boelaert et al, 1990; Tielemans et al, 1989; Seifert et al, 1987).

In addition to risks for allo-immunization and iron overload, transfusions carry risks of increased fluid retention (especially in CRF patients with comorbid cardiac disease), allergic reaction, hemolytic reaction, acute lung injury, and infection (Despotis et al, 2007). Although donor screening and testing procedures for infectious disease continue to improve, a wide range of infectious pathogens, such as human immunodeficiency virus, hepatitis B, hepatitis C, human herpes virus 8, Trypanosoma cruzi (Chagas' disease), and the prion responsible for variant Creutzfeldt-Jakob disease, may still be

transmitted through allogeneic blood transfusions (Blajchman and Vamvakas, 2006; FDA News Press Release, 2006). Recent estimates suggest that 1 in every 130,000 red blood cell transfusions results in death (including deaths due to transmitted infectious disease) (Despotis et al, 2007). Approximately one-third of these deaths are due to transfusion-related acute lung injury and hemolytic reactions.

Finally, dependence on chronic transfusions for this patient population may place a substantial burden on the healthcare system's blood supply. Before erythropoietin therapy was available, dialysis patients required an average of 6 to 8 units of blood per year (Churchill et al, 1992; Eschbach et al, 1989), which would translate to approximately 12% of the total US blood supply, based on the most current estimate (Sullivan et al, 2007).

2.4 ESAs Licensed in the United States

Amgen was the first to clone the gene for human erythropoietin (rHuEPO; Epoetin alfa) (Lin et al, 1985) and is the US license holder for Epoetin alfa. Epoetin alfa was approved for the treatment of anemia associated with CRF in 1989 and, subsequently, for the treatment of anemia in patients with nonmyeloid malignancies who are receiving chemotherapy, anemia in zidovudine-treated HIV-infected patients, and for the reduction of allogeneic blood transfusions in patients undergoing elective, noncardiac, nonvascular surgery. In the US, Epoetin alfa is marketed under the trade names EPOGEN® and PROCRIT®. Amgen manufactures both PROCRIT® and EPOGEN® and clinically develops, markets, and distributes EPOGEN® for use in dialysis patients. Ortho Biotech Products, LP, a subsidiary of J&J, is responsible for the clinical development, marketing, and distribution of PROCRIT® for all other indications in the US under license from Amgen. EPREX® is a branded Epoetin alfa product, manufactured and distributed by an affiliate of J&J in a separate facility and is marketed by affiliates of J&J outside the US under license from Kirin-Amgen.

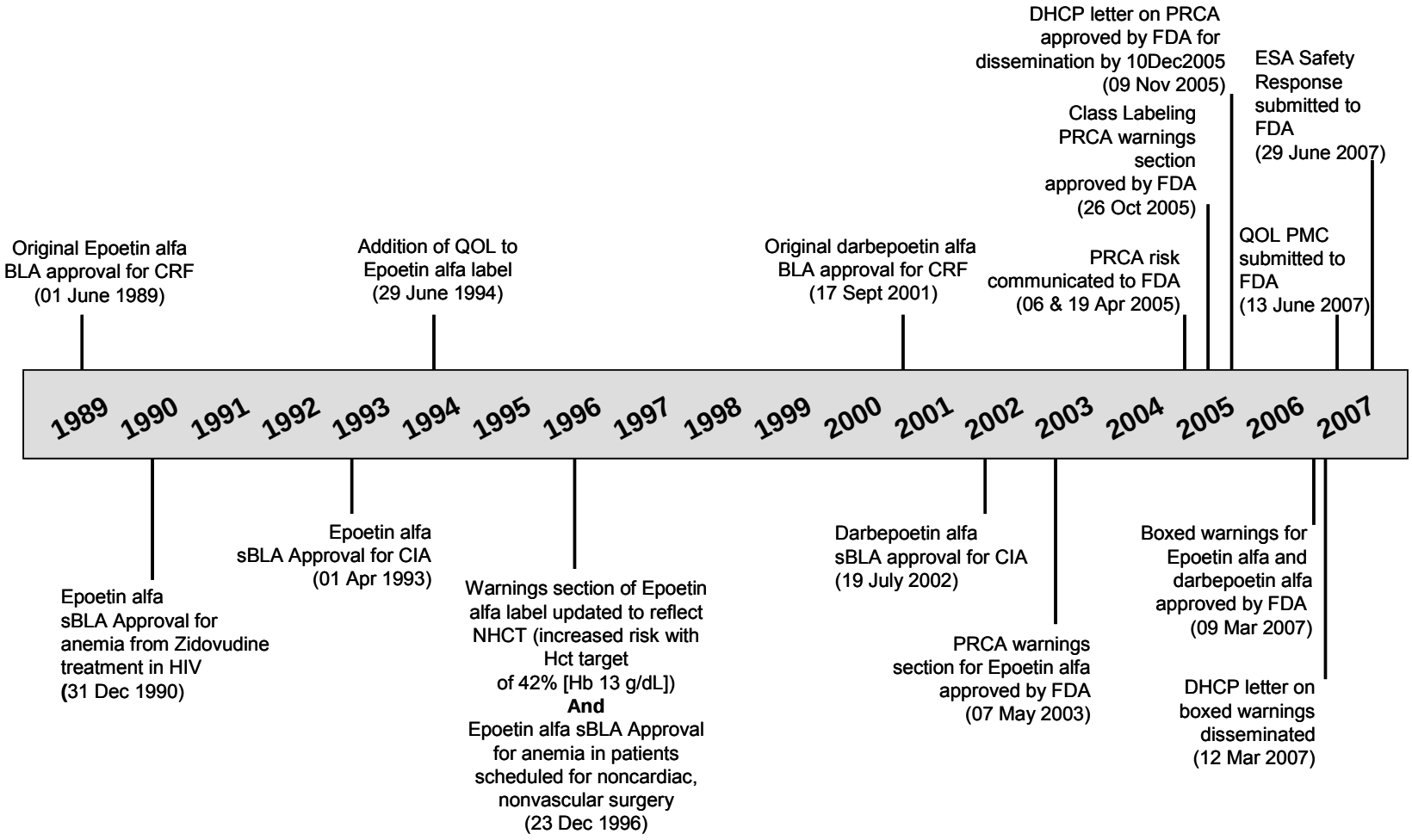
Amgen created, developed, and is the license holder for darbepoetin alfa (Aranesp®), a longer acting ESA (Egrie et al, 2003; Macdougall, 2000; Macdougall et al, 1999). Darbepoetin alfa was approved for the treatment of anemia associated with CRF in 2001 and for treatment of anemia in patients with nonmyeloid malignancies who are receiving chemotherapy in 2002.

Epoetin alfa and darbepoetin alfa have a combined postmarketing exposure of approximately 8 million person-years in CRF patients over a period of approximately

18 years. Throughout this time period, the benefit: risk profile for these ESAs (based upon postmarketing adverse event reporting) has remained favorable in the treatment of anemia in CRF patients.

Since the approval of Epoetin alfa in 1989, Amgen and J&JPRD have communicated information regarding the risks and benefits of these products to regulatory authorities and healthcare providers in a responsible and timely manner. In the US, these updates are accomplished through safety changes that are implemented immediately or through prior approval supplements to the product licenses. Prescribers are informed of important package insert changes through personal and publicly available communications such as Dear Health Care Professional (DHCP) letters. Figure 2 summarizes the timeline for critical regulatory submissions and communications from Amgen on safety issues for Epoetin alfa and darbepoetin alfa. Copies of the currently approved USPIs for EPOGEN®/PROCRIT® and Aranesp® are provided in Appendix 5.

Figure 2. Critical Regulatory Submissions and Safety Communications From Amgen for Epoetin alfa and Darbepoetin alfa



BLA =Biological License Application; CIA = chemotherapy-induced anemia; CRF = chronic renal failure; DHCP = Dear Healthcare Provider; Hb = hemoglobin concentration; HCP = healthcare provider; Hct =hematocrit; NHCT = Normal Hematocrit Cardiac Trial; PMC = post-marketing commitment; PRCA = pure red cell aplasia; QOL = quality of life; sBLA = supplemental BLA

3. CLINICAL BENEFITS OF ESA THERAPY IN PATIENTS WITH CRF

3.1 Key Points

- In the original registration trials, Epoetin alfa therapy targeted to achieve a hematocrit of 32% to 38% (hemoglobin 10.7 to 12.7 g/dL) resulted in almost complete transfusion independence and improved physician-assessed and patient-reported outcomes for dialysis subjects.
- Double-blind, randomized, controlled clinical trials demonstrate that treatment of anemia with ESAs improves functional ability, energy, muscle weakness, shortness of breath, and exercise capacity for dialysis patients.
- Clinical trial data demonstrate that ESAs correct and maintain hemoglobin concentrations in nondialysis patients. In addition, data also indicate that ESAs reduce transfusion requirements and improve physician-assessed and patient-reported outcomes in these patients.

Epoetin alfa and darbepoetin alfa were developed and approved as chronic, supportive therapies to elevate and maintain hemoglobin concentrations and reduce the need for transfusions in patients with CRF. The original registration studies for Epoetin alfa utilized hemoglobin response, transfusion reduction, and reduction of iron overload as the principal clinical efficacy endpoints. Based upon results from clinical trials and 18 years of clinical experience, ESAs provide clear clinical benefit in CRF patients with regard to transfusion avoidance and improvements in physician-assessed and patient-reported outcomes as described in Sections 3.2 and 3.3.

Although the clinical trials supporting the approval of these ESAs for use in CRF patients were not designed as outcomes trials, evidence from a variety of observational studies suggest that dialysis and nondialysis patients who receive ESA therapy have better outcomes than those who do not receive ESAs. These data are further discussed in Section 5.2.

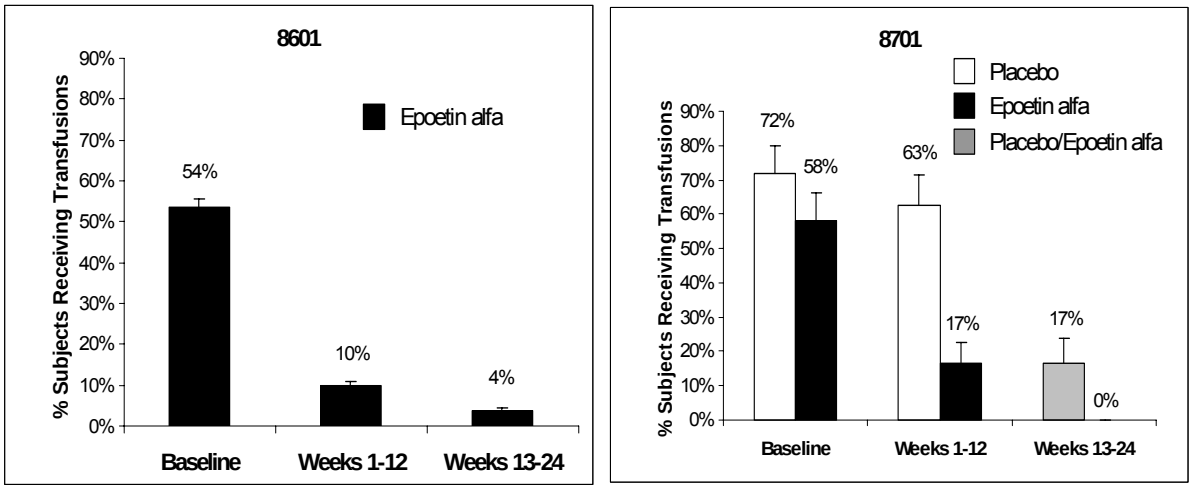
3.2 Transfusion Avoidance

3.2.1 Dialysis Patients

In registration clinical trials for Epoetin alfa targeting a hematocrit between 32% and 38% (hemoglobin 10.7 to 12.7 g/dL), chronic transfusion dependence was virtually eliminated as a result of ESA therapy in hemodialysis patients (Figure 3). In the open-label clinical

trial 8601 (N = 426), only 4% of subjects required transfusions after 3 months of treatment with Epoetin alfa compared with 54% over the 6 months before treatment was initiated (baseline). In the placebo-controlled trial 8701 (N = 68), the percentage of subjects requiring transfusions over a 3-month period decreased from 63% to 17% after they were switched from placebo (white bar) to Epoetin alfa (grey bar). In the same trial, none of the subjects initially randomized to Epoetin alfa required transfusions after 3 months of treatment (black bars).

Figure 3. Transfusion Requirements Before and After Epoetin alfa Treatment in Clinical Trials in Hemodialysis Patients (Amgen Studies 8601 and 8701)



N = 426 for Study 8601; N = 32 for Placebo in Study 8701; N = 36 for Epoetin alfa in Study 8701
Baseline rates are based on the 6 months before the start of the study.
Placebo/Epoetin alfa group: Transfusion requirements for subjects originally randomized to receive placebo in Study 8701 who began to receive Epoetin alfa after week 12.
Source: /stat/esp/ckd/docs/EPO_TRANSFUSIONS/8601 and 8701.xls

In addition, other clinical trials have assessed transfusion requirements for dialysis subjects when treated with Epoetin alfa to different hemoglobin target ranges. In the NHCT, hemodialysis subjects with clinically evident cardiac disease were randomized to treatment with Epoetin alfa to a target hematocrit of either 42% ± 3% or 30% ± 3% [hemoglobin 14 ± 1 g/dL or 10 ± 1 g/dL]) (Besarab et al, 1998). Over a median 14-month treatment period, significantly fewer subjects in the higher target group received transfusions than those in the lower target group (21% vs 31%, $p < 0.001$).

In a J&JPRD affiliate-sponsored EPREX® registration clinical trial (EP86-004), dialysis subjects were randomized to treatment with placebo or Epoetin alfa to a hemoglobin target of either 9.5 to 11.0 g/dL or 11.5 to 13.0 g/dL (Canadian Erythropoietin Study

Group, 1990). Based upon the clinical study report, 20 of 40 subjects (50%) in the placebo group received a blood transfusion during the study, while 2 of 78 subjects (3%) in the Epoetin alfa groups (1 subject from each target group) required transfusions in this 26-week study (of note, the publication states that 23 placebo-treated subjects received transfusions).

In a J&JPRD-sponsored clinical trial with EPREX® (EPO-INT-68), dialysis subjects were randomized to treatment with Epoetin alfa to a hemoglobin target of either 9.5 to 11.5 g/dL or 13.5 to 14.5 g/dL for up to 96 weeks (a 24-week initial phase followed by a 72-week maintenance phase) (Parfrey et al, 2005). During the trial, a greater proportion of subjects in the lower hemoglobin target group (19% [58/300]) were transfused compared with the higher hemoglobin target group (9% [27/296]) ($p < 0.001$). The achieved mean hemoglobin concentrations in the lower and higher target hemoglobin groups were 10.8 and 13.1 g/dL, respectively.

In addition to these clinical trial results, decreases in transfusion requirements were observed in the dialysis clinical setting following the introduction of Epoetin alfa (Eschbach, 1994), which contributed to increased access to kidney transplants and improved graft survival among kidney transplant patients (Lietz et al, 2003; Braun, 2002; Nicol et al, 1993).

3.2.2 Nondialysis Patients

The clinical benefit of transfusion avoidance in anemic dialysis patients established hemoglobin as the key outcome for approval of ESAs in the nondialysis setting. Registration clinical trials with Epoetin alfa and darbepoetin alfa evaluated hemoglobin response in nondialysis CRF subjects and demonstrated that hemoglobin targets of approximately 11.0 to 13.0 g/dL can be achieved and maintained in these subjects. Although transfusion rates were not a primary outcome of registration trials, in a large study (N = 1557) evaluating the safety and efficacy of Epoetin alfa 10,000 units once weekly dosing in nondialysis CRF subjects, transfusion rates significantly decreased from 11.1% (n = 149) during the 6-month pre-treatment period to 3.7% (n = 50) ($p < 0.0001$) during the 16-week study period (PR00-06-009 [POWER]; [Provenzano et al, 2004]). A survey of anemia management practices in Europe also revealed that patients treated with an ESA before initiation of dialysis had significantly lower rates of blood transfusion than patients who did not receive an ESA (17% vs 21%, $p < 0.05$)

(Valderrábano et al, 2003). These data indicate that a reduction in transfusion is also a clinical benefit in nondialysis CRF patients.

3.3 Physician-assessed and Patient-reported Outcomes

3.3.1 Dialysis Patients

3.3.1.1 Label Claims for Epoetin alfa Treatment of the Signs and Symptoms of Anemia in Dialysis Patients

The Clinical Experience section of the current Epoetin alfa USPI describes the positive impact of Epoetin alfa on the signs and symptoms of anemia in dialysis patients. Physician-assessed and patient-reported outcomes statements were approved by the FDA for Epoetin alfa in 1994 (Appendix 5). These claims were originally supported by the results of Amgen Study 8601, an open-label, single arm clinical trial (Evans et al, 1990), combined with those from a randomized, double-blind trial of exercise capacity (Ortho Study EP86-004; Lundin et al, 1991) (Table 1). Since the original approval, several randomized, controlled, double-blind, placebo-controlled trials have also found positive treatment effects for Epoetin alfa using several different patient-reported outcome measures that assessed the signs and symptoms of anemia.

In light of the FDA's published *Draft Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (February 2006) and in response to a request to Amgen by the FDA, Amgen has re-evaluated the physician-assessed and patient-reported outcomes claims in the Epoetin alfa label based on the results of 3 randomized, double-blind, placebo-controlled trials with Epoetin alfa in which patient-reported outcome measures were included. The remainder of this section summarizes the results from these 3 clinical trials, as well as additional published evidence from clinical trials with ESAs in dialysis subjects in which patient-reported outcomes were assessed. The results from the 3 randomized, double-blind, placebo-controlled trials support the retention of claims for functional ability, energy, muscle weakness, shortness of breath, and exercise capacity in the Epoetin alfa label for dialysis patients.

3.3.1.2 Analyses of Label Patient-reported Outcomes Statements Following 2006 FDA Draft Guidance

3.3.1.2.1 Results from Randomized, Double-Blind Clinical Trials

Ortho Study EP86-004 and Amgen Studies 8701 and 8904 are 3 randomized, double-blind, placebo-controlled trials that assessed patient-reported outcomes in dialysis subjects (Table 1). Ortho Study EP86-004 was a 3-arm study that evaluated

2 hemoglobin targets and a placebo arm. Patient-reported outcomes were assessed using the Kidney Disease Questionnaire (KDQ) and Sickness Impact Profiles (SIP). The patient-reported outcomes measures in this trial were analyzed using repeated-measures analysis of variance comparing the placebo group to the entire group of Epoetin alfa-treated subjects (combined data from the 2 active treatment arms). This trial was not powered to detect statistical difference in the patient-reported outcome measures. Tests for statistical significance were not adjusted for multiple comparisons.

Studies 8701 and 8904 were partial crossover trials, in which the control group received placebo for the first 12 weeks, and then were crossed over to Epoetin alfa for the subsequent 12 weeks. Patient-reported outcomes were assessed in these 2 trials using the Karnofsky Performance Status instrument administered as a patient-reported outcome, Nottingham Health Profile (NHP), and National Kidney Dialysis and Kidney Transplantation Study (NKDKTS) single item questions. These trials were not powered to detect statistical difference in the patient-reported outcome measures. Post-hoc statistical testing of differences between placebo and treatment groups at baseline and week 12 was performed for these 2 trials. A patient-reported outcomes score at week 12 was considered significant when there was a statistically significant difference at follow-up between the Epoetin alfa and placebo groups that did not exist at baseline. Tests for statistical significance were not adjusted for multiple comparisons. Amgen Study 8601 (Evans et al, 1990), the original registration trial that was the basis for the inclusion of patient-reported outcome statements in the Epoetin alfa label, is included for comparison.

Table 1. Designs for Epoetin alfa Studies Ortho EP86-004 and Amgen 8601, 8701, and 8904

	EP86-004	8904	8701	8601
Design	Randomized, double-blind	Randomized, double-blind, partial crossover	Randomized, double-blind, partial crossover	Single arm, open label
Sample size (placebo; active)	40; 78	74; 78	32; 36	0; 426
Inclusion criteria				
Dialysis status (eGFR [mL/min/1.73m2])	Hemodialysis	Peritoneal dialysis	Hemodialysis	Hemodialysis
Hemoglobin (g/dL)	< 9	≤ 10 [a]	≤ 10 [a]	≤ 10 [a]
Age (yrs)	18 - 75	≥ 18	≥ 18	≥ 18
Dose administration	3x/wk IV	3x/wk SC	3x/wk IV	3x/wk IV
Hemoglobin target				
Target 1	11.5 -13.0	10.7 - 12.7[a]	10.7 - 12.7 [a]	10.7 - 12.7 [a]
Target 2	9.5 - 11.0	-	-	-
Placebo	Yes	Yes	Yes	No
Hematopoietic endpoints	Hemoglobin	Hematocrit, blood transfusion		
Patient-reported outcome endpoints	KDQ, SIP, symptoms	Physical function & activity level, anemia symptoms, self-reported health status, sexual activity, sleep, eating behavior, well-being, satisfaction, happiness, work, and productivity		
Exercise endpoints	6-minute walk test, modified Naughton stress test	-	-	-
Patient-reported outcome assessment time points	Correction and maintenance: baseline, 2 mos, 4 mos, 6 mos	Correction: baseline, 12 wks Maintenance: 12 wks	Correction: baseline, 12 wks Maintenance: 12 wks	Correction: baseline, 12 wks Maintenance: 12 wks

[a] Hematocrit converted to hemoglobin concentration. Studies required hematocrit ≤ 30% and targeted hematocrit of 32% to 38%.

eGFR = estimated glomerular filtration rate; IV = intravenous; KDQ = Kidney Disease Questionnaire; SC = subcutaneous; SIP = Sickness Impact Profile

The instruments used to assess the patient-reported outcomes are summarized in Table 2 and the KDQ is described in Appendix 3.

Table 2. Summary of Instruments Used in the Randomized, Double-blind, Placebo-controlled Trials to Support the Retained Patient-reported Outcome Claims

Study	Functional Ability/ Physical Function	Tiredness/ Lack of Energy	Weakness	Shortness of Breath	Exercise Capacity
EP86-004	KDQ Physical[a] SIP	KDQ Fatigue[a]	Patient-generated[a]	Patient-generated[b]	Exercise Stress[a]
	Physical[a]	Patient-generated[a]			6-minute Walk[b]
	Body care movement[a]				
	Home maintenance[a]				
	Ambulation[a]				
8904	Karnofsky (PRO)[b]	NKDKTS item[a] Single item PRO[a] NHP Energy scale[b]	NKDKTS item[a] Single item PRO[a]	NKDKTS item[b]	
8701	Karnofsky (PRO)[c]	NKDKTS item[b] Single item PRO[b] NHP Energy scale[b]	NKDKTS item[b] Single item PRO[b]	NKDKTS item[b]	

[a] Statistically significant improvement in treated arms versus placebo
[b] Numerical improvements in treated arm(s) versus placebo
[c] Not significant and no numerical improvement
KDQ = Kidney Disease Questionnaire; NHP = Nottingham Health Profile; NKDKTS = National Kidney Dialysis and Kidney Transplantation Study; PRO = patient-reported outcome; SIP = Sickness Impact Profile

Amgen examined published anemia symptoms from physician organizations, including government, professional, hospital, and patient groups, to determine which symptoms physicians attribute to anemia. As shown in Table 3, the 4 widely agreed-upon symptoms of anemia are tiredness/decreased energy/fatigue, shortness of breath, dizziness/light-headedness, and weakness.

Table 3. Anemia Symptoms as Defined by Major Physician and Renal Organizations

	Leading physician and renal organizations			
	NHLBI	NKF	Mayo Clinic	RSN
Tiredness/Decreased energy/Fatigue	X	X	X	X
Shortness of breath	X	X	X	X
Dizziness/lightheadedness	X	X	X	X
Weakness	X		X	X

NHLBI = US National Heart, Lung and Blood Institute; NKF = National Kidney Foundation; RSN = Renal Support Network

Energy

Epoetin alfa therapy improved energy in dialysis subjects, when assessed using multiple validated measures in all 3 randomized, double-blind, placebo-controlled clinical trials (Table 2); results are summarized in Appendix Table 2 and Appendix Table 3. In Ortho Study EP86-004, there was a statistically significant improvement (indicated by higher values) in KDQ Fatigue Scale scores and Fatigue Symptom scores in the combined treatment groups compared to the placebo group ($p < 0.001$). In Amgen Study 8904, there were statistically significant differences between groups for the NKDKTS Energy item ($p = 0.006$) and single item patient-reported outcome ($p < 0.001$). The results were numerically consistent in Amgen Study 8701, but were not statistically significant. Although post-hoc statistical testing could not be performed for the NHP Energy scale, scores on the NHP Energy scale indicated a 50% improvement in Epoetin-alfa treated subjects compared to placebo in Amgen Study 8904, and a 30% improvement in Amgen Study 8701.

In addition to these 3 clinical trials, 5 open-label, single- or double-arm trials in the literature measured energy in dialysis patients (Appendix Table 4). Each of these trials reported statistically significant improvements in energy from baseline to follow-up in subjects treated with Epoetin alfa.

Weakness

Epoetin alfa therapy decreased weakness in dialysis subjects, when assessed using multiple validated measures in all 3 randomized, double-blind, placebo-controlled clinical trials (Table 2); results are summarized in Appendix Table 2 and Appendix Table 3.
In Ortho Study EP86-004, there was a statistically significant improvement in the Decreased Strength symptom scores in the treatment groups compared to the placebo group ($p < 0.001$). In Amgen Study 8904, there were statistically significant differences between groups for the NKDKTS Weakness/Lack of strength item ($p = 0.01$) and single item Muscle Weakness patient-reported outcome ($p = 0.001$). The results were numerically consistent in Amgen Study 8701, but were not statistically significant.
In addition to these 3 clinical trials, one open-label, single-arm trial (Harris et al, 1991) reported a statistically significant improvement ($p < 0.01$) in weakness from baseline to follow-up in subjects treated with Epoetin alfa.

Shortness of Breath

Epoetin alfa therapy improved shortness of breath in dialysis subjects, when assessed using multiple validated measures in all 3 randomized, double-blind, placebo-controlled clinical trials (Table 2); results are summarized in Appendix Table 2 and Appendix Table 3. In Ortho Study EP86-004, there was a numerical improvement in shortness of breath in all groups relative to baseline, but the effect was not statistically significant. It should be noted that the effect size for shortness of breath was equivalent to or larger than the effect observed for weakness and energy in this trial; however, the sample size was smaller for evaluating shortness of breath than for those 2 endpoints. In Amgen Studies 8904 and 8701, shortness of breath was measured using the NKDKTS Symptom Checklist and the results were directionally consistent with the improvements shown in Ortho Study EP86-004. In addition to these 3 clinical trials, one open-label, single-arm trial (Harris et al, 1991) reported a statistically significant improvement in dyspnea from baseline to follow-up in subjects treated with Epoetin alfa ($p < 0.01$).

Functional Ability and Activity Level; Physical Function

Epoetin alfa therapy improved physical function and functional ability in dialysis subjects, when assessed using multiple validated measures in all 3 randomized, double-blind, placebo-controlled clinical trials (Table 2); results are summarized in Appendix Table 2 and Appendix Table 3. In Ortho Study EP86-004, there were statistically significant improvements in the KDQ Physical Symptoms scores and the SIP Physical Function scale ($p < 0.001$; $p = 0.005$) in the combined treatment groups compared to the placebo group. There were also statistically significant improvements in all of the remaining SIP scales (Body Care Movement; Home Maintenance; and Ambulation). In Amgen Studies 8904 and 8701, Functional Ability was measured using the patient-reported Karnofsky Performance Scale. In Study 8904, numerical improvement in the Karnofsky patient-reported outcome favored the treatment group compared to placebo for the Karnofsky patient-reported outcome. No difference was observed between groups in Study 8701.

In addition to these 3 clinical trials, 15 open label, single- or double-arm trials in the literature measured Functional Ability or Physical Function in CRF patients (Appendix Table 5). Statistically significant improvements in Functional Ability or

Physical Function from baseline to follow-up in subjects treated with Epoetin alfa were observed in 13 of 17 analyses from these trials.

Exercise Capacity

In addition to functional ability, exercise capacity was assessed through standardized measures. The most commonly used exercise capacity measures are VO_2 max, exercise stress test (maximal exercise test), and the 6-minute walk test. VO_2 max measures the maximum amount of oxygen in milliliters that can be consumed in one minute per kilogram of body weight. The exercise stress test measures the maximum number of minutes exercised on a treadmill or stationary bicycle under changing conditions that include speed and incline. The 6-minute walk test evaluates the distance (in meters) covered in 6 minutes.

In Ortho 8604, exercise capacity was assessed using an exercise stress test and a 6-minute walk test. As shown in Appendix Table 2, a statistically significant improvement in minutes walked was observed in the treatment groups compared to the placebo group ($p < 0.05$). Although there was a numerical improvement in distance walked in the 6-minute walk test, the effect was not statistically significant.

In addition to this randomized, double-blind, placebo-controlled trial, 9 open-label, single-arm clinical trials in the literature measured exercise capacity using VO_2 max (7 trials), exercise time (5 trials) and/or 6-minute walk distance (1 trial). In the 13 analyses from these trials, statistically significant improvements in exercise capacity were observed from baseline to follow-up in subjects treated with Epoetin alfa (Appendix Table 6). Minimally important improvements in exercise capacity were observed in 11 of 13 analyses in which minimally important differences could be assessed.

3.3.1.3 Summary

The results from 3 randomized, double-blind, placebo-controlled clinical trials and published literature support the numerical or statistically significant improvements in physician-assessed and patient-reported outcomes and exercise capacity in dialysis subjects treated with Epoetin alfa relative to those administered placebo. Statistically significant differences or numerical improvements in physician-assessed and patient-reported outcomes were observed in 3 randomized, double-blind, placebo-controlled trials with Epoetin alfa (Ortho Study EP86-004 and Amgen Studies 8904 and 8701). These results were attained using several different patient-reported

outcomes measures that appear to be adequately validated in this population. The results were of sufficient magnitude to be clinically meaningful by standard criteria.

For Ortho Study EP86-004, all measures for energy, weakness, physical function, and exercise stress show statistically significant improvements in treated subjects compared with placebo. Numerical improvements in shortness of breath and 6-minute walk favored treatment over placebo.

In Amgen Studies 8701 and 8904, all scores for energy, weakness, and shortness of breath favored treatment with Epoetin alfa. In Amgen Study 8904, measures of energy and weakness were statistically significant. A numerical improvement in the Karnofsky Performance Status Instrument, administered as a patient-reported outcome, was observed among treated subjects in Study 8904, with no differences in Study 8701.

In addition, published clinical trials measuring physical function, exercise capacity, energy, or weakness have shown improvements associated with Epoetin alfa treatment. In 31 of 37 analyses, the results were statistically significant.

Chronic renal failure requiring dialysis is a debilitating illness. Before the introduction of ESA therapy, anemia was a universal complication and contributed greatly to the inability of dialysis patients to maintain a functional lifestyle. Data and clinical experience over 18 years of use provide strong evidence for the beneficial impact of ESA therapy on patients symptoms and functional ability. Therefore, physician-assessed and patient-reported outcomes claims for functional ability, energy, muscle weakness, shortness of breath, and exercise capacity should be retained in the Epoetin alfa label for dialysis patients.

3.3.2 Nondialysis Patients

Due to the interest of the nephrology community and regulatory authorities in health-related quality of life, a summary of the current physician-assessed and patient-reported outcomes in nondialysis subjects is also provided. Ten clinical trials in anemic, nondialysis CRF subjects treated with Epoetin alfa or epoetin beta were identified in which physician-assessed and patient-reported outcomes were evaluated. Result of these clinical trials are summarized in Appendix Table 7.

Two of the trials (The US Recombinant Human EPO Group, 1991; Kleinman et al, 1989) used a double-blind, randomized, placebo-control design and were included in the original registration application. G86-011, a study conducted in collaboration with the US Recombinant Human Erythropoietin Group, randomized 117 subjects to 1 of

3 Epoetin alfa groups or placebo. Study duration was 8 weeks. A questionnaire was used to collect measurements of patient-reported energy and work capacity. More subjects in the Epoetin-alfa treated groups reported increased energy or work capacity compared with those in the placebo group. In addition, overall quality of life as measured by visual analogue scale was statistically significantly improved with Epoetin alfa treatment compared with placebo in a small (N = 14), 12-week study (Kleinman et al, 1989).

The remaining 8 trials used open-label designs. Three of the trials (Rossert et al, 2006; Provenzano et al, 2004; Revicki et al, 1995) evaluated the relationship between hematocrit and patient-reported outcomes; correlations ranged from r = 0.15 to 0.45, reflecting small to moderate associations between increased hematocrit and improvements in patient-reported outcomes. Three of the trials (Benz et al, 2007; Singh et al, 2006; Provenzano et al, 2004) were recent J&JPRD-sponsored studies with available databases that evaluated quality of life using Linear Analogue Self Assessment, KDQ, and SF-36. The analysis of the latter 3 trials used an accepted definition for a clinically meaningful difference in patient-reported outcome in chronic disease of approximately 50% of the standard deviation of scores at baseline (Norman et al, 2003). Clinically relevant differences in the context of anemia correction with Epoetin alfa were identified for energy, activity, physical symptoms, fatigue, depression, relationship, and vitality (Appendix Table 7).

This literature review for health-related quality of life in nondialysis CRF patients provides further evidence of the beneficial impact of ESA therapy on physician-assessed and patient-reported outcomes in patients with CRF.

4. RISKS OF ESA THERAPY IN PATIENTS WITH CRF

4.1 Key Points

- Risks of ESA therapy in patients with CRF include:
    - increased mortality and serious cardiovascular and thromboembolic events when targeting higher-than-approved hemoglobin concentrations
    - hypertension
    - seizure
    - serious allergic reactions
    - antibody-mediated PRCA
- Each of these risks are prominently communicated, with the first risk included in a boxed Warning, in the current prescribing information for Epoetin alfa (EPOGEN®/PROCRIT®) and darbepoetin alfa (Aranesp®).

Although Epoetin alfa (EPOGEN®/PROCRIT®) and darbepoetin alfa (Aranesp®) are associated with important improvements in transfusion requirements and both physician-assessed and patient-reported outcomes, safety considerations have been well recognized. Since the introduction of Epoetin alfa in 1989, risks associated with ESA use in CRF patients have been prominently identified in the prescribing information for these products. Risks observed in clinical trials with ESAs include hypertension and seizures, which are contained in the Warnings section of the USPIs for these products. ESA use is contraindicated in patients with uncontrolled hypertension. Blood pressure may rise during treatment of anemia. Therefore, healthcare providers are advised to closely monitor and control blood pressure in patients administered ESAs. This may include initiation or intensification of antihypertensive therapy during the early phase of ESA treatment when the hemoglobin concentration is increasing, as well as ESA dose adjustment if blood pressure is difficult to control by pharmacologic or dietary measures.

To minimize the risk for seizures with ESA use, close monitoring of premonitory neurologic symptoms, as well as blood pressure, is recommended during the first several months of therapy. While the relationship between seizures and the rate of rise of hemoglobin is uncertain, dose reductions are recommended if the rate of rise for hemoglobin concentration exceeds 1.0 g/dL in any 2-week period.

Potentially serious allergic reactions associated with ESA use are rarely-reported events in clinical trials and postmarketing surveillance. Symptoms have recurred with rechallenge, suggesting a causal relationship in some cases. Permanent withholding of the ESA and appropriate treatment is recommended in these cases, according to the Precautions section of the ESA USPIs.

Cases of PRCA and of severe anemia, with or without other cytopenias, associated with neutralizing antibodies to erythropoietin have been reported through postmarketing surveillance in patients treated with all ESAs, including Epoetin alfa and darbepoetin alfa. These events are very rare and have been reported predominantly in patients with CRF receiving ESAs by subcutaneous administration, which may enhance immunogenicity. As a result, intravenous administration is preferred in patients receiving ESAs chronically for whom this route is feasible and appropriate. The reported incidence for antibody-mediated PRCA is < 1 per 100,000 patient-years of exposure to both Epoetin alfa (EPOGEN®/PROCRIT® brands) and darbepoetin alfa. Warnings for antibody-mediated PRCA are included in the USPIs for Epoetin alfa and darbepoetin alfa. Evaluation for the etiology of loss of effect, including the presence of neutralizing antibodies to erythropoietin, is recommended in any patient who develops a sudden loss of ESA response with severe anemia and low reticulocyte count. Erythropoiesis-stimulating agent dosing guidance and access to testing for anti-ESA antibodies is also provided in the USPIs.

Importantly, the Warnings section of the USPI for Epoetin alfa was initially revised in 1996 to include risk communication regarding the increased risk of mortality and cardiovascular/thromboembolic events observed when targeting hemoglobin concentrations > 12.0 g/dL. This revision was based upon data from the NHCT, a controlled clinical trial in dialysis patients (Besarab et al, 1998). In that trial, a greater incidence of mortality (183 vs 150 deaths) and nonfatal myocardial infarction (19 vs 14 events) (composite risk ratio [95% confidence interval (CI)]: 1.3 [0.9, 1.9]) and vascular access thrombosis (39% vs 29% of subjects; p = 0.001) were observed in subjects randomized to a normal hematocrit target (42% ± 3% [hemoglobin 14 ± 1 g/dL] compared with subjects randomized to a lower hematocrit target (30% ± 3% [hemoglobin 10 ± 1 g/dL]). This information was also included in the Warnings section of the original USPI for darbepoetin alfa in 2001.

In 2007, these risks were further emphasized, including the addition of a boxed Warning, in the USPIs for both Epoetin alfa and darbepoetin alfa (Appendix 5) when increased risks were observed in a recently reported clinical trial in nondialysis CRF patients (CHOIR) (Singh et al, 2006) and in other clinical settings. In the CHOIR study, a greater risk of composite cardiovascular events (death, myocardial infarction, hospitalization for congestive heart failure without renal replacement therapy, and stroke) was observed in subjects randomized to a hemoglobin target of 13.5 g/dL compared with those randomized to a hemoglobin target of 11.3 g/dL. Of note, the observed increased risks were associated with hemoglobin targets higher than that approved for use in CRF patients. Subsequently, several important questions have been asked regarding the clinical considerations for ESA dose optimization in patients with CRF, specifically with respect to the following:

- What hemoglobin target results in an optimal benefit: risk profile for ESAs?
- Do higher ESA doses and/or poor ESA response cause adverse clinical outcomes, including mortality?
- How should ESA responsiveness be defined and how should hypo-responsive patients be managed?

These questions are addressed in Section 5 and the NHCT and CHOIR study are discussed further in Sections 5.3.2 and 5.4.2.

In summary, ESA use in CRF patients is associated with specific and well-described risks that are primarily cardiovascular or immunologic in origin. These risks are generally mitigated when patient health status is closely monitored and ESAs are used with appropriate guidance not to exceed a hemoglobin target of 12.0 g/dL (eg, hypertension and other serious cardiovascular events) or are rare in frequency (eg, antibody-mediated PRCA). Thus, the benefit: risk profile for ESAs remains positive in patients with CRF. Furthermore, Amgen and J&JPRD continuously monitor reports of adverse events through global pharmacovigilance programs and update safety information provided in the USPIs, if indicated from analyses of these reports. Other aspects of the risk management plan for these products are described in Section 6.

5. CLINICAL CONSIDERATIONS FOR ESA THERAPY

5.1 Key Points

- Clinical practice data suggest no evidence of harm as a result of ESA therapy, compared with no treatment, for anemia in CRF patients. Furthermore, the mortality risk appears to be lower for CRF patients treated with ESAs compared with those not receiving an ESA.
- Achieved hemoglobin concentrations between 11.0 to 13.0 g/dL are associated with the lowest clinical risk in CRF patients.
- The use of a hemoglobin target range is appropriate to guide clinical practice, maximizing benefit and minimizing risk in these patients.
    - Evidence supports 12.0 g/dL as the upper end of the target range to provide a safety margin against higher hemoglobin targets (> 13.0 g/dL).
    - The preponderance of available evidence supports 11.0 g/dL as the lower end of the target range. Given the lack of definitive data and limited feasibility to delineate between narrow hemoglobin targets, it may be reasonable to consider a lower boundary. Amgen and J&JPRD believe the lower boundary of the target should not be less than 10.0 g/dL.
- The relationship between ESA dose and clinical outcomes is confounded because ESA dose is dependent on 2 key factors:
    - the targeted hemoglobin level, and
    - the ability of an individual patient to generate a hematopoietic response to ESA therapy.
- Patients with poor responsiveness to ESA therapy:
    - appear to have a greater underlying burden of illness and, therefore, a greater inherent risk of mortality and cardiovascular morbidity; and
    - require higher ESA doses to reach any given hemoglobin target.
- Because ESA responsiveness reflects underlying patient health status, it is a better indicator of clinical risk than ESA dose alone.
- Iron treatment is commonly used with ESA therapy. Because iron utilization has been associated with an increased risk of infection and cardiovascular events in dialysis patients, further consideration of iron and its impact on morbidity and mortality in ESA-treated patients is warranted.

- Amgen and J&JPRD believe that the area of hypo-responsiveness to ESAs warrants further evaluation. At the joint Advisory Committee meeting, Amgen and J&JPRD will present the results of ongoing analyses to facilitate discussion regarding an appropriate definition of hypo-responsiveness, as well as trial design options to evaluate appropriate ESA treatment for hypo-responsive patients.

To thoroughly investigate the safety profile of ESAs in patients with CRF, Amgen and J&JPRD have explored the association between ESA therapy and the risks for mortality and cardiovascular morbidity using observational data from a variety of sources. In addition, we investigated the complex relationships between achieved hemoglobin concentrations, hemoglobin targets, ESA dose and response, and clinical outcomes by conducting analyses of NHCT and CHOIR, pooled clinical trials, relevant observational data, and published literature regarding ESA therapy in patients with CRF. There are several general strengths to this approach. Data from a wide variety of sources have been used, including comprehensive resources providing patient-level data with more than 50,000 person-years of follow-up. Analyses have been performed on multiple datasets using a variety of analysis methods to examine the relationship of ESA dose and its effect on outcome. As such, results from the various analyses should be viewed in the larger context as a body of evidence addressing the use of ESA in the nephrology setting.

Nonetheless, there are also several limitations to these analyses. The majority of the Amgen-sponsored and J&JPRD-sponsored clinical trials were not designed to assess the relationship between hemoglobin target or ESA dose/responsiveness and mortality or cardiovascular morbidity. As such, these clinical trial data, as well as the observational data, were evaluated retrospectively using standard and accepted techniques for analysis of observational cohort data. These analyses, however, may be subject to uncontrolled bias. For example, confounding-by-indication is always a potential concern when evaluating drug treatment effects in analyses with non-randomized treatment groups. In addition, studies of relationships between ESA dose, achieved hemoglobin and clinical outcomes may be confounded by a patient's ability to generate a hematopoietic response to ESA therapy. This is discussed in detail in Section 5.4. Although causal effects cannot be conclusively proven by these analyses, a wide variety of known prognostic indicators have been accounted for and a

number of analytic approaches have been used to describe relationships with a high degree of accuracy and validity.

Amgen and J&JPRD believe that these are relevant, appropriate, and comprehensive analyses to characterize the important relationships between clinical outcomes and ESA use and dose, achieved and target hemoglobin, and response to ESA therapy. These results will be central in providing further guidance on optimal treatment paradigms for risk management in CRF patients and identifying conditions that may require heightened awareness by healthcare providers.

5.2 ESA Use and Mortality/Cardiovascular Morbidity

Epoetin alfa and darbepoetin alfa were developed and approved as supportive therapies to alleviate the symptoms of anemia and to reduce the need for transfusions in patients with CRF, including those receiving and not receiving dialysis. As such, the clinical trials supporting the approval of these ESAs for use in CRF patients were not designed as survival trials. However, the impact of anemia correction by ESAs on mortality and cardiovascular morbidity has been an area of interest for the clinical community due to evidence that anemia is an independent risk factor for increased mortality, cardiovascular morbidity, and hospitalization in CRF patients (Astor et al, 2006; Collins, 2003; McClellan et al, 2002; Al-Ahmad et al, 2001; Holland and Lam, 2000; Foley et al, 1996; Foley et al, 1995; Greaves et al, 1994).

5.2.1 Dialysis Patients

Currently, 93% of dialysis patients in the US are administered an ESA to treat anemia (Regidor et al, 2006). Conducting placebo-controlled clinical trials to assess the impact of ESA therapy on mortality and cardiovascular morbidity has presented ethical and feasibility challenges in dialysis patients since the early 1990's, given the widespread use of ESAs and the lack of clinical equipoise. Consequently, randomized, placebo-controlled clinical trials to evaluate the impact of ESA therapy on survival and cardiovascular events cannot be conducted in dialysis patients. This is not a unique situation. For example, placebo-controlled trials evaluating the impact of diuretic use on mortality in patients with acute decompensated heart failure patients have not been done due to ethical considerations and the perceived lack of clinical equipoise.

Given this limitation, the impact of ESA therapy on clinical outcomes has been assessed using data from several well-recognized sources that capture treatment, anemia outcomes, and clinical outcome data on CRF patients (eg, large automated claims and

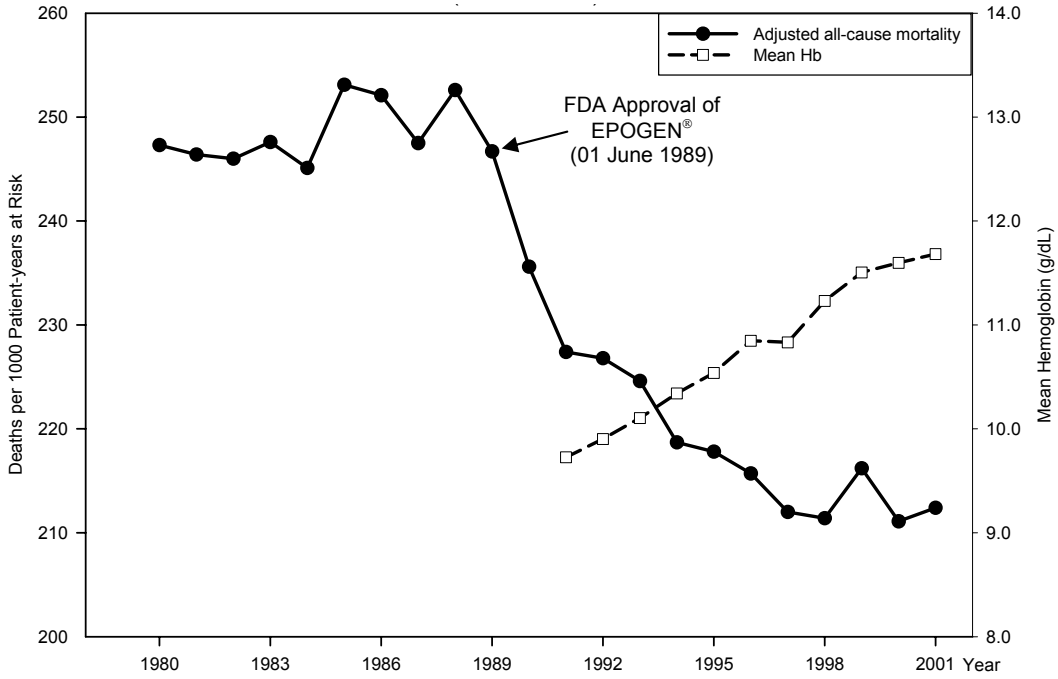
major dialysis provider databases). These sources allow analyses of product exposure and patient outcomes and are consistent with the March 2005 FDA Guidance on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. For instance, the United States Renal Data System (USRDS) is a National Institutes of Health-supported system that has collected, analyzed, and annually distributed data (including individual ESA doses and hemoglobin concentrations), from the US ESRD program. This program began in 1972 with the granting of Medicare coverage to ESRD patients as a central public health initiative and covers approximately 90% of the US dialysis patient population. The USRDS and other medical databases have afforded a unique opportunity for examining clinical outcomes and practice patterns in this large patient population over time. Moreover, these data facilitate large-scale, population-based pharmacovigilance and may be interpreted as additional evidence regarding the clinical impact of ESA therapy in this patient population.

Although observational data cannot conclusively demonstrate causality between ESA therapy and clinical outcomes, these data sources are valuable for informing a number of issues because:

- the sample sizes are considerably larger with longer patient follow-up than those available in other patient populations, thus ensuring a greater number of events (particularly for infrequent events);
- the patients included in these datasets are representative of the general dialysis patient populations;
- ESA dosing reflects general clinical practice; and
- the data routinely include extensive information on confounding factors and clinical outcomes (particularly mortality).

Data from the USRDS indicate that the widespread adoption of Epoetin alfa was associated with an increase in hemoglobin concentration and a marked decline in adjusted all-cause mortality rates in dialysis patients (Figure 4). These data do not provide definitive evidence of a survival benefit from ESA therapy since they do not account for the impact of concurrent advances in both dialysis care and medical therapy for this patient population.

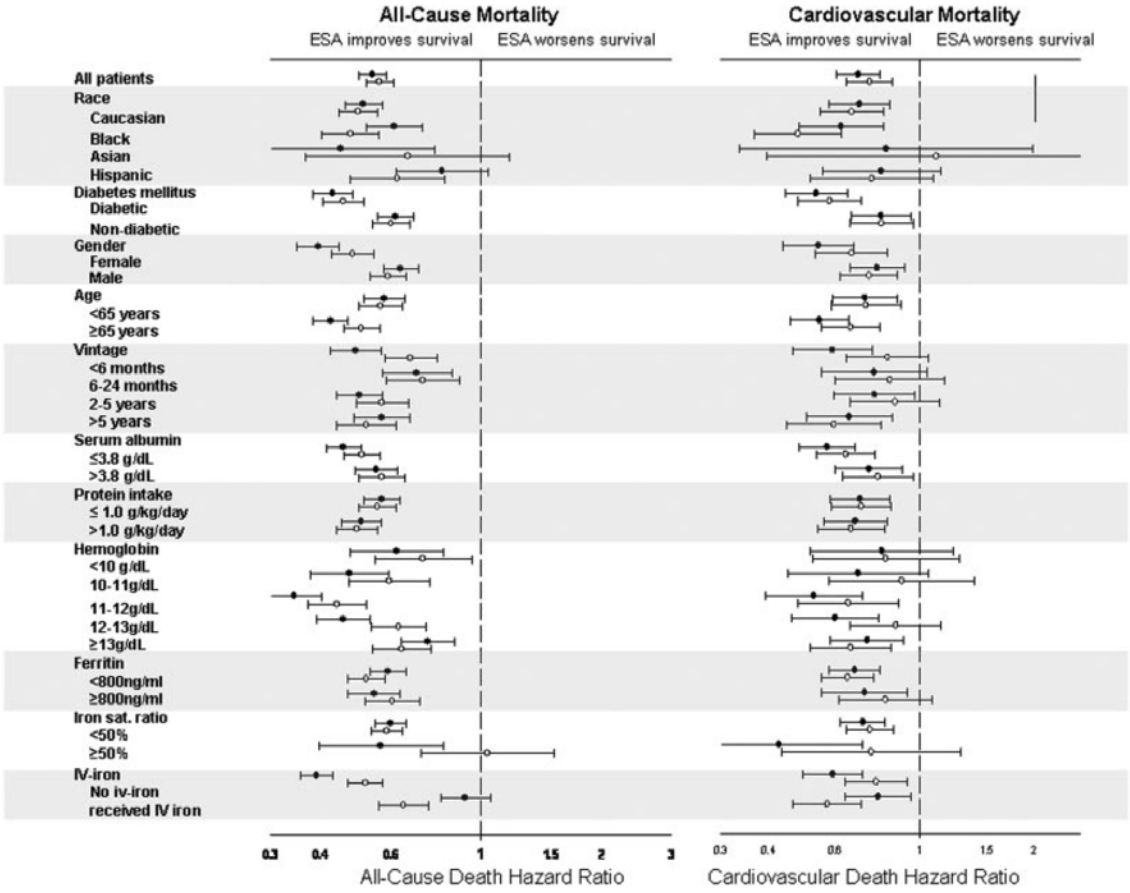
Figure 4. Adjusted All-cause Mortality Rate and Mean Hemoglobin Concentration by Year
(Prevalent Dialysis Patients - USRDS)



Data Source: 2003 USRDS ADR
1. Adjusted all-cause mortality rate is from Table H3: Reference cohort is 2001 prevalent ESRD patients. Overall mortality rates are adjusted for age, gender, race, & primary diagnosis. Includes all patients who have reached day 91 of ESRD by December 31 of each calendar year. Patient age is determined on January 1 of each calendar year.
2. Mean Hb of period prevalent dialysis patients with EPO claims is from worksheet 5.10 in 05 clin ind 03 for web.xls. December of each year are presented.
Graph: \\Filesrv04\Stat\esp\ckd\docs\USRDS\adhoc_20070618\AdjMortality_Hb.doc

The association between ESA use and mortality has been further explored in various analyses. For example, in a 2-year historical cohort of approximately 60,000 maintenance hemodialysis patients, ESA therapy was associated with a lower risk of death compared to no ESA treatment, regardless of dose, measured demographic characteristics, laboratory parameters, or length of time on dialysis (Figure 5; Regidor et al, 2006).

Figure 5. Association between ESA Use and Relative Risk for All Cause and Cardiovascular Mortality in Hemodialysis Patients (DaVita, Inc, N = 58,058)



Closed circles, unadjusted death hazard ratios; error bars = 95% CIs
Open circles, fully multivariate (case mix and malnutrition-inflammation complex syndrome) adjusted death hazard ratios.
Source: Regidor et al, 2006

Similar findings were observed in a 1-year observational study of Italian dialysis patients (N = 5302) (Locatelli et al, 1998). The incidence of all-cause mortality was lower for ESA-treated patients (11.1%) compared with those not receiving ESA therapy (15.2%) (unadjusted odds ratio: 0.70). After adjustment for known risk factors (eg, age, gender, comorbid conditions, and baseline hematocrit level), the estimated risk for all-cause mortality was 35% lower for ESA-treated patients (adjusted odds ratio [95% CI]: 0.65 [0.52, 0.81]). The estimated risk for cardiovascular mortality was also lower for ESA-treated patients (adjusted odds ratio [95% CI]: 0.61 [0.43, 0.86]).

A positive association between anemia management and survival was also observed in a study across 2858 dialysis facilities in the US (Wolfe et al, 2005). The results of this study indicate that facilities with the largest improvements in both anemia management (ie, percentage of patients with hematocrit ≥ 33% [hemoglobin ≥ 11.0 g/dL]) and dialysis adequacy over time achieved an average reduction in mortality of > 12% over the 4 years studied. Importantly, improvements in anemia management were consistently associated with improvements in mortality, regardless of the degree of change in dialysis adequacy.

In summary, data from observational studies suggest that ESA therapy is associated with better clinical outcomes compared with no ESA treatment in dialysis patients. Although these results do not provide conclusive evidence of a survival benefit, placebo-controlled trials in this population are not feasible or ethical given the lack of clinical equipoise.

5.2.2 Nondialysis Patients

Similar to the dialysis population, performing rigorous, placebo-controlled trials in nondialysis CRF patients has been challenging due to the perceived lack of clinical equipoise. Nevertheless, understanding the potential impact of anemia management with ESAs on mortality and cardiovascular morbidity is also relevant in nondialysis CRF patients. In the clinic, anemia management with ESAs in nondialysis CRF patients is associated with reduced hospitalization after the initiation of dialysis therapy (median days 2 vs 3; p = 0.019) (Zawadzki et al, 2003). Published analyses of observational data also suggest that CRF patients treated with ESAs before dialysis initiation have better outcomes after they progress to dialysis compared with patients who did not receive ESA therapy (Table 4).

Table 4. Mortality Risk for CRF Patients Receiving ESA Therapy Before Initiation of Dialysis Compared with No ESA Therapy

Patient population (N)	Hazard ratio (95% CI)	Citation
Medicare patients ≥ 67 years (109,321)	0.86 (0.82, 0.92) with inconsistent ESA use[a] 0.76 (0.72, 0.80) with consistent ESA use[a]	Khan et al, 2005
Medicare patients ≥ 18 years (12,085)	0.73 (0.66, 0.80) at 1 year post-dialysis 0.87 (0.82, 0.92) at 7 years post-dialysis	Lu et al, 2005

[a] relative risk in first year after dialysis initiation; adjusted for Charleson Comorbidity Index.
Inconsistent ESA use was defined as treatment for less than half or up to two-thirds of the months between the start of ESA treatment and dialysis initiation for those patients who began ESA therapy ≥ or < 3 months before dialysis initiation, respectively.
Consistent use was defined as treatment for more than half or all of the months between the start of ESA treatment and dialysis initiation for those patients who began ESA therapy ≥ or < 3 months before dialysis initiation, respectively.

Furthermore, a survey of patients with CRF in Europe found that patients treated with an ESA had significantly lower incidences of heart failure (20% vs 24%, $p < 0.05$) and ischemic heart disease (17% vs 21%, $p < 0.05$) in the year before initiating dialysis compared with those not receiving an ESA (Valderrábano et al, 2003). Similar results were also observed when event rates were assessed within the month before dialysis was initiated (heart failure 20% vs 23%, $p < 0.05$; ischemic heart disease 12% vs 16%, $p < 0.001$).

The association between ESA use and cardiovascular events in nondialysis CRF patients with diagnosed anemia was also examined within a large healthcare insurance database (Ingenix) by Amgen; methods are provided in Appendix 4. Briefly, Cox proportional hazards regression was used to estimate the hazard ratio (95% CI) for the association between ESA use (yes vs no and duration) during a 6-month entry period and the risk of myocardial infarction or stroke during a 1-year follow-up period. A similar risk of cardiovascular events was observed for patients receiving ESA therapy compared with those not receiving an ESA (Table 5). Also, no association was observed between the duration of ESA use and cardiovascular events.

Table 5. Hazard Ratios (95% CIs) for Associations Between ESA Use, Duration of ESA Administration and Risk of All-Cause Cardiovascular Events (Ingenix Database; N = 4752)

	Counts		Unadjusted		Full adjustment†	
Exposure variable	Event	No event	HR	95% CI	HR	95% CI
Ever used						
No	200	3950	1.0	--	1.0	--
Yes	25	577	0.91	0.60-1.37	0.84	0.54-1.31
Months on ESA						
None	200	3950	1.0	--	1.0	--
1-3	17	402	0.90	0.55-1.47	0.80	0.48-1.34
4-6	8	175	0.93	0.46-1.88	0.96	0.46-1.99
Months on ESA						
Per 1 month ESA admin	225	4527	0.98	0.86-1.11	0.97	0.84-1.11

† Adjusted for age, sex, Modification of Diet in Renal Disease estimated glomerular filtration rate , cardiologist visit, nephrologist visit, hematologist visit, chronic obstructive pulmonary disease, heart failure, atherosclerotic heart disease, treated diabetes, treated hypertension, treated hyperlipidemia, number of hospitalizations, peripheral vascular disease, and treatment with alpha blockers, treatment with angiotensin-converting enzyme inhibitors, treatment with angiotensin II receptor blockers, treatment with calcium- channel blockers, and treatments with loop diuretics
Source: \\filesrv04\epi\projects\epidemiology\p07_035_cwc\repository\Project_2.04\ESA use and CV events overall

In summary, although no clinical trial data directly address the impact of ESA therapy on mortality in nondialysis CRF patients, data from a variety of sources suggest that treatment with ESAs before initiation of dialysis, compared with no ESA therapy, is associated with a lower mortality risk after progression to ESRD. In addition, no negative association was observed between ESA therapy or duration of ESA use and cardiovascular events compared with no treatment with ESAs.

Amgen is currently conducting a large (N = 4000), randomized, placebo-controlled, double-blind trial (TREAT) to assess whether treatment of anemia with darbepoetin alfa compared with no treatment decreases mortality and cardiovascular morbidity in anemic, nondialysis subjects with CRF and type 2 diabetes. This study is included in the risk management plan, which is described in Section 6.

5.3 Recommended Hemoglobin Target For ESA Therapy In Patients With CRF

The use of a therapeutic target to guide dosing algorithms is inherent to the clinical practice of anemia management in CRF, as it is in the management of blood pressure in hypertension and hemoglobin A1c in diabetes mellitus. In the treatment of anemia with

ESAs, the objectives are transfusion avoidance, reduction in anemia symptoms and sequelae, and minimizing the risk for ESA-related adverse outcomes. These objectives are accomplished by adjusting the ESA dose to achieve and maintain hemoglobin levels within a target.

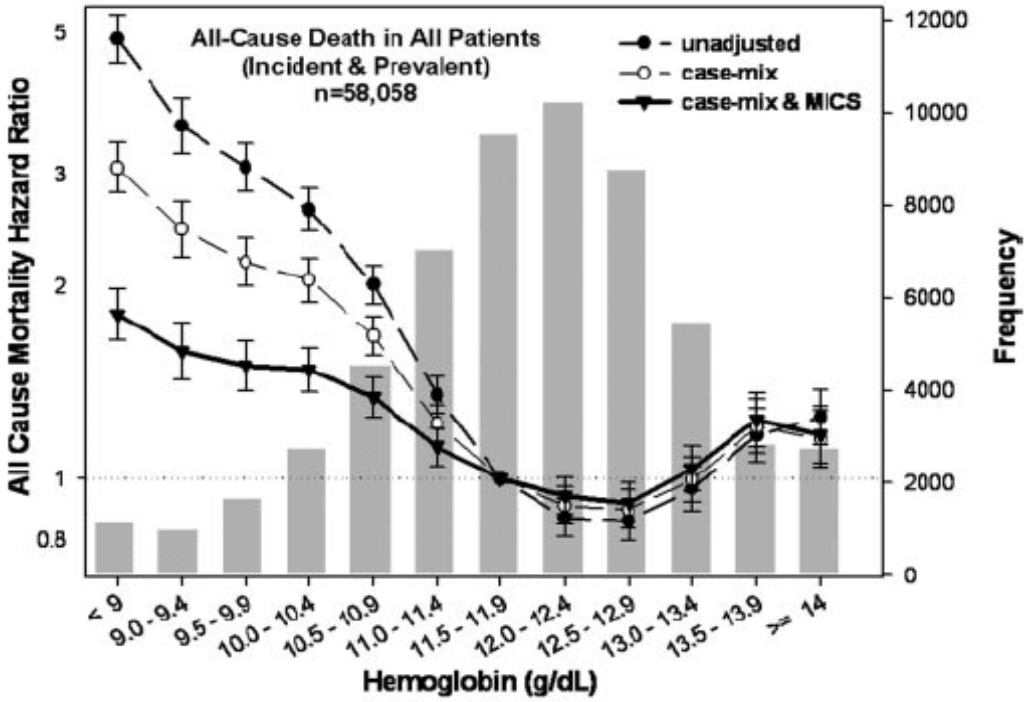
The March 2007 revisions to the ESA USPIs, which replaced the concept of a target hemoglobin with the instruction to utilize ESA therapy to avoid transfusion, have had the unintended consequence of confusing physicians and other healthcare providers and potentially placing patients at risk for clinical sequelae of severe anemia (American Association of Kidney Patients, 2007; Hartwell, 2007; Renal Physicians Association, 2007). These consequences were acknowledged in a recent review of hemoglobin targets for ESA therapy (Fishbane and Nissenson, 2007). The authors noted that the current USPI language may imply a hemoglobin target of 10.0 g/dL for ESA therapy, since few physicians would recommend transfusion above that level unless a patient was symptomatic or had significant cardiopulmonary compromise. As discussed below, this target is below the range of hemoglobin concentrations associated with optimal clinical benefit and low risk for adverse clinical outcomes.

5.3.1 Achieved Hemoglobin Concentrations and Clinical Outcomes in Patients with CRF

The goal of ESA therapy is to achieve and maintain a hemoglobin level that results in an optimal benefit: risk profile for individual patients. Achievement and maintenance of hemoglobin concentrations between approximately 11.0 and 13.0 g/dL resulted in clinical benefits of transfusion independence, improved physician-assessed and patient-reported outcomes, and increased exercise capacity in the Epoetin alfa registration clinical trials (Section 3).

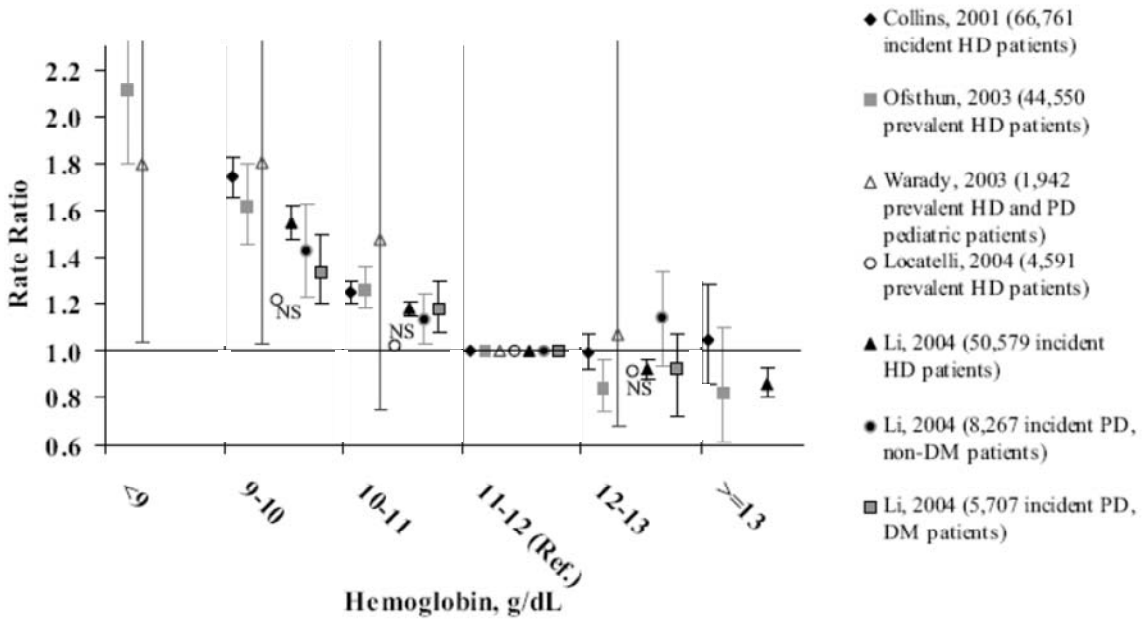
Observational studies of dialysis patients have consistently shown that patients who achieve a hemoglobin level between 11.0 and 13.0 g/dL have a lower risk for death (Figure 6 and Figure 7) and improved clinical outcomes (Table 6) compared with patients with achieved hemoglobin concentrations < 11.0 g/dL. Furthermore, results from analyses of pooled clinical trials sponsored by either Amgen or J&JPRD show a lower risk for mortality and cardiovascular events with higher achieved hemoglobin concentrations (Appendix 2).

Figure 6. Association Between Time-varying Blood Hemoglobin Values and the Relative Risk for All-cause Death in Prevalent Hemodialysis Patients



Unadjusted models included hemoglobin as the predicting variable and quarter of entry into the database as a covariate.
Case mix-adjusted models included additional covariates of age; gender; race and ethnicity; diabetes; vintage; catheter as dialysis access; primary insurance; marriage status; standardized mortality ratio of the dialysis clinic during entry quarter; continuous values of Kt/V, serum ferritin, and serum iron saturation ratio; administered doses of each of the 3 intravenous iron medications, vitamin D analogs, and ESA within each calendar quarter; and comorbid states and smoking status at baseline.
Case mix- and malnutrition inflammation complex syndrome (MICS)-adjusted models included all of the case-mix covariates plus 12 indicators of nutritional status and inflammation, including the time-varying body mass index, and 11 time-varying laboratory values as surrogates of MICS (serum iron saturation ratio, serum ferritin, serum albumin, normalized protein, nitrogen appearance or normalized protein catabolic rate, serum total iron binding capacity, serum creatinine; serum phosphorus, serum calcium, serum bicarbonate, peripheral white blood cell count, and lymphocyte percentage).
error bars = 95% CIs
Source: Regidor et al, 2006

Figure 7. Relationship Between Achieved Hemoglobin Level and Mortality in Dialysis Patients: Observational Studies With Reference Group 11.0 to 12.0 g/dL



error bars = 95% CIs
Source: Volkova and Arab, 2006

Table 6. Patient Outcomes With Hemoglobin Levels ≥ 11.0 g/dL Compared with < 11.0 g/dL

Outcome	Reference
7% to 22% at lower risk for hospitalization	Collins et al, 2001; Xia et al, 1999
4% to 25% lower relative risk for death	Collins et al, 2001; Collins et al, 1998; Ma et al, 1999
6% to 14% lower Medicare expenditures	Collins et al, 2001; Collins et al, 2000
18% improved Sickness Impact Profile	Moreno et al, 2000
4% improvement in the Karnofsky scale	Moreno et al, 2000
8% greater peak exercise capacity	McMahon et al, 1999
18% greater maximum oxygen consumption	McMahon et al, 1999

Source: Modified from Lacson et al, 2003

To investigate whether patient characteristics, including cardiovascular risk factors, change the optimal achieved hemoglobin range (11.0 to 13.0 g/dL), the association between hemoglobin and mortality risk was examined for patients stratified by these characteristics. Data from a cohort of approximately 40,000 hemodialysis patients from a large dialysis provider database (Fresenius Medical Care-North America [FMC-NA])

was analyzed using Cox proportional hazards modeling; methods are provided in Appendix 4.

The results of this analysis indicate that a higher achieved hemoglobin concentration is consistently associated with a lower mortality rate, regardless of the baseline patient characteristic assessed (Appendix Figure 1 to Appendix Figure 10). For each baseline characteristic category, the lowest mortality risk was observed with achieved hemoglobin concentrations > 11.0 g/dL, although the data were limited at hemoglobin concentrations > 13.0 g/dL.

In summary, achieved hemoglobin concentrations between 11.0 and 13.0 g/dL appear to result in optimal benefit: risk profile for patients with CRF. Stratified analyses of observational data show that the association between hemoglobin concentration and clinical outcomes is not influenced by patient characteristics, including the cardiovascular risk factors of age, gender, and diabetes, and support the contention that optimal hemoglobin targets are not different among patients based upon these characteristics. It is important to note, however, that target and achieved hemoglobin concentrations are not equivalent and the ability of a patient to achieve a specific hemoglobin level is dependent upon their health status. Therefore, the results observed for achieved hemoglobin concentrations can be informative, but not definitive, for determining the optimal hemoglobin target.

5.3.2 High Hemoglobin Targets in Patients with CRF

The original registration clinical trials for Epoetin alfa demonstrated a clinical benefit in dialysis subjects with partial correction of anemia using a target range of approximately 11.0 to 13.0 g/dL. Following these trials, several studies specifically tested the hypothesis that correction of anemia with an ESA to higher target hemoglobin levels (> 13.0 g/dL) would lead to improved clinical outcomes compared with partial anemia correction. Most notably, these studies included 2 trials in dialysis subjects (NHCT [Besarab et al, 1998] and J&JPRD Study EPO-INT-68 [Parfrey et al, 2005]) and 2 trials in nondialysis CRF patients (Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta [CREATE] [Drüeke et al, 2006] and CHOIR [Singh et al, 2006]). These 4 trials are summarized in Table 7.

An increased risk for adverse clinical outcomes with higher hemoglobin target was not observed in the EPO-INT-68, another study in dialysis subjects (Foley et al, 2000), and several small studies in nondialysis CRF subjects (Ritz et al, 2007; Rossert et al, 2006;

Levin et al, 2005; Roger et al, 2004). However, results from the NHCT, CREATE, and CHOIR studies suggested an increased risk in CRF patients administered ESAs to target hemoglobin concentrations > 13.0 g/dL relative to a lower target hemoglobin level. The NHCT was included in the Warnings section of the USPI for Epoetin alfa (EPOGEN®/PROCRIT®) in December 1996 and in the original USPI for darbepoetin alfa (Aranesp®) in September 2001. The CHOIR study was added to the Warnings sections of the USPIs for licensed ESAs in December 2006. Risk for increased mortality and cardiovascular events with hemoglobin targets > 12.0 g/dL was elevated to a boxed warning in March 2007.

Table 7. Clinical Trials Comparing High Versus Low Hemoglobin Targets in CRF Patients

	NHCT	CREATE	CHOIR	EPO-INT-68
Design	Randomized, open label	Randomized, open label	Randomized, open label	Randomized, Double-blind
Agent (Sponsor)	Epoetin alfa (Amgen)	epoetin beta (Roche)	Epoetin alfa (J&JPRD)	Epoetin alfa (J&JPRD)
Sample size	1233	603	1432	596
Study status	terminated early for safety concern	completed	terminated early for futility	completed
Inclusion Criteria				
Dialysis status (eGFR [mL/min/1.73m^2])	hemodialysis	nondialysis (15-35)	nondialysis (15-50)	hemodialysis
IHD/CHF	yes	no	no	no
Hb (g/dL)	9-11	11-12.5	< 11	8-12
Hb target				
High	14 $\pm$ 1	13-15	13.5	13.5-14.5
Low	10 $\pm$ 1	10.5-11.5	11.3	9.5-11.5
Primary endpoint	time to mortality or first nonfatal MI	time to cardiovascular event[a]	time to death or cardiovascular event[b]	change in LVVI
Primary result	1.3 (0.9, 1.9)[c]	1.3 (0.9, 1.9)[c]	1.34 (1.03, 1.74)[c]	7.6% (high)[d] 8.3% (low)[d] p = 0.87

CHF = congestive heart failure; Hb = hemoglobin; IHD = ischemic heart disease; LVVI = left ventricular volume index; MI = myocardial infarction

[a] cardiovascular events included sudden death, myocardial infarction, acute heart failure, stroke, transient ischemic attack, angina pectoris resulting in hospitalization for 24 hours or more or prolongation of hospitalization, complication of peripheral vascular disease (amputation or necrosis), or cardiac arrhythmia resulting in hospitalization for 24 hours or more

[b] cardiovascular events included myocardial infarction, hospitalization for congestive heart failure without renal replacement therapy, and stroke

[c] Hazard ratio (95% CI) (reference group is the low target Hb group)

[d] Percent change in LVVI (target Hb group)

Table 7. Clinical Trials Comparing High Versus Low Hemoglobin Targets in CRF Patients

	NHCT	CREATE	CHOIR	EPO-INT-68
Other findings	higher vascular access thrombosis in high Hb group (39% vs 29%; p = 0.001); significant association between Hb and patient-reported physical; functioning (p = 0.03)	hazard ratio (95% CI) for high:low target groups: all-cause mortality 1.52 (0.87, 2.63); cardiovascular mortality 1.35 (0.59, 3.03) Significantly greater general health (p = 0.003) and physical function (p < 0.001) in high Hb group similar decline in GFR over the study period (3.4 vs 3.1 mL/min), but more patients in the high Hb group initiated dialysis (127 vs 111, p = 0.03).	hazard ratio (95% CI) for high:low target groups: death 1.48 (0.97, 2.27) hospitalization for CHF without renal replacement therapy 1.41 (0.97, 2.05) MI 0.91 (0.48, 1.73) stroke 1.01 (0.45, 2.25).	greater improvement in SF-36 Vitality score in high Hb group (1.21 vs -2.31; p = 0.036); more transfusions in low Hb group (19% vs 9%; p < 0.001)
Citation	Besarab et al, 1998	Drüeke et al, 2006	Singh et al, 2006	Parfrey et al, 2005

Hb = hemoglobin; LVVI = left ventricular volume index; MI = myocardial infarction

Taken together, these data show an increased risk of mortality and cardiovascular morbidity when targeting hemoglobin concentration > 13.0 g/dL in CRF patients. Nevertheless, important limitations in the 3 outcome studies exist (eg, open-label study design and use of subjective endpoints, such as hospitalization). In addition to these issues, the limitations in the design and conduct of the CHOIR trial affect the interpretation of the findings, as has been discussed in the literature (Levin, 2007). Subjects randomized to the higher hemoglobin target group had significantly higher baseline rates of important cofactors prognostic for mortality and cardiovascular

morbidity, namely hypertension (95.8% vs 93.2%), prior coronary artery bypass grafting (17.4% vs 13.4%), and more severe congestive heart failure (≥ stage 3 National Health and Nutrition Examination Survey [NHANES] congestive heart failure score: 26.6% vs 21.1%) (Ortho Biotech Clinical Affairs, LLC, 2006; Singh et al, 2006). Although the impact is unknown, 38% of subjects in each treatment group withdrew before study termination and before experiencing a primary endpoint; 17% withdrew because of initiation of renal replacement therapy as specified by the protocol and 21% were lost to follow-up.

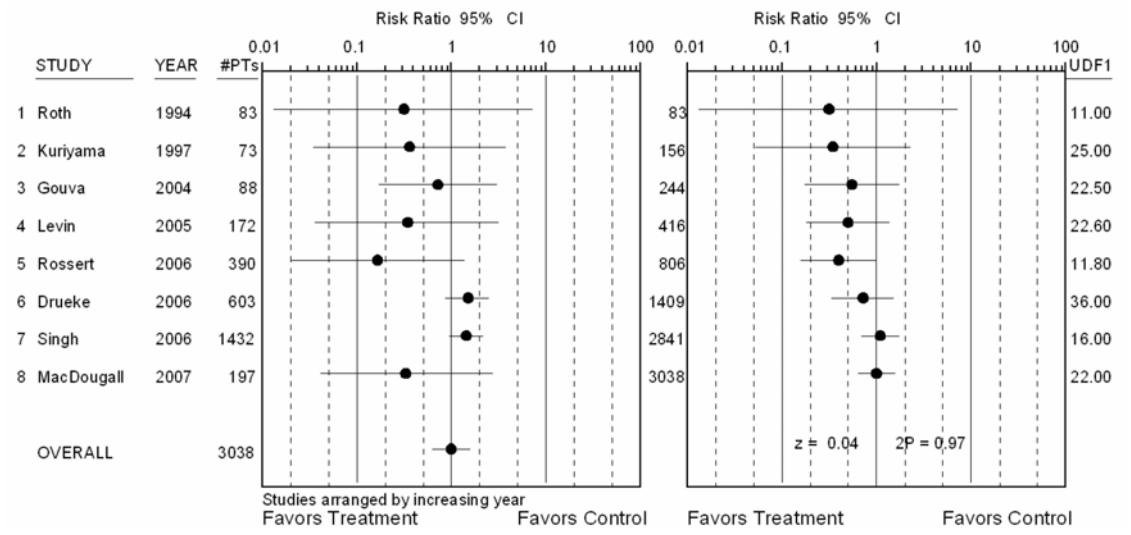
The results of these and other clinical trials comparing higher (eg, > 13.0 g/dL) and lower (eg, ≤ 12.0 g/dL) hemoglobin targets were recently examined in 2 meta-analyses that assessed the association between target hemoglobin and mortality and cardiovascular events in dialysis and nondialysis CRF subjects (Phrommintikul et al, 2007; draft NKF-KDOQI™ 2007 guideline). The KDOQI™ analyses included 26 randomized clinical trials identified through an extensive literature search for all studies that compared hemoglobin targets in patients with CRF and had a follow-up of at least 2 months. Of these 26 trials, 10 enrolled dialysis subjects (N = 2616), 15 enrolled nondialysis CRF subjects (N = 3432), and 1 enrolled both dialysis (N = 344) and nondialysis (N = 72) subjects. Four trials enrolling dialysis subjects (N = 2391) and 8 trials enrolling nondialysis CRF subjects (N = 3038) compared higher to lower hemoglobin targets. The largest of the dialysis studies was NHCT, which enrolled 1233 subjects and the largest of the nondialysis studies were CHOIR (N = 1432) and CREATE (N = 603). Phrommintikul included only 9 of the trials (N = 5143) analyzed by KDOQI™ due to differences in meta-analysis inclusion and exclusion criteria and to an earlier cut-off date. Three studies included dialysis subjects (N = 1975), 5 included nondialysis CRF subjects (N = 2752), and 1 included both dialysis (N = 339) and nondialysis (N = 72) subjects.

Evidence of excess mortality risk was observed when dialysis and nondialysis CRF studies were combined in analyses by Phrommintikul et al (risk ratio [95% CI] 1.17 [1.01, 1.35]). No statistically significant differences in mortality risk were observed for the higher compared with the lower target hemoglobin arms in either dialysis patients (risk ratio [95% CI] 1.11 [0.94, 1.31]) or nondialysis patients (risk ratio [95% CI] 1.33 [0.98, 1.81]) analyzed separately.

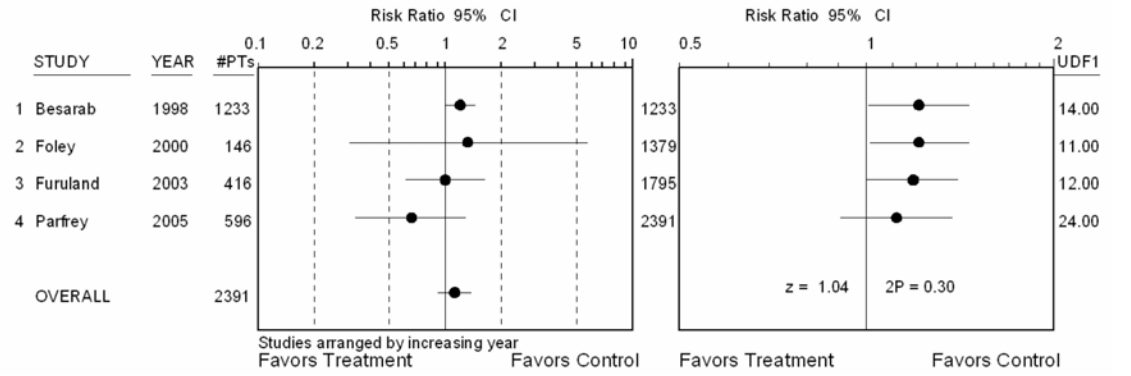
KDOQI™ only analyzed dialysis and nondialysis studies separately because they considered that differences in underlying clinical conditions between these 2 patient populations precluded a combined analysis. No statistically significant differences in mortality risk were observed for the higher compared with the lower target hemoglobin arms in either dialysis patients (risk ratio [95% CI] 1.12 [0.91, 1.37]) or nondialysis patients (risk ratio [95% CI] 1.01 [0.63, 1.61]) (Figure 8). No difference in cardiovascular event risk between target ranges was observed for dialysis patients (risk ratio [95% CI] 1.14 [0.79, 1.64]); however, an increased risk was observed for the higher hemoglobin targets in nondialysis patients (risk ratio [95% CI] 1.24 [1.02, 1.51]).

Figure 8. Relative Mortality Risk for Assignment to Higher Hemoglobin Treatment Targets

Nondialysis CRF Patients



Dialysis Patients



Standard (left) and cumulative (right) meta-analysis plots according to random effects model
Source: draft NKF-KDOQI™ 2007 guidelines

Based on the results of their meta-analysis, KDOQI™ recommended that the hemoglobin target should be generally in the range of 11.0 to 12.0 g/dL and should not exceed 13.0 g/dL in dialysis and nondialysis patients.

This guidance was supported by another recent review of hemoglobin targets for ESA therapy (Fishbane and Nissenson, 2007). The authors concluded from their review that the target range recommended by KDOQI™ would result in an optimal benefit: risk profile for ESA therapy in CRF patients, while acknowledging the need for individualized treatment in these patients.

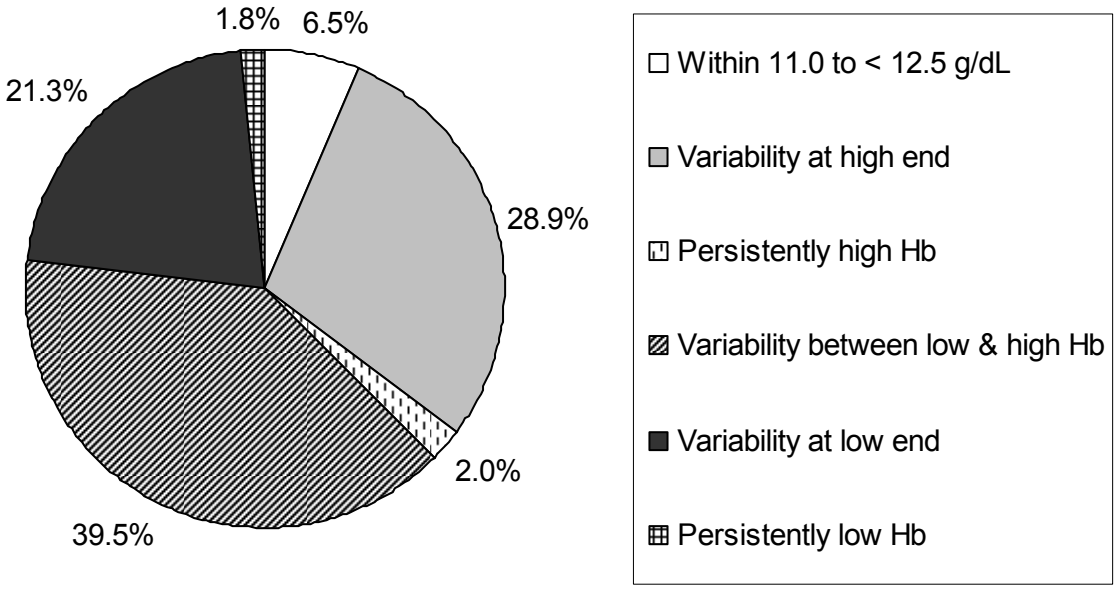
Clinical outcomes for subjects enrolled in trials with hemoglobin targets ≤ 12.0 g/dL were compared to those for subjects enrolled in trials with hemoglobin targets > 12.0 g/dL in exploratory analyses of pooled data from clinical trials with darbepoetin alfa or rHuEPO sponsored by either Amgen or J&JPRD. The pooled clinical trial data included trials that prospectively compared different hemoglobin targets (eg, NHCT, CHOIR), as well as trials that did not. The results of these exploratory analyses are provided in Appendix 2. Although there is some suggestion of increased risk in certain analyses, the data did not suggest consistent evidence of an increased or decreased risk for adverse clinical outcomes associated with hemoglobin target ranges with upper limits > 12.0 g/dL compared with target ranges with upper limits ≤ 12.0 g/dL.

In summary, when the safety signals from CHOIR and NHCT are considered in the context of the existing data for ESAs from other randomized clinical trials and large provider and claims databases, the evidence supports the view that achieved hemoglobin concentrations ≥ 11.0 and ≤ 13.0 g/dL are associated with better clinical outcomes than achieved concentrations < 11.0 or > 13.0 g/dL. Therefore, based on these data, a hemoglobin target range represents appropriate guidance for anemia management in CRF patients and should be reflected in the ESA USPIs. Amgen and J&JPRD believe the data support 12.0 g/dL as the upper end of the target range to provide a safety margin against higher hemoglobin targets (ie, > 13 g/dL). Available evidence also supports 11.0 g/dL as the lower end of the target range. Given the lack of definitive data and limited feasibility to delineate between narrow hemoglobin targets, it may be reasonable to consider a lower boundary. Amgen and J&JPRD believe the lower boundary of the target should not be less than 10.0 g/dL.

5.3.3 Targeting a Hemoglobin Concentration Acknowledges Inter- and Intra-patient Variability

The use of a hemoglobin target range must recognize that transient excursions above and below this target will occur due to hemoglobin variability. This variability occurs within individual patients, as a result of normal physiologic variation, as well as intercurrent clinical events, and/or comorbidity. As shown in Figure 9, a study of 152,846 hemodialysis patients from a Medicare claims database found that, over a 6-month period, only 7% of patients were persistently within a range (11.0 to < 12.5 g/dL) that corresponded to community consensus hemoglobin targets at the time of data collection (Ebben et al, 2006). Similarly, only 2% of patients had levels persistently within a higher (≥ 12.5 g/dL) or lower (< 11.0 g/dL) hemoglobin range. A greater percentage of patients (50%) cycled between the intermediate and high or low hemoglobin ranges (ie, they had low variability at either the high or low end of the intermediate hemoglobin range). Further, 40% of patients exhibited large hemoglobin variability with concentrations that fluctuated across all 3 hemoglobin ranges (ie, fluctuations between < 11.0 and ≥ 12.5 g/dL) during this time period.

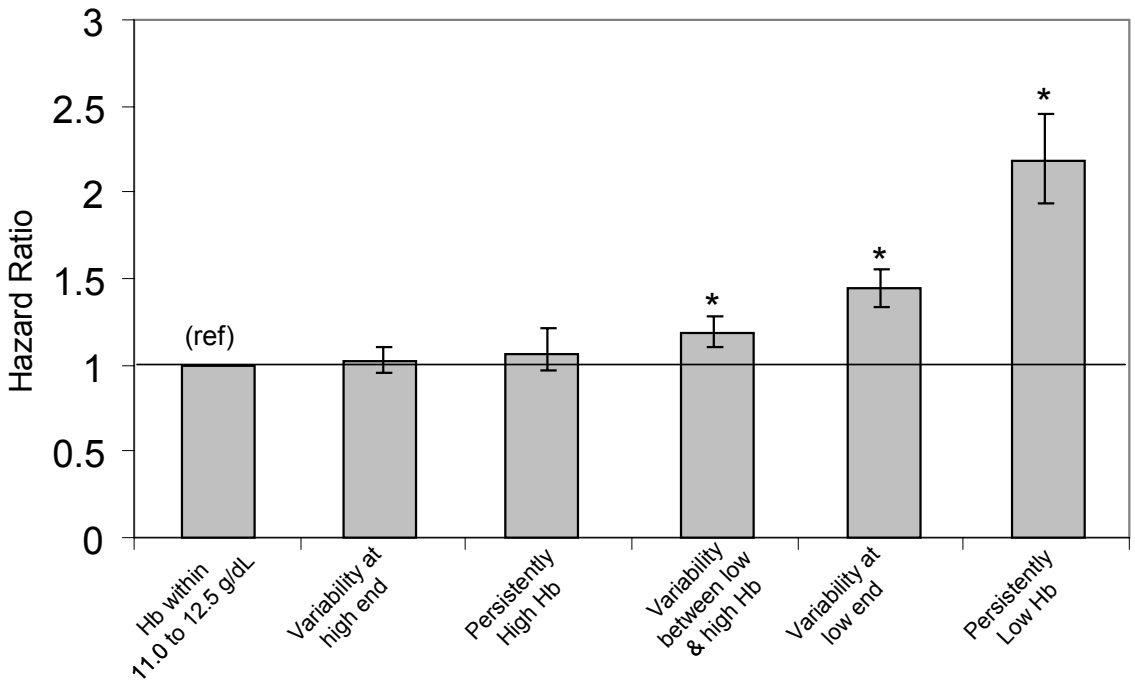
Figure 9. Proportion of Hemodialysis Patients by Hemoglobin Variability Over 6 Months (N = 152,846)



Source: Modified from Ebben et al, 2006

These variability patterns are associated with mortality risk. In a follow-up analysis to this study, the association between hemoglobin variability patterns and 1-year mortality was examined in 159,720 hemodialysis patients (Gilbertson et al, 2007 [provisionally accepted]; methods are provided in Appendix 4). The greatest increase in mortality risk was observed for patients with persistently low hemoglobin (hazard ratio [95% CI]: 2.18 [1.93, 2.45]) compared with patients with hemoglobin concentrations persistently within 11.0 to 12.5 g/dL (Figure 10). The mortality risk was also higher for patients with large hemoglobin variability (ie, fluctuations between < 11.0 and > 12.5 g/dL) (hazard ratio [95% CI]: 1.19 [1.10, 1.28]) and those with low hemoglobin variability at the low end of the range (hazard ratio [95% CI]: 1.44 [1.33, 1.56]).

Figure 10. Adjusted Hazard Ratios (95% CIs) for Mortality in Hemodialysis Patients by Hemoglobin Variability Over 6 Months (N = 159,720)



* p < 0.0001
Hb = hemoglobin
Hazard ratios were adjusted for age, race, gender, hospital admissions during the entry period, and the presence of the following comorbid conditions: atherosclerotic heart disease, congestive heart failure, dysrhythmia, other cardiac disease (including valvular disease), cerebrovascular accident/transient ischemic attack, peripheral vascular disease, chronic obstructive pulmonary disease, cancer, gastrointestinal bleeding, and hepatic disease.
Source: modified from Gilbertson et al, 2007 (provisionally accepted)

In addition to a higher mortality risk, patients with hemoglobin concentrations persistently < 11.0 /dL had the highest percentage of hospital admissions, the highest percentage of admissions for infection, the longest duration of hospital stays, and the highest number of comorbid conditions compared with any of the other groups (Ebben et al, 2006). Conversely, the patients with hemoglobin levels persistently within 11.0 to 12.5 g/dL had the lowest percentage of hospital admissions, the lowest percentage of admissions for infection, the shortest duration in hospital stays, and the fewest number of comorbid conditions compared with the other groups.

A high degree of hemoglobin variability in dialysis patients was also observed from other analyses of data from within and outside the US (Bárány et al, 2007; USRDS, 2006; Lacson et al, 2003). Thus, although strategies to identify and minimize hemoglobin variability are appropriate, hemoglobin variability appears to be a characteristic of CRF patients, regardless of region or treatment practices. As a result, any attempt to ensure that individual patient hemoglobin concentrations do not exceed 12.0 g/dL will have the unintended, but predictable, consequence of increasing the number of patients with hemoglobin concentrations < 11.0 g/dL. Therefore, the KDOQI™ 2007 draft clinical practice guidelines for anemia management stipulate the need to differentiate between the target and achieved hemoglobin, highlighting explicitly that normal intrapatient hemoglobin variability and a patient's responsiveness to ESAs must be acknowledged.

In summary, intra- and inter-patient hemoglobin variability over time are common within the dialysis patient population such that transient excursions above and below a target range will occur. Hemoglobin fluctuations around 11.0 g/dL, as well as large fluctuations between hemoglobin concentrations < 11.0 and > 12.5 g/dL, are associated with an increased risk for mortality. However, consistent with previously described data (Figure 6 and Figure 7), the greatest risk for mortality is associated with hemoglobin concentrations < 11.0 g/dL. Therefore, appropriate ESA dosing and other anemia management practices should be adjusted at the individual patient level to maintain the highest proportion of the population within the target hemoglobin.

5.3.4 Dosing Practices to Maintain Hemoglobin Concentrations

As discussed in Section 5.3.3, dosing guidelines for ESAs should take into account the target hemoglobin level and the inherent inter- and intra-patient hemoglobin variability that affects the proportion of patients who can achieve and maintain the intended hemoglobin concentration. Because ESA dosing decisions are driven by preceding

hemoglobin concentrations, usually in the setting of an ESA titration protocol, ESA doses should be adjusted appropriately as hemoglobin varies outside of the intended target range. Indeed, examination of observational data from large dialysis provider databases indicates that healthcare providers adjust ESA doses appropriately following hemoglobin excursions above and below the target. Analysis of data from a cohort of hemodialysis patients (N = 1660) in the FMC-NA database found that Epoetin alfa doses were reduced in 99% of patients with hemoglobin concentrations persistently > 12 g/dL over a 6-month period (Collins et al, 2005). Similarly, ESA doses were decreased in 96% of dialysis patients who experienced a hemoglobin excursion > 13.0 g/dL in a separate observational study using the Amgen Outcomes Plus dataset, which contains data from approximately 80% of US dialysis centers (N = 311,000) (Khan et al, 2007 [abstract submitted]). ESA doses were increased in 91% of patients with a hemoglobin < 11.0 g/dL in this same study, indicating that healthcare providers appropriately respond to increases and decreases in hemoglobin in CRF patients.

5.4 ESA Dose Requirements and Clinical Outcomes in Patients With CRF

Examination of the potential contribution to cardiovascular and/or thromboembolic risk from ESA therapy is complicated by at least 3 considerations of the relationship between ESA dose and hemoglobin response.

- ESA dose and hemoglobin are strongly correlated because ESA dose is titrated in response to specific hemoglobin levels.
- ESA response is dependent on a patient's overall health status.
- Hemoglobin response to ESAs changes over time in individual patients.

Section 5.3.4 discussed the correlation between ESA dose and hemoglobin, noting that ESA dosing decisions are triggered by preceding hemoglobin concentrations and providing evidence of this pattern using physician prescribing behavior. It is particularly important that analyses of the potential association between ESA dose and cardiovascular risk also account for the second and third considerations described above (ie, dependence of ESA responsiveness on underlying biological factors and time-dependent relationship between ESA dose and hemoglobin), both of which highlight the analytic difficulty of accounting for a ‘confounding-by-indication’ bias.

An analogous situation exists in the case of insulin and glucose control in the critical care setting. While prospective randomized trials targeting blood glucose to lower levels using intensive insulin therapy have demonstrated a significant reduction in mortality

(van den Berghe et al, 2001), analysis of blood glucose levels and administered insulin doses has shown a consistent association between higher insulin doses and greater mortality regardless of the prevailing blood glucose level (Finney et al, 2003). The authors of the latter investigation into this relationship recognized the complexity of targeting blood glucose levels and considered that control of glucose levels, rather than insulin levels, was the important determinant in the beneficial results observed with lower target blood glucose levels. This same concept can be applied to ESA therapy and maintenance of hemoglobin concentration.

5.4.1 The Association Between ESA Dose and Outcome is Substantially Influenced by Patient Health Status and ESA Responsiveness

Factors most commonly associated with persistent poor ESA response include frequent hospitalization, infection, use of a percutaneous catheter as vascular access, hypoalbuminemia, and elevated C-reactive protein (Kausz et al, 2005). Each of these factors is independently associated with greater risk of both mortality and cardiovascular events, making it difficult to attribute independent risk to either a specific ESA dose for an individual patient or to the patient's underlying biologic factors that are responsible for the dose required to generate a hemoglobin response. Therefore, any analysis relating ESA dose to a future clinical event that does not take into account important baseline markers of patient health status and the dynamic interaction of dose and hemoglobin may inadvertently attribute the mortality risk to ESA dose rather than to underlying patient health status.

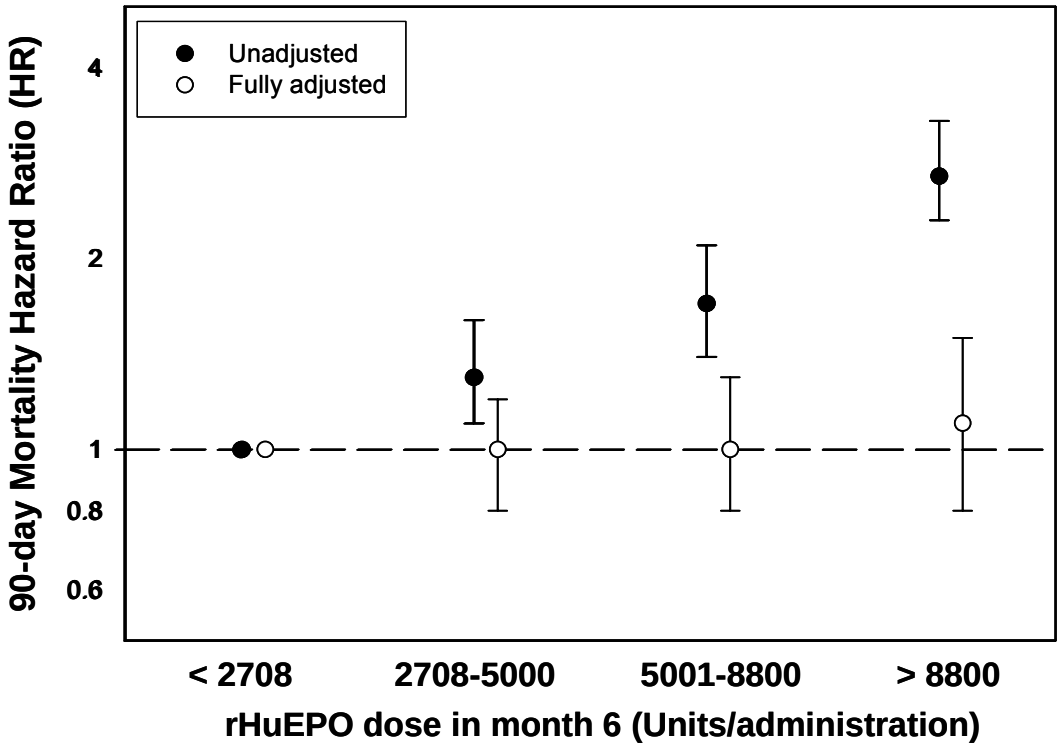
The importance of correcting for the impact of patient characteristics, especially in analyses of observational data, is illustrated in Appendix Table 8. Clear differences in patient characteristics, particularly those related to cardiovascular disease, infection, and percutaneous catheter use, are observed across ESA dose categories, even for a cohort of patients with a relatively tight range of hemoglobin values (between 10.0 and < 12.0 g/dL).

The influence of patient health status and ESA responsiveness on the association between ESA dose and mortality is demonstrated in an analysis examining this association over a 3-month period for a larger cohort of dialysis patients selected from the FMC-NA dataset (N = 23,804); methods are provided in Appendix 4. When patient characteristics collected over a 6-month entry period were not accounted for in an analysis across this cohort, a greater mortality risk was observed for patients receiving higher ESA doses in the month before the 90-day follow-up period (ie, month 6)

compared with patients receiving the lowest ESA doses (hazard ratio [95% CI]: 2.7 [2.3, 3.3]) (Figure 11). However, this association was markedly attenuated when a limited number of predictive covariates were included in the analysis (hazard ratio [95% CI]: 2.1 [1.7, 2.6]). When all of the available patient characteristics were accounted for in the analysis, the association between ESA dose and mortality was further attenuated (hazard ratio [95% CI]: 1.7 [1.4, 2.1]).

When previous ESA dose and hemoglobin concentration were accounted for, the association between higher ESA dose and increased mortality risk was reduced at all levels of adjustment for patient characteristics. Importantly, when all of the available predictive patient characteristics, including previous ESA dose and hemoglobin concentrations, were considered in the analysis, higher ESA dose was not related to an increased mortality risk (hazard ratio [95% CI]: 1.1 [0.8, 1.5]) (Figure 11).

Figure 11. 90-Day Mortality Hazard Ratio (HR) Estimates and 95% CIs by rHuEPO Dose Quartile and Level of Adjustment (FMC-NA Hemodialysis Patients; N = 23,804)



Fully adjusted = Adjustment for age, sex, race, diabetes as cause of ESRD, duration on dialysis, urea reduction ratio, number of hospitalizations, vascular access type, vascular access-related hospitalizations, albumin, parathyroid hormone, transferrin saturation, ferritin, number of unexcused missed dialysis visits, mean rHuEPO dose and hemoglobin during months 1 to 5
Source: \\filesrv04\epi\projects\epidemiology\p07_035_cwc\repository\Project_6.16\Exposure history adjustment

As shown above, determining the independent contribution of ESA dose to clinical outcome is difficult to address through analyses of observational data because of a large confounding-by-indication bias. This is supported by a study using dialysis patient data from USRDS (Zhang et al, 2004). The results of this study indicate that mortality increases with increasing baseline Epoetin alfa dose at each hematocrit level examined and, within each dose quartile, as hematocrit level decreases. The results of this analysis have been used to suggest that higher ESA doses are associated with increased risk of death. However, the authors concluded that the results demonstrate the importance of ESA responsiveness in determining clinical outcomes (ie, patients with the highest ESA doses and lowest achieved hemoglobin levels have the worst prognosis), which is consistent with the results in Figure 11.

In addition to this confounding-by-indication, the time-dependent nature of the relationship between ESA dose and hemoglobin needs to be accounted for because ESA dose reflects previous hemoglobin levels and also influences subsequent hemoglobin levels. To further address the influence of time-dependent confounding and to allow intermediate effects through changes in hemoglobin concentration, 2 other contemporary methods of adjusting for the confounding-by-indication bias, a marginal structural model and instrumental variable analysis, have theoretical advantages. Amgen is currently conducting analyses using both of these methods.

The effect of ESA dose on clinical outcomes was also investigated across pooled clinical trials with either darbepoetin alfa or rHuEPO sponsored by Amgen or J&JPRD. Results for these analyses are provided in Appendix 2. Higher ESA dose in the pooled clinical trials was in many cases associated with increased cardiovascular outcome risk. Analogous to the investigation of insulin dose and mortality in the critical care setting (Finney et al, 2003), the causal nature of this association is difficult to assess, in part because of the confounding issues of achieved hemoglobin and underlying patient health status.

5.4.2 ESA Responsiveness, Rather than ESA Dose or Hemoglobin Concentration Alone, Appears to be Associated With Clinical Outcome

ESA dose and responsiveness to ESA therapy are related, but not identical, concepts. ESA response is a measure of hemoglobin change following administration of a specified ESA dose, reflecting the erythron's ability to respond to erythropoietin with an increase in red blood cells. Due to biologic and environmental variables, patients with CRF have widely divergent ESA dosing requirements to maintain a given hemoglobin

level. In the pivotal Epoetin alfa study in hemodialysis subjects, for example, doses between 12.5 and 525 units/kg three times weekly were required for maintenance of hematocrit levels between 32% and 38% (hemoglobin 10.7 to 12.7 g/dL) over a 1-year period (Eschbach et al, 1989). Therefore, Amgen and J&JPRD classified ESA responsiveness and examined the association between ESA responsiveness and cardiovascular risk by conducting post-hoc analyses on data from 2 prospective clinical outcome studies, NHCT and CHOIR, that used an initial, uniform ESA dose challenge, independent of hemoglobin concentration.

5.4.2.1 Association Between ESA Dose, ESA Response, and Clinical Outcomes in the Normal Hematocrit Cardiac Trial (NHCT)

As discussed in Section 5.3.2, the results of the randomized NHCT with Epoetin alfa in hemodialysis subjects with clinically evident cardiac disease suggested that a higher target hematocrit (42% ± 3% compared with 30% ± 3% [hemoglobin 14 ± 1 g/dL compared with 10 ± 1 g/dL]) was associated with a greater risk of nonfatal myocardial infarction and all-cause death, although the risk ratio was not significantly different between groups (Besarab et al, 1998). Because subjects in the higher target hemoglobin arm were randomized to receive a protocol-specified 50% increase from baseline in Epoetin alfa dose at the start of the clinical trial, the results of this study have led to the hypothesis that these patients may have been at risk due to a higher ESA dose. However, Besarab et al also noted that a higher Epoetin alfa dose was not associated with increased mortality and that the rate of vascular access thrombosis did not increase at higher achieved hematocrit values or Epoetin alfa dose in either treatment group.

To further investigate the hypothesis that adverse clinical outcomes are related to ESA dose, analyses were conducted to evaluate the association between clinical outcomes and Epoetin alfa dose and responsiveness using data from subjects in the higher hematocrit arm of the NHCT (Kilpatrick et al, 2007 [submitted]; methods are provided in Appendix 4). The study cohort included all subjects randomized to the normal target hematocrit group (42% ± 3% [hemoglobin 14 ± 1 g/dL]) who received an initial increase from their baseline Epoetin alfa dose of between 30% and 70% (n = 321).

A prospective measure of responsiveness (EPO response index), defined as the ratio of weekly hematocrit change per Epoetin alfa dose increase (1000 units/week), was calculated for each subject. The EPO response index discriminated ESA responsiveness across all dose levels and was not correlated with baseline Epoetin alfa

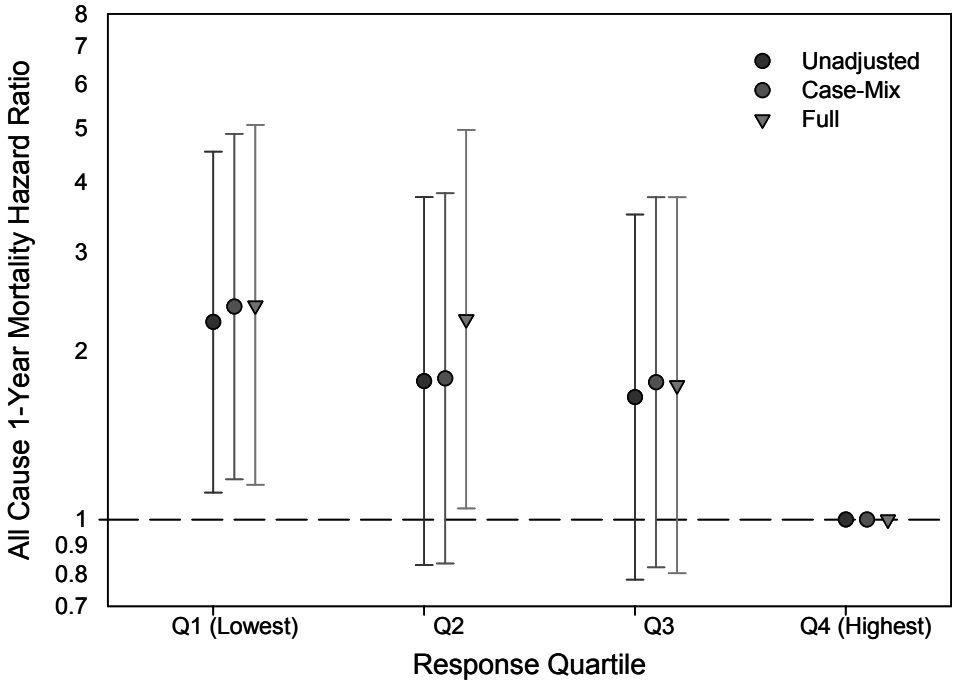
dose (Pearson correlation coefficient = 0.01). The association between EPO response index and all-cause or cardiovascular mortality was examined using Cox proportional hazards regression. Three levels of adjustment were performed:

- adjustment for baseline Epoetin alfa dose
- adjustment for case-mix (age, gender, race, history of diabetes mellitus, length of time on dialysis [dialysis vintage], and type of vascular access).
- full adjustment (baseline dose, case-mix, and body mass index, lymphocytes, albumin, transferrin saturation, Kt/V, and history of hypertension)

Patients in the lowest EPO response index quartile (ie, those least responsive to Epoetin alfa) had a 2.25-fold increased risk of death in the following year compared with those in the lowest quartile (p = 0.02) (Figure 12). This association did not attenuate when adjusted for known prognostic factors, indicating that ESA responsiveness is an independent proxy for otherwise unmeasured patient health status.

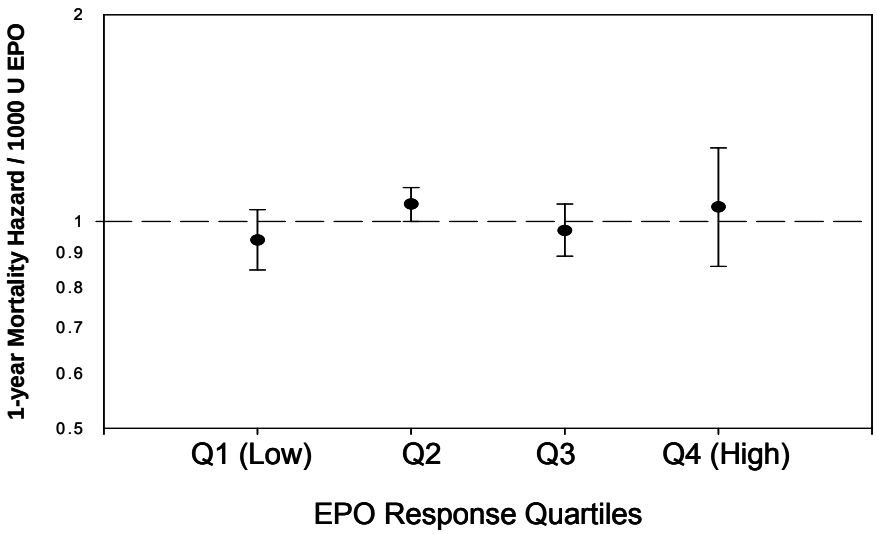
Finally, when assessed within EPO response quartiles, higher ESA dose was not associated with an increased risk of death (Figure 13). These results highlight that ESA responsiveness is strongly associated with adverse clinical outcomes and suggest that ESA dose does not independently influence mortality.

Figure 12. Crude and Adjusted 1-Year All-Cause Mortality Hazard Ratio Estimates (95% CIs) by EPO Response Index



NOTE: Unadjusted = adjusted for baseline Epoetin alfa dose only
Source: modified from Kilpatrick et al, 2007 (submitted)

Figure 13. Adjusted[a] Mortality Risk (95% CI) Associated with Every 1000 Unit Increase in ESA Dose



[a] Adjusted for age, sex, race, duration on dialysis, diabetes status, vascular access type, lymphocytes count, albumin, transferrin saturation, ferritin, body mass index, Kt/V, urea reduction ratio and NYHA class
Source: modified from Kilpatrick et al, 2007 (submitted)

5.4.2.2 Association Between ESA Response and Clinical Outcomes in the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) Study

An analysis to evaluate the association between clinical outcomes and responsiveness, similar to that undertaken for NHCT, was performed for the CHOIR study (Singh et al, 2006).

Subjects enrolled in CHOIR were EPO-naïve at baseline (mean baseline hemoglobin 10.1 g/dL) and were randomly assigned to either a high-hemoglobin target group (13.5 g/dL) or low-hemoglobin target group (11.3 g/dL). Both groups were to receive Epoetin alfa 10,000 units weekly for the first 3 weeks, followed by protocol-specified dose adjustments as needed to achieve and maintain the assigned target hemoglobin concentration. The maximum dose was not to exceed 20,000 units per week. Hemoglobin concentration was measured every other week until stable, and monthly thereafter during the study. As discussed in Section 5.3.2, the prespecified analyses (Singh et al, 2006) showed that there was an increased risk of composite events in the high-hemoglobin target group compared with the low-hemoglobin target group (hazard ratio 1.34, [95% CI: 1.03, 1.74]; p = 0.03).

The EPO response index was calculated for each subject as the ratio of weekly hemoglobin change per Epoetin alfa dose administered (1000 units/week) over the first 4 weeks of the study. The numerator of the index was defined as the change in weekly hemoglobin modeled as the slope parameter obtained from a simple linear regression of each subject's hemoglobin over the first 4 weeks in the study, including baseline hemoglobin. The last hemoglobin measurement utilized in this calculation was obtained 1 week after the protocol-defined dose adjustment; however, sensitivity analyses excluding this hemoglobin value show similar results. Subjects were categorized into EPO response index quartiles, with quartile 1 representing the least responsive subjects and quartile 4 representing the most responsive subjects. Included in this analysis were all subjects that received the initial dose, had at least 3 hemoglobin measurements, including the baseline, and did not experience a composite event during first 4 weeks of the study.

Baseline characteristics, event rates, and other study parameters by EPO response index quartile for both hemoglobin target groups are provided in Appendix Table 9. Older age, prior history of congestive heart failure, and atrial fibrillation/flutter were more frequent in the lower quartiles in both hemoglobin target groups, suggesting a potential relationship between prior cardiovascular morbidity and poor responsiveness to Epoetin alfa treatment. Within each quartile, baseline characteristics appeared to be equally distributed between treatment groups with the possible exception of a higher proportion of subjects with congestive heart failure and atrial fibrillation/flutter in the high-hemoglobin target in quartile 2. As the EPO response index quartile increased, the mean weekly Epoetin alfa dose during the study decreased, and the mean achieved hemoglobin concentration increased within both the high- and low-hemoglobin target groups.

The association between EPO response index and composite events was examined using Cox proportional hazards regression, unadjusted and adjusted for baseline factors identified using the previously performed multivariate modeling analysis of the CHOIR study. These baseline factors include age, prior medical history of congestive heart failure, prior medical history of atrial fibrillation/flutter, baseline NHANES I congestive heart failure score ≥ 3, baseline serum albumin, and baseline percent reticulocyte count.

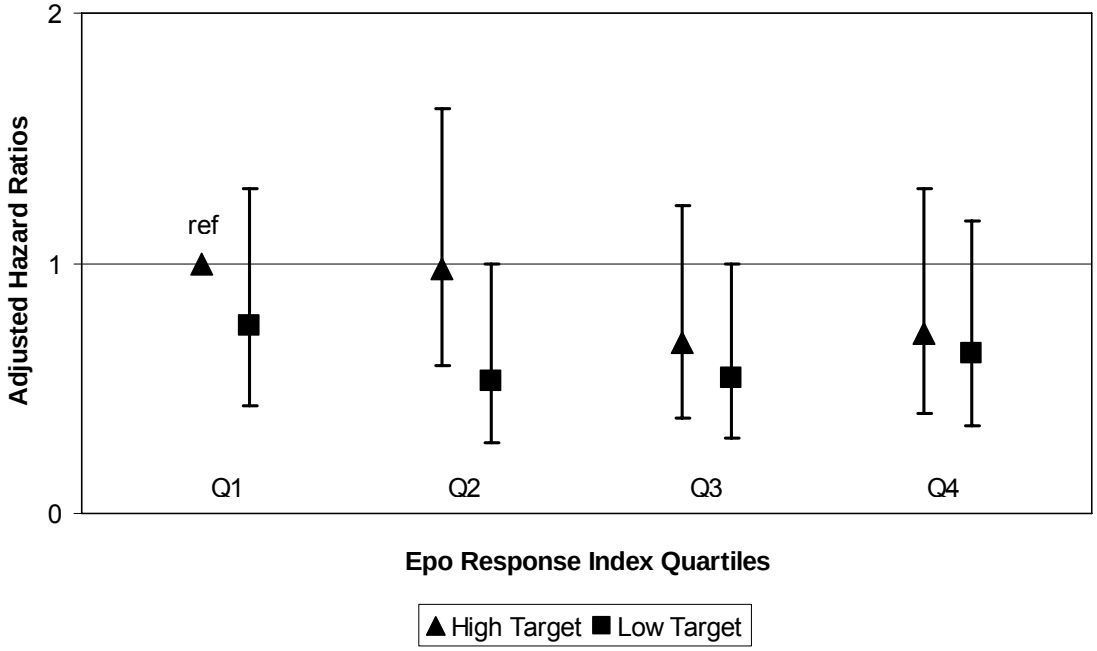
Analyses were conducted for the high-hemoglobin target group, the low-hemoglobin target group, both groups combined, and within each EPO response index quartile.

Hazard ratios are provided in Appendix Table 10. Figure 14 shows the composite event hazard ratio estimates by EPO response quartiles for both target groups.

Subjects in the highest 2 EPO response index quartiles in the high-hemoglobin target group and the combined target group had the lowest risk of composite events (Appendix Table 10). For example, in the high-hemoglobin target group, a statistically significant reduction in the risk of composite events was observed for the third and fourth quartiles relative to the first quartile. The hazard ratios (95%CIs) were 0.56 (0.31, 0.99, p = 0.05) and 0.51 (0.29, 0.91, p = 0.02) for the third and fourth quartiles, respectively. In the low-hemoglobin target group, the risk for the second, third, and fourth quartiles was also reduced compared with the first quartile; however, these results were not statistically significant. Further analysis comparing the 2 hemoglobin target groups shows that subjects in the high-hemoglobin target group were at higher risk for experiencing a composite event compared with the low-hemoglobin target group, and this remained after adjustment for responsiveness (hazard ratio 1.42 [95% CI: 1.04, 1.93]; p = 0.03) (Appendix Table 10). When adjusted for baseline factors in all models, the hazard ratios tended to be closer to unity and to lose statistical significance. While the test for interaction between treatment group and responsiveness quartiles was not significant, there appear to be differences in the risk of experiencing a composite event between treatment groups across quartiles of responsiveness.

These results suggest that, while the high-hemoglobin target group demonstrated a higher risk for the primary composite event endpoint, the risk is predominantly observed for the subjects within this group who exhibited poor ESA response. A similar relation between poor response and increased risk was also observed in the low-hemoglobin target group. Thus, the combination of ESA responsiveness and hemoglobin target appear to be associated with clinical outcomes. Moreover, as ESA dose, ESA responsiveness, and hemoglobin target are confounded, it is not possible to determine the contribution of dose alone to adverse outcomes in this clinical trial.

Figure 14. Adjusted[a] Composite Event Hazard Ratios (95% CIs) by EPO Response Index



Q1 (lowest response quartile) for the high-hemoglobin target group is the reference group.
[a] Adjusted for age, prior medical history of congestive heart failure, prior medical history of atrial fibrillation/flutter, baseline National Health and Nutrition Examination Survey I (NHANES) congestive heart failure score ≥ 3, baseline serum albumin, and baseline percent reticulocyte count
Source: \\na.jnj.com\OBIusdfsroot\Clinical Affairs Biostats\RO\NEPHROLOGY\PR00-06-014\FDA200706\FINAL

In summary, the results of the post-hoc analyses of data from NHCT and CHOIR suggest that studies evaluating the association between ESA dose and clinical outcomes that do not account for ESA responsiveness may inadvertently attribute an excess mortality risk to ESA dose. Nevertheless, after adjustment for responsiveness, an increased risk of mortality and cardiovascular morbidity is still observed when targeting hemoglobin levels > 13.0 g/dL in CRF patients.

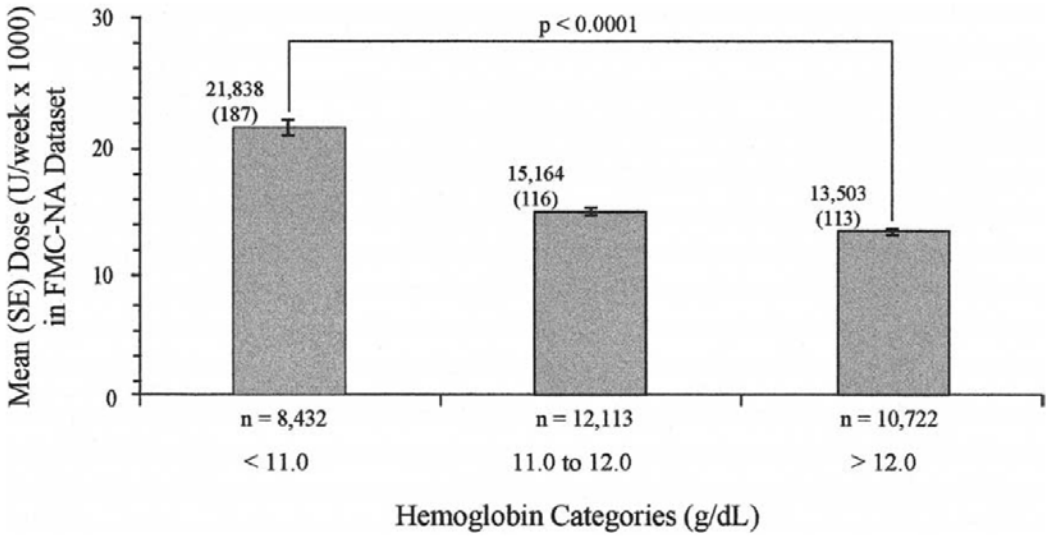
5.4.3 Considerations for Hypo-responsive Patients

5.4.3.1 Dose-response in Patients with Hemoglobin < 11.0 g/dL

Attempts to identify predictors for ESA responsiveness have met with limited success (Rossert et al, 2007; Singh et al, 2007). Guidance on the evaluation of causative factors for nonresponse to ESA therapy is provided in the "Precautions, Lack or Loss of Effect to [ESA]" sections of the current ESA USPIs. However, Amgen and J&JPRD believe that the area of hypo-responsiveness warrants evaluation and refinement of existing

analyses. Observational data demonstrate that the highest ESA doses are typically used in patients with hemoglobin concentrations < 11.0 g/dL (ie, patients with the poorest response) (Figure 15; Jacobs et al, 2005). Observational and clinical trial data also indicate that lower hemoglobin concentrations are associated with greater risk for adverse clinical outcomes (Section 5.3.1). Therefore, an important clinical question is whether an increase in ESA dose among these patients is associated with either increases in hemoglobin concentration and/or an increased mortality risk.

Figure 15. Distribution of Epoetin alfa Dose by Hemoglobin Level (FMC-NA Dataset; N = 31,267)



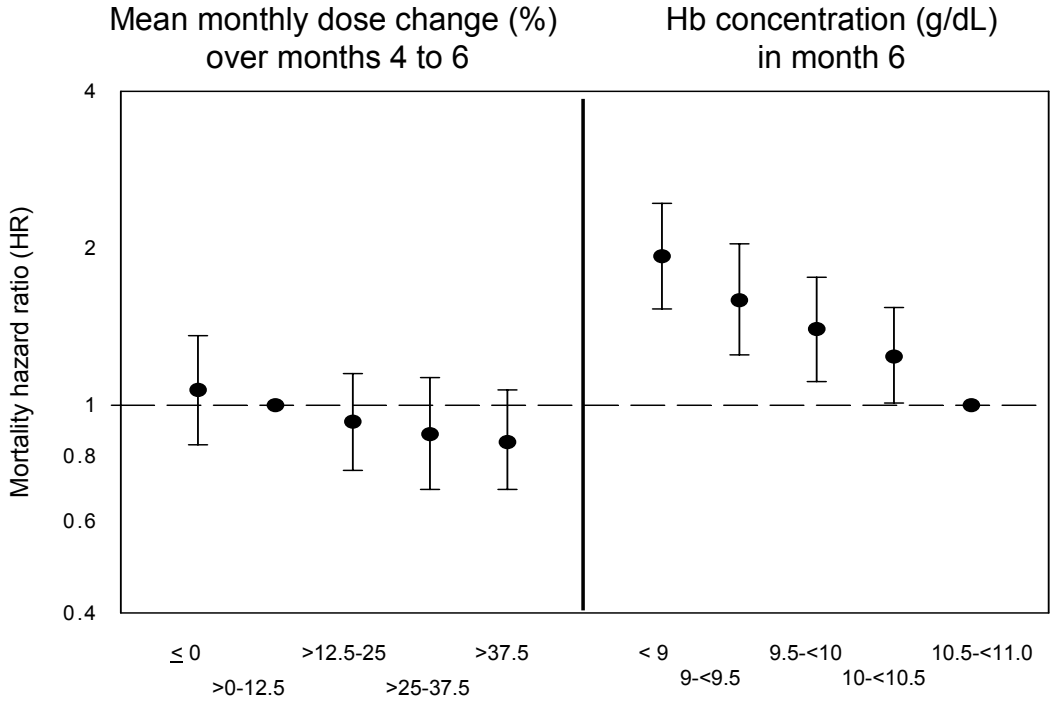
Source: Collins et al, 2005

This question was explored using the FMC-NA dialysis provider database to evaluate the association between high rHuEPO dose and 6-month mortality among patients with persistently low hemoglobin values (ie, hypo-responsive patients); methods are provided in Appendix 4. Patients with data from at least 6 consecutive months (entry period = study months 1 to 6), including non-missing ESA dose and monthly hemoglobin levels, and hemoglobin concentrations < 11.0 g/dL in each of the last 3 months of the entry period (study months 4 to 6) were included in the analyses. The index date was the last day of study month 6. Mortality was assessed over the 6 months following the index date (study months 7 to 12) and changes in hemoglobin were assessed over the 3 months following the index date (study months 7 to 9).

Patients with hemoglobin concentrations < 11.0 g/dL for 3 consecutive months were identified (n = 6133). Patients with the highest dose increases during the observation period were approximately twice as likely to achieve a hemoglobin ≥ 11.0 g/dL compared with those whose doses were decreased or unchanged. The proportion of patients achieving hemoglobin values ≥ 11.0 g/dL during study months 7 to 9 according to categories of dose increases experienced in the 3 previous months (study months 4 to 6) are shown in Appendix Table 11.

Mean dose changes during the 3-month index period when hemoglobin concentrations were persistently < 11.0 g/dL (study months 4 to 6) were then examined in relation to mortality over the next 6 months. After adjustment for potential confounders, greater average dose changes during the index period were not associated with an increased risk of death; however, mortality was strongly and inversely associated with the hemoglobin concentration at the end of the index period (study month 6; $p < 0.0001$, $p < 0.0001$, $p = 0.0005$, and $p = 0.0192$ for hemoglobin values < 9, 9 to <9.5, 9.5 to < 10, and 10 to <10.5 compared to 10.5 to < 11 g/dL, respectively) (Figure 16).

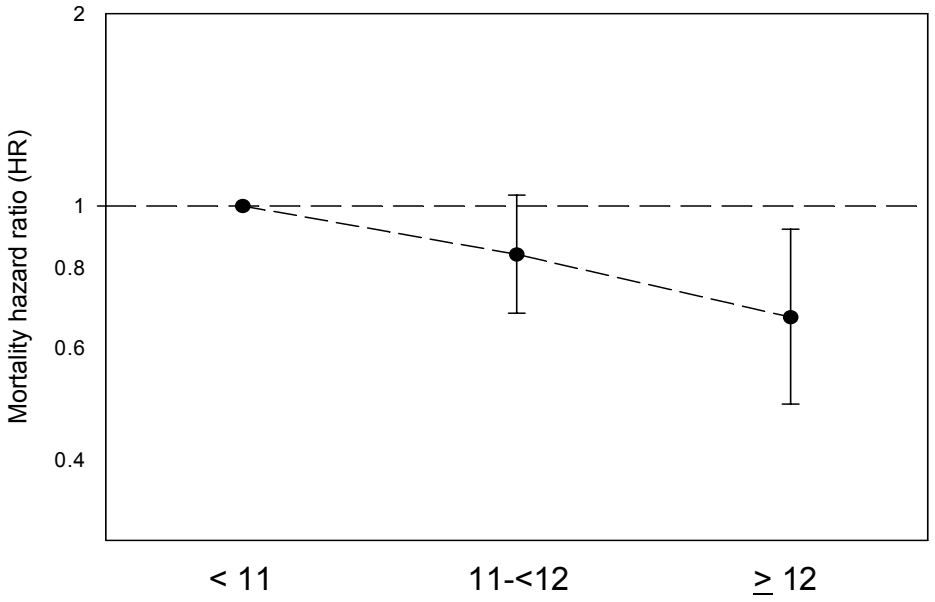
Figure 16. Association of Mean rHuEPO Dose Change or Absolute Hemoglobin Concentration with Mortality Over the Subsequent 6 Months (FMC-NA, N = 5974)



Hazard ratios and 95% CIs are plotted
Adjusted for age, sex, race, body mass index, diabetes as the cause of CRF, vascular access type, urea reduction ratio, systolic and diastolic blood pressure, number of hospitalizations, albumin, ferritin, transferrin saturation, and number of unexcused missed dialysis visits.
Source: \\filesrv04\epi\projects\epidemiology\p07_035_cwc\repository\Project_4.01\Cox models - EPO and Hb

An analysis examining the impact of achieved hemoglobin in the month following the 3-month period with hemoglobin < 11.0 g/dL (study month 7) suggested that, after accounting for relevant confounding factors and dose changes and hemoglobin concentrations during the index period, patients who achieved hemoglobin concentrations between 11.0 and < 12.0 g/dL or ≥ 12.0 g/dL during study month 7 were at a substantially lower risk of death in the next 5 months compared to patients whose hemoglobin concentrations remained < 11.0 g/dL: hazard ratios (95% CI) were 0.8 (0.7, 1.0) and 0.7 (0.5, 0.9), respectively (Figure 17).

Figure 17. Five-month Adjusted[a] Mortality Hazard Ratio (95%CI) by Achieved Hemoglobin Concentration in the Initial Month After 3 Months with Hemoglobin < 11 g/dL (FMC-NA, N = 5794)



[a] Adjusted for rHuEPO dose change, hemoglobin concentration in the last month of the 3-month index period, age, sex, race, body mass index, diabetes as the cause of CRF, vascular access type, urea reduction ratio, systolic and diastolic blood pressure, number of hospitalizations, albumin, ferritin, transferrin saturation, and number of unexcused missed dialysis visits.
Source: \\filesrv04\epi\projects\epidemiology\p07_035_cwc\repository\Project_4.01\Cox models - Hb month 7

These analyses demonstrate the following:

- Patients with sustained hemoglobin concentrations < 11.0 g/dL are more likely to achieve hemoglobin > 11.0 g/dL with greater increases in ESA dose.
- Hemoglobin concentration, not ESA dose, is highly correlated with subsequent mortality.
- Achieved hemoglobin concentrations between 11.0 and < 12.0 g/dL or ≥ 12.0 g/dL after prolonged periods of < 11.0 g/dL are associated with increased survival.

These results complement the published literature on ESA dose and ESA responsiveness, suggesting that the latter, in particular, is important as a reflection of both underlying health status and future cardiovascular risk. These results further

underscore the complexity of assigning causality in terms of cardiovascular risk to any specific component of the factors influencing anemia therapy with ESAs (ie, hemoglobin concentrations, underlying health status, ESA responsiveness, and ESA dose).

5.4.3.2 Clinical Considerations for Hypo-responsiveness

Published reports have associated measures of ESA responsiveness with adverse clinical outcomes, including mortality (Regidor et al, 2006; Kalantar-Zedah et al, 2004; Cooper et al, 2003). Examination by Amgen and J&JPRD of both observational and clinical trial data have also found that patients who responded poorly to ESAs, using several definitions of responsiveness, were at greater risk for mortality and cardiovascular outcomes compared to patients with better ESA response. While poor response to ESA therapy (ESA hypo-responsiveness) seems to be an attractive measure by which to both gauge clinical risk and determine therapeutic decision-making, 2 areas of investigation are required to gain confidence regarding the clinical utility of ESA responsiveness as a prognostic or clinical stratification measure. First, a definition of ESA hypo-responsiveness must be determined that readily identifies patients at increased risk of adverse clinical outcomes, including mortality. Second, the optimal anemia management paradigm for hypo-responsive patients should be determined. The former can likely be accomplished through refinement of analyses using existing data, while the latter will require prospectively designed clinical trials.

The primary challenge in identifying hypo-responsive patients is the lack of a validated, quantitative measure of ESA responsiveness that is associated with an increased risk of adverse clinical outcomes relevant to the CRF patient population. Efforts to overcome this challenge should include the following.

- defining a measure of ESA responsiveness that is predictive of relevant clinical outcomes
- demonstrating that this measure is equally applicable in patients actively titrating their dose to correct anemia and in those maintaining their hemoglobin level.
- demonstrating that such a measure is reliable, reproducible, and is feasible in the clinical setting

In addition to ESA responsiveness definitions described in literature or recommended by international clinical practice guidelines (eg, NKF-KDOQI™), Amgen and J&JPRD are currently exploring several definitions. Such measures should include measurements of dose and hemoglobin and should reflect a biologically plausible temporal relationship

(eg, ESA dose challenge that results in a subsequent change in hemoglobin).

ESA responsiveness definitions that Amgen and J&JPRD are exploring include:

- measures based on dose
- measures based on hemoglobin
- hemoglobin in response to a dose challenge:
    - serial increases in ESA dose without a subsequent hemoglobin increase
    - hemoglobin response to a dose increase among patients with a hemoglobin level < 11 g/dL
- during an initiation or correction phase:
    - ratio of hemoglobin change to dose
    - ratio of hemoglobin change to dose change
- during a maintenance phase:
    - ratio of average dose to average hemoglobin
    - hemoglobin < 11 g/dL and dose > 500 U/kg/wk (NKF-KDOQI™ definition)
    - ratio of dose to a subsequent hemoglobin concentration
    - slope of dose-to-hemoglobin ratio

Amgen and J&JPRD are actively evaluating these definitions in statistical analyses of several datasets. These analyses include:

- applying multiple definitions within each dataset to compare adequacy of the models relating the response definition to clinical outcomes (eg, evaluation of statistical model fit)
- determining the appropriate definition that is the most predictive of adverse clinical outcomes
- evaluating the sensitivity and specificity of each definition relative to clinical outcomes to ensure that patients are appropriately identified as hypo-responsive
- validating the definition in an independent dataset using different patient populations

Amgen and J&JPRD will provide the results of ongoing analyses to facilitate discussion regarding an appropriate definition of hypo-responsiveness at the joint Advisory Committee meeting on 11 September 2007.

When an optimal responsiveness definition has been determined. clinical trials should be conducted to evaluate how best to manage anemia with ESA therapy, depending on the level of ESA responsiveness. Currently, the optimal ESA treatment paradigm to mitigate adverse clinical outcomes in hypo-responsive patients is unknown. Because patients who are hypo-responsive typically require greater ESA doses and have greater risk of adverse clinical outcomes, maintaining or limiting ESA dosing in these patients in the presence of hemoglobin concentrations below community consensus standards (ie, < 11 g/dL) might seem to be a reasonable approach. However, as discussed in Section 5.4.3.1, analyses of patients with persistent hemoglobin concentrations < 11 g/dL demonstrates that greater increases in ESA dosing are associated with achievement of hemoglobin levels > 11 g/dL, and these dose increases are not associated with risk of mortality over the subsequent 6 months. Furthermore, among patients who are able to achieve an increase in hemoglobin concentration to > 11 g/dL after being persistently < 11 g/dL, a reduction in risk of mortality is evident. As a result, equipoise exists regarding the appropriate management strategy in patients who demonstrate hypo responsiveness to ESA therapy.

Amgen and J&JPRD, therefore, believe that the area of hypo-responsiveness to ESAs warrants further evaluation. This would include ongoing analyses to determine an appropriate definition for responsiveness and clinical trials to further evaluate appropriate ESA treatment for hypo-responsive patients. At the joint Advisory Committee meeting, Amgen and J&JPRD will present the results of ongoing analyses to facilitate discussion regarding an appropriate definition of hypo-responsiveness, as well as trial design options to evaluate appropriate ESA treatment for hypo-responsive patients. These discussions will facilitate the inclusion of the concept of hypo-responsiveness into all ESA labels, as described in the risk management plan (Section 6.2).

5.4.3.3 Concomitant Iron Use and Clinical Outcomes

The impact of iron administration on clinical outcomes in patients with CRF is not known. Inadequate iron stores to support hematopoiesis is one of the most common reasons for lack of robust response to ESA therapy (NKF, 2006). Therefore, iron therapy is commonly administered in conjunction with ESAs to treat anemia in CRF, particularly in the dialysis setting where iron is predominantly administered intravenously. Although iron therapy may improve ESA response, a variety of preclinical and clinical studies and epidemiological analyses have shown that iron administration has been associated with

augmented oxidative stress, increased carotid artery thickness, accelerated atherosclerosis, higher risk of infection, and increased risk of cardiovascular morbidity and all-cause mortality (Zheng, et al, 2006; Afzali and Goldsmith, 2004; Guz et al, 2004; Drüeke et al, 2002; Besarab et al, 1999).

Consideration of the association between iron utilization and clinical outcomes is subject to many of the same confounding issues that are present with ESA therapy. In addition, analyses of ESA therapy and clinical outcomes have typically not accounted for formulation, dose, or route of iron administration. Thus, it is currently not known whether iron administration plays an independent and causal role regarding cardiovascular risk, or whether iron administration explains some or all of the cardiovascular risks associated with ESA therapy. To date, no clinical trials of iron utilization and subsequent impact on mortality and cardiovascular risk have been conducted. Similarly, the use of iron in randomized clinical trials of ESA therapy has not been fully evaluated and future studies should monitor and analyze iron utilization as a covariate.

6. RISK MANAGEMENT PLAN

6.1 Key Points

- Safety concerns regarding increased mortality and cardiovascular events were raised by 2 prospective clinical trials, NHCT and CHOIR, each of which evaluated higher-than-approved hemoglobin targets in CRF patients.
    - Amgen and J&JPRD updated the product labelling and informed healthcare providers, investigators, clinical trial subjects, and data safety monitoring committees (DSMCs).
    - Amgen and J&JPRD will sponsor additional educational programs that specifically highlight the increased risk of mortality and cardiovascular/thromboembolic events when targeting higher-than-approved hemoglobin concentrations.
    - Amgen and J&JPRD recommend that the label should reflect the use of a hemoglobin target range to guide clinical practice.
- Exploratory analyses of observational and clinical trial data suggest a higher risk of cardiovascular morbidity and mortality in hypo-responsive patients.
    - Amgen and J&JPRD will provide draft concepts for precautionary ESA label language relating to the evaluation and management of hypo-responsive patients at the CRDAC and DSRM AC joint meeting on 11 September 2007. This language will be finalized in collaboration with the FDA using input received from the CRDAC and DSRM AC.
    - Amgen and J&JPRD will sponsor additional educational programs that highlight the increased risk of mortality and cardiovascular events in hypo-responsive patients.
- Amgen and J&JPRD perform continuous postmarketing pharmacovigilance activities to monitor the safety of Epoetin alfa and darbepoietin alfa.
- Ongoing clinical trials (eg, TREAT) are addressing important unanswered questions that will further inform our understanding of the benefit: risk profile of ESA therapy. For example, the primary objective of TREAT, a randomized, placebo controlled trial, is to evaluate the effect of anemia therapy with darbepoetin alfa on the composite event of all-cause mortality and nonfatal cardiovascular events in nondialysis CRF subjects with type 2 diabetes mellitus.
- Amgen and J&JPRD will present draft concepts for clinical trial designs to evaluate the appropriate dosing paradigm for hypo-responsive patients at the CRDAC and DSRM AC joint meeting on 11 September 2007.

The Risk Management Plan described below provides the risk minimization activities that have already been implemented, ongoing pharmacoviligance activities along with additional risk management activities to address 2 specific safety signals that have been recently identified:

- an observed increased risk of death and cardiovascular events in some clinical trials with higher-than-approved hemoglobin targets
- Exploratory analyses of observational and clinical trial data suggest a higher risk of cardiovascular morbidity and mortality in hypo-responsive patients. ESA dose in relationship to these risks is not well understood.

6.2 Risk Minimization Activities Implemented

The following risk minimization activities have been implemented to address the observed increased risk of death and cardiovascular events when targeting higher-than-approved hemoglobin concentrations in clinical trials, as shown in Figure 2:

- The Epoetin alfa and darbepoetin alfa USPIs have been updated as follows :
    - A boxed Warning was added, which includes the following statement:

      "Aranesp and other ESAs increased the risk for death and for serious cardiovascular events when administered to target a hemoglobin of greater than 12 g/dL".
    - The following statement was added in the Warnings section for Increased Mortality, Serious Cardiovascular and Thromboembolic Events:

      "… erythropoiesis-stimulating agents (ESAs) increased the risk for death and for serious cardiovascular events in controlled clinical trials when administered to target a hemoglobin of greater than 12 g/dL. There was an increased risk of serious arterial and venous thromboembolic events, including myocardial infarction, stroke, congestive heart failure, and hemodialysis graft occlusion. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may also contribute to these risks."
- A DHCP letter highlighting the changes to the label, to which a copy of the revised USPI was attached, was sent jointly by Amgen and J&JPRD to nephrologists, oncologist and other physicians who prescribe Epoetin alfa and/or darbepoetin alfa.

- The DHCP letter and the revised USPI were also sent to all investigators participating in TREAT and other Amgen-sponsored trials with Epoetin alfa and darbepoetin alfa in all countries where clinical trials were ongoing.
- The DSMC for TREAT was informed about the label changes, along with the results of the key trials that identified the safety signal. In addition, the DSMC further strengthened the safety monitoring guidelines for this clinical trial.
- The Patient Information Leaflet was updated for patients who are receiving commercial product.
- The risk communication section of the Informed Consent for ongoing studies was updated and distributed to principle investigators participating in all clinical trials with instructions to reconsent study subjects.
- The Amgen and Ortho Biotech Products, LP websites were updated with the revised prescribing information and revised patient information leaflet for access by prescribers and patients.

6.3 Postmarketing Pharmacovigilance Surveillance

Amgen and J&JPRD continuously monitor the safety of darbepoetin alfa through postmarketing adverse event reporting, both from trials and clinical practice. All spontaneously reported serious adverse events are reviewed by Amgen health care professionals as part of a comprehensive pharmacovigilance system. This includes case level review and aggregated adverse event analyses, proactive signal detection, and product safety profile comparisons across products in the same therapeutic class. This system also includes completed clinical trial safety assessments and periodic analysis of pooled clinical trails. In addition, quarterly Product Safety Review Meetings (PSRMs) are conducted to review safety observations from any source for consideration in product labeling. Further, the safety profile of Epoetin alfa and darbepoetin alfa is systematically reviewed and analyzed on a periodic basis and the results of this analysis are shared with the Agency on an ongoing basis (biannually for Aranesp and annually for Epogen) in the form of a periodic safety update report (PSUR) submitted to the FDA.

6.4 Proposed Risk Minimization and Communication

Amgen and J&JPRD propose the following proactive communication and education activities beyond those already implemented for CRF patients:

- update the label to reflect the use of a hemoglobin target range to guide clinical practice for anemia management. Amgen and J&JPRD believe the data support 12.0 g/dL as the upper end of the target range to provide a safety margin against higher hemoglobin targets (ie, > 13 g/dL). Available evidence also supports 11.0 g/dL as the lower end of the target range. Given the lack of definitive data and limited feasibility to delineate between narrow hemoglobin targets, it may be reasonable to consider a lower boundary. Amgen and J&JPRD believe the lower boundary of the target should not be less than 10.0 g/dL.
- additional educational programs that specifically highlight the overall risks of ESA use along with the risk of mortality and serious cardiovascular/thromboembolic events when targeting higher-than-approved hemoglobin concentrations. These programs will include continuing medical education, presentations or collaboration with medical societies, and patient education.
- Amgen will conduct a utilization study to assess practice patterns for use of ESAs pre- and post-label change to determine effectiveness of labeling changes.

The observational and clinical trial data suggest that patients with poor ESA responsiveness are at a greater risk of mortality and cardiovascular morbidity. To mitigate this risk, Amgen proposes a risk management plan that proactively communicates and educates physicians by providing:

- draft concepts for precautionary ESA label language relating to the evaluation and management of hypo-responsive patients at the CRDAC and DSRM AC joint meeting on 11 September 2007. This language will be finalized in collaboration with the FDA using input received from the CRDAC and DSRM AC.
- additional educational programs that specifically highlight the apparent higher risk category for hypo-responsive patients.

6.5 Clinical Research

Amgen and J&JPRD continue to research specific questions associated with the use of ESAs post-approval to ensure that maximum benefits are made available to patients and to understand the scope of risk and safety associated with this class of therapeutics.

6.5.1 TREAT

TREAT is a large (N = 4000), randomized, placebo-controlled, double-blind trial to assess whether treatment of anemia with darbepoetin alfa compared with no treatment

decreases mortality and cardiovascular morbidity in anemic, nondialysis subjects with CRF and type 2 diabetes. Because TREAT is an adequately powered and placebo-controlled cardiovascular outcomes trial, it represents the best research opportunity to determine the clinical outcome benefits of ESA therapy beyond transfusion and health-related quality of life measures in anemic, nondialysis CRF patients. TREAT will also directly address the question of cardiovascular risk associated with ESA therapy and, thus, provide important information regarding the benefit: risk profile of ESA therapy in this patient population.

In TREAT, ESA-naïve patients are randomized (1:1) to receive either treatment with darbepoetin alfa to achieve a hemoglobin target of 13.0 g/dL or placebo. Rescue therapy with darbepoetin alfa is instituted for subjects randomized to placebo when hemoglobin concentrations decrease to < 9.0 g/dL. The hemoglobin target of 13.0 g/dL is supported by many observational studies associating achieved hemoglobin concentrations within this range with improved clinical outcomes (Volkova and Arab, 2006) and is lower than the target used in other anemia correction trials in CRF patients in which safety signals were observed (ie, NHCT, CHOIR). The primary endpoint is the time to the composite event comprising all-cause mortality and nonfatal cardiovascular events, including acute myocardial ischemia, congestive heart failure requiring medical attention, myocardial infarction, and cerebrovascular accident.

The planned sample size is 4000 subjects. TREAT began enrolling subjects in 2004 and is projected to end in 2009, when 1203 primary events are expected to have occurred. TREAT currently has more than twice the enrolled sample size and primary endpoint events than CHOIR and CREATE.

TREAT is closely monitored by an independent, external DSMC that reviews safety data quarterly. Since the inception of the study, the DSMC has met a total of 10 times. At the 23 March 2007 meeting, the DSMC also reviewed the publicly available data from CHOIR (Singh et al, 2006) and CREATE (Drüeke et al, 2006) and the recent US label changes for ESAs, including heightened warning statements for mortality and cardiovascular risk when targeting higher hemoglobin concentrations. Based upon these reviews, the DSMC recommended that TREAT continue as planned with no alteration to study design. Subjects were reconsented following: 1) publication of the CHOIR and CREATE study data and 2) the resultant changes to the ESA labels to ensure that they are aware of the recently reported safety signals with ESA use.

The TREAT Executive Committee and DSMC modified the interim monitoring procedures used for safety before the second planned interim analysis. The monitoring procedures for efficacy remain unchanged. The interim monitoring procedure for safety employs a constant significance level of 0.05 for all remaining analyses. The DSMC recommendation would be to stop the study if safety analysis detects risk for harm that has a one-sided p-value < 0.05. This rule is conservative and the stopping boundary would detect a 16% to 11% increase in the risk of either mortality alone or the primary composite endpoint over the remaining planned analyses. The stopping rule enables transparency for participating patients, the medical community, and the public regarding the amount of risk for harm that can be ruled out at each planned safety analysis.

The last DSMC safety review was on 18 July 2007, which included the second planned interim analysis (with 40% of primary endpoints) and an evaluation of the totality of the unblinded and blinded data. The sample size for this review was over 3400 subjects and included 501 adjudicated primary endpoints. Therefore, this sample represents the largest subject dataset from a single randomized, controlled trial in patients with CRF and anemia. After their review of the subject data using the revised safety monitoring procedures and examining publicly available information, the DSMC saw no cogent reasons to recommend alteration or termination of TREAT. As a result of the revised safety stopping rule, the continuation of this trial provides assurance that the hazard ratio point estimate for the primary composite endpoint does not exceed 1.16.

The DSMC will continue to review safety information monthly, conduct quarterly meetings to provide formal recommendations regarding safety analyses, and perform planned interim analyses for both safety and efficacy when 60% and 80% of primary endpoints are collected. The outcome of all formal DSMC recommendations will be communicated to the FDA.

6.5.2 Clinical Trial to Evaluate Hypo-responsive Patients

Although data suggest that ESA responsiveness is associated with clinical outcomes, the appropriate dosing paradigm for hypo-responsive subjects has not been determined. Amgen and J&JPRD are discussing the design and feasibility of prospective well-controlled clinical trials to examine these issues. Further studies in these areas must be clinically relevant, practical, operationally feasible, and provide insight into the optimal benefit: risk profile for these patients. Any potential clinical trial must balance the adequacy of the study to meet its objectives with ethical and feasibility considerations (ie, with respect to the patient population, ethics committees, and regulatory agencies).

To facilitate discussions, Amgen and J&JPRD will present draft concepts for clinical trial design for the evaluation of hypo-responsive patients at the CRDAC and DSRM AC joint meeting on 11 September 2007. These will be finalized in collaboration with the FDA using input received from the CRDAC and DSRM AC.

7. CONCLUSIONS

- The benefit: risk profile of ESA therapy in CRF patients is favorable with appropriate guidance not to exceed a hemoglobin target of 12.0 g/dL.
- ESAs provide clear clinical benefit in CRF patients with regard to transfusion avoidance and improvements in physician-assessed and patient-reported outcomes.
- ESA use in CRF patients is associated with specific and well-described risks that are primarily cardiovascular or immunologic in origin. Importantly, an increased risk for mortality and cardiovascular morbidity has been observed in clinical trials targeting hemoglobin concentrations > 13.0 g/dL in CRF patients. These risks are prominently reflected in the product labeling.
- Amgen and J&JPRD believe that risk management through the following appropriately addresses the known safety concerns:
    - inclusion of hemoglobin target range in ESA product labeling;
    - precautionary ESA label language regarding hypo-responsiveness;
    - communication of overall risks of ESA use to healthcare providers;
    - continuous monitoring of ongoing clinical trials (eg, TREAT); and
    - a clinical trial to evaluate the appropriate dosing paradigm for hypo-responsive patients.

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9. APPENDICES

Appendix 1. Post-text Tables and Figures

Post-Text Tables

Post-Text Figures

Appendix Table 1. Clinical Consequences Associated With Anemia in CRF Patients

Symptom/Outcome	Citation
Decreased oxygen delivery & utilization	Horina et al, 1993; Braumann et al, 1991; Robertson et al, 1990
Impaired cognition Decreased mental acuity	Marsh et al, 1991
Increased: Cardiac output Cardiac enlargement Left ventricular hypertrophy Angina Congestive heart failure	Levin et al, 1999; Tucker et al, 1997; Levin et al, 1996; Foley et al, 1995; Greaves et al, 1994; Harnett and Parfrey, 1994; Wizemann et al, 1993; Pascual et al, 1991; Cannella et al, 1990; Macdougall et al, 1990
Reduced rehabilitation & long-term survival	Lowrie et al, 2003; Ofsthun et al, 2003; Al-Ahmad et al, 2001; Mocks, 2000; Ma et al, 1999; Madore et al, 1997; Foley et al, 1996; Harnett et al, 1995;
Decreased physical functioning & anemia symptoms	Furuland et al. 2003; Foley et al. 2000; Bárány et al, 1993; Muirhead et al, 1992b; Bahlmann et al, 1991; Canadian Erythropoietin Study Group, 1990; Evans et al, 1990
Increased hospitalizations	Ofsthun et al, 2003; Collins et al, 2001; Holland and Lam, 2000; Xia et al, 1999; Churchill et al, 1995; Harris et al, 1991

Appendix Table 2. Analysis of Baseline and Month 6 Scores Comparing Combined Epoetin alfa Groups to Placebo in Ortho Study EP86-004 (Dialysis Subjects)

	EP86-004			
Mean (SD)	Placebo	Low Erythropoietin Group	High Erythropoietin Group	p-value
Energy				
KDQ Fatigue Scale				
Baseline	4.5 (1.1)	4.0 (1.3)	4.3 (1.4)	
Month 6	4.5 (1.2)	5.0 (1.1)	5.3 (1.1)	< 0.001[a]
Patient-generated Fatigue				
Baseline	4.1	3.1	3.7	
Month 6	4.1	5.4	5.0	< 0.001[b]
Weakness				
Patient-generated Weakness/Decreased Strength				
Baseline	4.1	2.8	4.0	
Month 6	4.2	5.3	5.3	< 0.001[b]
Shortness of Breath				
Patient-generated Shortness of Breath				
Baseline	3.6	4.3	4.2	
Month 6	4.4	5.9	5.8	NS
Functional Ability/Physical Function				
KDQ Physical				
Baseline	4.2 (1.0)	3.7 (1.1)	3.9 (1.0)	
Month 6	4.6 (1.0)	5.2 (1.1)	5.3 (1.0)	< 0.001[a]
SIP Physical				
Baseline	4.3 (4.8)	6.6 (7.3)	6.1 (6.4)	
Month 6	4.2 (5.7)	2.6 (3.4)	2.4 (3.9)	0.005[a]
Exercise Capacity				
Exercise Stress Test (min)				
Baseline	11.9 (5.3)	11.9 (5.0)	14.9 (5.6)	
Month 6	13.2 (5.7)	15.0 (5.2)	19.7 (6.4)	0.025[a]
6-minute Walk Test (m)				
Baseline	446 (115)	426 (102)	469 (110)	
Month 6	440 (120)	451 (109)	524 (174)	NS

[a] p-values are based on the change from baseline using analysis of variance comparing placebo versus the combined erythropoietin group at each time point

[b] p-values are based on the response profile comparing placebo versus the combined erythropoietin group

NS = Not significant

Appendix Table 3. Post-hoc Analysis of Baseline and First Follow-up Scores Comparing Epoetin alfa and Placebo Goups for Anemia Symptoms in Amgen Studies 8904 and 8701 (Dialysis Subjects)

		8904			8701		
		Placebo	EPO	p-value	Placebo	EPO	p-value
Energy	NKDKTS Energy item (% reporting Tires easily/ No energy)						
	Baseline	97.4%	89.2%	0.146	87.5%	76.7%	0.289
	12 Weeks	97.5%	76.5%	0.006	77.3%	60.0%	0.159
	Single item PRO (% reporting Very full of energy/Fairly energetic)						
	Baseline	10.0%	16.2%	0.419	26.9%	39.4%	0.314
	12 Weeks	4.9%	52.8%	<0.001	40.7%	53.3%	0.336
	Nottingham Health Profile Energy Scale						
	Baseline (mean)	64.8	48.5	n/a [a]	47.2	31.5	n/a [a]
	12 Weeks (mean)	63.1	33.4	n/a [a]	34.3	24.2	n/a [a]
Muscle weakness	NKDKTS Energy item (% reporting Weakness/Lack of strength)						
	Baseline	94.9%	77.8%	0.027	84.0%	67.7%	0.152
	12 Weeks	87.2%	61.8%	0.010	76.0%	51.6%	0.055
	Single item PRO (% reporting Muscle weakness)						
	Baseline	76.9%	63.9%	0.211	60.0%	60.0%	1.000
	12 Weeks	82.5%	47.1%	0.001	56.0%	34.4%	0.097
Shortness of breath	NKDKTS Shortness of Breath Symptom Score (% Reporting Shortness of Breath/Difficulty Breathing)						
	Baseline	60.0%	54.1%	0.601	46.2%	51.6%	0.680
	12 Weeks	43.9%	35.3%	0.441	46.2%	33.3%	0.313
Physical function	Karnofsky PRO (% ≥ 90/normal)						
	Baseline	12.5%	25.0%	0.158	25.0%	23.0%	0.858
	12 Weeks	27.5%	44.5%	0.120	45.2%	44.4%	0.951

[a] n/a = not available: standard deviations were not reported and post-hoc statistical testing could not be performed; PRO = patient-reported outcome

Appendix Table 4. Summary of Literature on Epoetin alfa Trials Measuring Energy (Dialysis Subjects)

Measure	Study	Design	Improvement	MID
NHP Energy Scale	Auer et al, 1990	Single-arm	stat sig	62%[a*]
	Auer et al, 1992	Single-arm	stat sig	66% [b*]
KDQ Fatigue	Muirhead et al, 1992a	RCT	stat sig	0.5 point [c*]
	Foley et al, 2000	RCT	stat sig	0.01 point [c†]
Other: Fatigue Symptoms	Harris et al, 1991	Single-arm	stat sig	N/E

KDQ = Kidney Disease Questionnaire; N/E = not evaluable; NHP = Nottingham Health Profile; RCT = randomized clinical trial; stat sig = statistically significant; MID = minimally important difference

* Change meets criteria for clinically meaningful or minimally important difference

† Change does not meet criteria for clinically meaningful or minimally important difference

[a] approximate 50% reduction of % patients with 'low energy' is clinically meaningful

[b] Standard response mean (SRM) ≥0.5 is clinically meaningful and SRM > 0.8 is large change

[c] 0.5 mean change in score represents minimally important difference; 1.0 mean change represents large change

Appendix Table 5. Summary of Literature on Epoetin alfa Trials Measuring Functional Ability/Physical Functioning (Dialysis Subjects)

Measure	Study	Design	Improvement	MID
Physician-assessed Karnofsky	Evans et al, 1990 (Amgen 8601)	single-arm	stat sig	a*
	Delano, 1989	single-arm	NS	11 points [b*]
	Harris et al, 1991	single-arm	stat sig	12 points [b*]
	Lee et al, 2004	Open-label, High vs low Hematocrit groups	NS	N/E
Patient-reported Karnofsky	Moreno et al, 1996	controlled	stat sig	12.6 points [b*]
	Moreno et al, 2000	single-arm	stat sig	2.8 points [b†]
SIP Physical Function	McMahon and Dawborn, 1992	crossover	stat sig	4.4 SD [c*]
	Moreno et al, 1996	controlled	stat sig	0.43 SD [c†]
	McMahon et al, 2000	DB, crossover	Numerical	1.7 SD [c*]
KDQ Physical Symptoms	Muirhead et al, 1992a	RCT	stat sig	0.9 point [d*]
	Foley et al, 2000	RCT	Numerical	1.17 points [d*]
	Furuland et al, 2003	RCT	stat sig	0.66 point [d*]
SF-36 Physical Functioning	Beusterien et al, 1996	controlled	stat sig	3.7 point [e†]
	Besarab et al, 1998	RCT	stat sig	N/E
Other				
Percent 'Very Active'	Eschbach et al, 1989 (Amgen 8601)	single-arm	stat sig	a*
Physical Activity	Bárány et al, 1990	single-arm	stat sig	0.5 SD [c*]
Physical Activity	Bárány et al, 1993	controlled	stat sig	N/E

DB = double-blind; KDQ = Kidney Disease Questionnaire; N/E = not evaluable;
RCT = randomized clinical trial; SD = standard deviation; SIP = Sickness Impact Profile;
stat sig = statistically significant; MID = minimally important difference; NS = not significant
* Change meets criteria for clinically meaningful or minimally important difference
† Change does not meet criteria for clinically meaningful or minimally important difference
[a] approximate doubling of % of patients with 'normal' function is clinically meaningful
[b] > 10.0 mean change from baseline is clinically meaningful
[c] effect size ≥ 0.5 SD is clinically meaningful
[d] 0.5 mean change in score represents minimally important difference; 1.0 mean change represents large change
[e] 8.0 mean change is clinically meaningful

Appendix Table 6. Summary of Literature on Epoetin alfa Trials Measuring Exercise Capacity (Dialysis Subjects)

Measure	Study	Design	Improvement	MID
VO_2 max	Lundin et al, 1991	single-arm	stat sig	1.54 SD [a]
	Robertson et al, 1990	single-arm	stat sig	0.48 SD [b]
	Mayer et al, 1998	single-arm	stat sig	1.23 SD [a]
	Grunze et al, 1990	single-arm	stat sig	0.7 SD [a]
	Lewis et al, 1993	single-arm	stat sig	1.21 SD [a]
	Metra et al, 1991	single-arm	stat sig	1.24 SD [a]
	Marrades et al, 1996	single-arm, health control	stat sig	1.77 SD [a]
Exercise stress test (min)	Lundin et al, 1991	single-arm	stat sig	1.17 SD [a]
	Robertson et al, 1990	single-arm	stat sig	0.47 SD [b]
	Lewis et al, 1993	single-arm	stat sig	1.15 SD [a]
	Hase et al, 1993	single-arm	stat sig	1.42 SD [a]
	Metra et al, 1991	single-arm	stat sig	0.89 SD [a]
6-minute Walk Test (m)	Harris et al, 1991	single-arm	stat sig	0.58 SD [a]

MID = minimally important difference, defined as effect size ≥ 0.5 standard deviation (SD); SD = standard deviation; Stat sig = statistically significant
[a] Clinically meaningful or minimally important difference
[b] Change does not meet criteria for clinically meaningful or minimally important difference

Appendix Table 7. Summary of Physician-assessed and Patient-reported Outcomes From 10 Clinical Trials with Epoetin alfa and Epoetin beta in Nondialysis CRF Subjects

Study	Physician Assess/ PRO Measure (Hematologic Measure)	Study Design	Hematologic Improvement	Physician Assess/PRO Improvement	CMD[a]
Singh et al (2006)[b]	LASA, KDQ, SF-36 (Hb)	Open-label, randomized High vs low Hb target	Stat sig	Stat sig	LASA: Energy: 68.38%, Activity: 55.04%
Benz et al (2007)[c]	LASA, SF-36 (Hb, Hct)	Open-label, single arm	Stat sig	Stat sig	LASA: Energy: 100.49%, Activity: 74.24% Overall: 66.67% SF-36: Vitality: 59.75%
Provenzano et al (2004)[d]	KDQ, LASA (Hb, Hct)	Open-label, single arm	Stat sig	Stat sig	LASA: Energy: 138.12%, Activity: 106.52% Overall: 98.69% KDQ: Physical Symptoms 136.36% Fatigue 93.33% Depression 50.00% Relationship 57.14% Total: 87.10%
The US Recombinant Human EPO Group (1991)	Energy Level and Work Capacity (Hct)	Placebo-controlled	Stat sig	Stat sig	Not reported

Appendix Table 7. Summary of Physician-assessed and Patient-reported Outcomes Results From 10 Clinical Trials with Epoetin alfa and Epoetin beta in Nondialysis CRF Subjects

Study	Physician Assess./ PRO Measure (Hematologic Measure)	Study Design	Hematologic Improvement	Physician Assess/PRO Improvement	CMD[a]
Kleinman et al (1989)	LASA (Hct)	Placebo-controlled	Stat sig	Stat sig	Not reported
Revicki et al (1995)	SIP, SF-36 (Hct)	Open-label, parallel group Treated vs untreated	Stat sig	Stat sig	Not reported
Roger et al (2004)	SF-36, RQLP (Hb)	Open-label, randomized High vs low Hb target	Stat sig	Numerical (RQLP)	Not reported
Rossert et al (2006)	SF-36 (Hb, Hct)	Open-label, randomized Early-complete vs delayed-partial anemia correction	Not available	Stat sig	Not reported
Drüeke et al (2006)	SF-36	Open-label, parallel group	Not applicable	Stat sig	Not reported
Ritz et al (2007)	SF36 (Hb)	Open-label, parallel group High vs low Hb target	Stat sig	Stat sig	Not reported

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Assess = assessment; CMD = clinically meaningful difference; Hb = hemoglobin; Hct = hematocrit; KDQ = Kidney Disease Questionnaire; LASA = Linear Analogue Self Assessment; RQLP = Renal Quality of Life Profile; SF-36 = Medical Outcomes Study 36-Item Health Survey; PRO = patient-reported outcome; SIP = Sickness Impact Profile; Stat sig = statistically significant change from baseline

[a] Mean change from baseline as a fraction of the baseline standard deviation was ≥ 50%.

[b] PR00-06-014 (CHOIR)

[c] PR03-06-001

[d] PR00-06-009 (POWER)

Appendix Table 8. Baseline Characteristics for Patients With Hemoglobin Between 10.0 and < 12.0 g/dL During Month Before 90-Day Follow-up Period by ESA Dose Quartile
(FMC-NA Hemodialysis Patients; N = 12,004)

Patient Characteristic[a]	rHuEPO Dose (U)			
	≤ 2800	2801 - 5000	5001 - 8800	> 8800
	N = 2932	N = 3208	N = 2829	N = 3035
Age, years	61.7 (14.9)	61.1 (15.0)	60.9 (14.5)	58.5 (14.6)
Female (%)	46.1	49.7	51.7	51.3
Black (%)	40.2	40.7	42.1	47.9
Duration on dialysis, years	3.7 (3.6)	3.4 (3.5)	3.3 (3.5)	3.4 (3.6)
Urea reduction ratio, %	72.9 (6.9)	71.8 (7.4)	71.0 (7.9)	69.4 (8.6)
Catheter use (%)	25.2	30.9	35.0	40.0
Any recent hospitalizations (%)	17.8	26.0	33.1	43.9
Any cardiac-specific hospitalizations (%)	4.6	6.8	8.5	11.2
Any vascular access-specific hospitalizations (%)	2.8	4.5	5.9	8.8
Any infection-specific hospitalizations (%)	3.5	4.9	6.4	9.7
Albumin, g/dL	4.0 (0.3)	3.9 (0.4)	3.9 (0.4)	3.8 (0.4)
Ferritin, mg/mL	601.0 (261.8)	569.0 (248.3)	552.0 (267.6)	525.3 (268.6)
Hemoglobin, g/dL	11.3 (0.5)	11.2 (0.5)	11.2 (0.5)	11.1 (0.6)
Transferrin saturation (%)	31.0 (10.1)	28.3 (9.6)	26.7 (9.5)	25.5 (9.4)

[a] Values are mean (standard deviation) unless otherwise indicated.
Source: \\filesrv04\epi\projects\epidemiology\p07_035_cwc\repository\Project_6.16\Patient characteristics by dose quartile

Appendix Table 9. EPO Response Index Analysis for CHOIR

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Quartile cutoffs (g/dL/week/1,000 U)	0.014393	0.028482	0.046405	
Total Subjects (N)				
High target (N=563)	150	142	131	140
Low target (N=537)	125	134	143	135
All (N=1100)	275	276	274	275
Baseline characteristics				
Mean age (years)				
High target	67.6	66.8	65.6	64.0
Low target	69.5	66.2	66.0	64.4
All	68.4	66.5	65.8	64.2
Sex				
High target				
Male, n (%)	70 (47)	63 (44)	52 (40)	60 (43)
Female, n (%)	80 (53)	79 (56)	79 (60)	80 (57)
Low target				
Male, n (%)	62 (50)	63 (47)	70 (49)	62 (46)
Female, n (%)	63 (50)	71 (53)	73 (51)	73 (54)
Mean albumin (g/dL)				
High target	3.7	3.7	3.7	3.8
Low target	3.8	3.8	3.9	3.7
All	3.7	3.7	3.8	3.7
Mean reticulocyte count (%)				
High target	2.6	2.4	2.3	2.4
Low target	2.4	2.5	2.5	2.5
All	2.5	2.5	2.4	2.4
Mean hemoglobin (g/dL)				
High target	10.3	10.1	10.0	10.0
Low target	10.4	10.1	10.1	9.8
All	10.4	10.1	10.1	9.9

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N=total number of subjects in hemoglobin-target group; n=number of subjects in the subgroup
Source: \\na.jnj.com\OBIusdfsroot\Clinical Affairs Biostats\RO\NEPHROLOGY\PR00-06-014\FDA200706\FINAL

Appendix Table 9. EPO Response Index Analysis for CHOIR

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Prior congestive heart failure				
High target (%)	28.9	28.5	18.5	16.5
Low target (%)	28.3	20.8	21.2	20.6
All (%)	28.6	24.7	19.9	18.5
Prior atrial fibrillation/flutter				
High target (%)	14.1	9.5	8.9	5.3
Low target (%)	15.8	5.4	6.6	7.1
All (%)	14.9	7.5	7.7	6.2
Mean weight (kg)				
High target	86.1	89.2	85.2	75.5
Low target	86.8	87.2	82.8	75.7
All	86.4	88.3	83.9	75.6
Study Outcomes				
Primary events				
High target (N=98)	32	30	18	18
Low target (N=67)	21	14	16	16
All (N=165)	53	44	34	34
Mean weekly dose on study (IU)				
High target	13483	12800	10760	8172
Low target	8083	6686	5724	4961
All	11029	9832	8131	6596
Mean post-baseline hemoglobin (g/dL)				
High target	12.0	12.5	12.7	13.1
Low target	11.2	11.4	11.5	11.6
Mean post-baseline maximum hemoglobin (g/dL)				
High target	13.8	14.3	14.5	15.0
Low target	12.8	12.8	13.0	13.3

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N=total number of subjects in hemoglobin-target group; n=number of subjects in the subgroup
Source: \\na.jnj.com\OBIusdfsroot\Clinical Affairs Biostats\RO\NEPHROLOGY\PR00-06-014\FDA200706\FINAL

Appendix Table 10. Hazard Ratios for Composite Events by EPO Response Index or Target Hemoglobin (CHOIR)

Analysis by EPO Response Index Quartile	n	No. Events	Hazard Ratio (95% CI)	p value
Hemoglobin target 13.5 g/dL				
Unadjusted				
1st quartile (least responsive)	150	32	reference group	
2nd quartile	142	30	0.88 (0.54, 1.45)	0.624
3rd quartile	131	18	0.56 (0.31, 0.99)	0.047
4th quartile (most responsive)	140	18	0.51 (0.29, 0.91)	0.023
Adjusted				
2nd quartile			1.02 (0.61, 1.69)	0.942
3rd quartile			0.69 (0.38, 1.26)	0.228
4th quartile			0.73 (0.40, 1.31)	0.287
Hemoglobin target 11.3 g/dL				
Unadjusted				
1st quartile (least responsive)	125	21	reference group	
2nd quartile	134	14	0.60 (0.31, 1.19)	0.143
3rd quartile	143	16	0.62 (0.32, 1.19)	0.152
4th quartile (most responsive)	135	16	0.71 (0.37, 1.36)	0.300
Adjusted				
2nd quartile			0.67 (0.33, 1.34)	0.257
3rd quartile			0.70 (0.36, 1.37)	0.298
4th quartile			0.83 (0.42, 1.63)	0.595
Combined target groups				
Unadjusted				
1st quartile (least responsive)	275	53	reference group	
2nd quartile	276	44	0.77 (0.52, 1.15)	0.201
3rd quartile	274	34	0.58 (0.37, 0.89)	0.012
4th quartile (most responsive)	275	34	0.59 (0.38, 0.91)	0.017
Adjusted				
2nd quartile			0.88 (0.58, 1.32)	0.526
3rd quartile			0.70 (0.45, 1.08)	0.104
4th quartile			0.77 (0.50, 1.20)	0.250

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CI=confidence interval; n=number of subjects; no.=number
Adjusted: Cox proportional hazard model including the following covariates: age, prior medical history of congestive heart failure, prior medical history of atrial fibrillation/flutter, baseline National Health and Nutrition Examination Survey I (NHANES) congestive heart failure score ≥ 3, baseline serum albumin, and baseline percent reticulocyte count.
Source: \\na.jnj.com\OBIusdfsroot\Clinical Affairs Biostats\RO\NEPHROLOGY\PR00-06-014\FDA200706\FINAL

Appendix Table 10. Hazard Ratios Composite Events by EPO Response Index or Target Hemoglobin (CHOIR)

Analysis by EPO Response Index Quartile	n	No. Events	Hazard Ratio (95% CI)	p value
Comparison of target groups				
Unadjusted				
Low hemoglobin target	537	67	reference group	
High hemoglobin target	563	98	1.42 (1.04, 1.93)	0.028
1st quartile (least responsive)	275	53	reference group	
2nd quartile	276	44	0.77 (0.52, 1.15)	0.206
3rd quartile	274	34	0.59 (0.38, 0.90)	0.015
4th quartile (most responsive)	275	34	0.59 (0.38, 0.91)	0.017
Adjusted				
High hemoglobin			1.39 (1.01, 1.90)	0.041
2nd quartile			0.87 (0.58, 1.31)	0.518
3rd quartile			0.71 (0.46, 1.10)	0.122
4th quartile			0.78 (0.50, 1.21)	0.270
Comparison of responsiveness across target groups				
Unadjusted				
1st quartile - high target	150	32	reference group	
2nd quartile - high target	142	30	0.89 (0.54, 1.46)	0.637
3rd quartile - high target	131	18	0.56 (0.31, 0.99)	0.046
4th quartile - high target	140	18	0.51 (0.29, 0.91)	0.024
1st quartile - low target	125	21	0.71 (0.41, 1.23)	0.222
2nd quartile - low target	134	14	0.43 (0.23, 0.81)	0.008
3rd quartile - low target	143	16	0.44 (0.24, 0.80)	0.008
4th quartile - low target	135	16	0.50 (0.28, 0.92)	0.026
Adjusted				
2nd quartile - high target			0.98 (0.59, 1.62)	0.941
3rd quartile - high target			0.68 (0.38, 1.23)	0.207
4th quartile - high target			0.72 (0.40, 1.30)	0.274
1st quartile - low target			0.75 (0.43, 1.30)	0.300
2nd quartile - low target			0.53 (0.28, 1.00)	0.049
3rd quartile - low target			0.54 (0.30, 1.00)	0.048
4th quartile - low target			0.64 (0.35, 1.17)	0.145

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CI=confidence interval; n=number of subjects; no.=number
Adjusted: Cox proportional hazard model including the following covariates: age, prior medical history of congestive heart failure, prior medical history of atrial fibrillation/flutter, baseline National Health and Nutrition Examination Survey I (NHANES) congestive heart failure score ≥ 3, baseline serum albumin, and baseline percent reticulocyte count.
Source: \\na.jnj.com\OBIusdfsroot\Clinical Affairs Biostats\RO\NEPHROLOGY\PR00-06-014\FDA200706\FINAL

Appendix Table 10. Hazard Ratios Composite Events by EPO Response Index or Target Hemoglobin (CHOIR)

Analysis by EPO Response Index Quartile	n	No. Events	Hazard Ratio (95% CI)	p value
Comparison of targets in each quartile				
1st quartile (least responsive)				
Low target	125	21	reference group	
High target (unadjusted)	150	32	1.40 (0.81, 2.43)	0.231
High target (adjusted)			1.34 (0.76, 2.36)	0.310
2nd quartile				
Low target	134	14	reference group	
High target (unadjusted)	142	30	2.04 (1.08, 3.84)	0.028
High target (adjusted)			1.70 (0.88, 3.28)	0.117
3rd quartile				
Low target	143	16	reference group	
High target (unadjusted)	131	18	1.24 (0.63, 2.43)	0.533
High target (adjusted)			1.50 (0.75, 3.01)	0.251
4th quartile (most responsive)				
Low target	135	16	reference group	
High target (unadjusted)	140	18	1.01 (0.52, 1.98)	0.973
High target (adjusted)			1.20 (0.58, 2.48)	0.619

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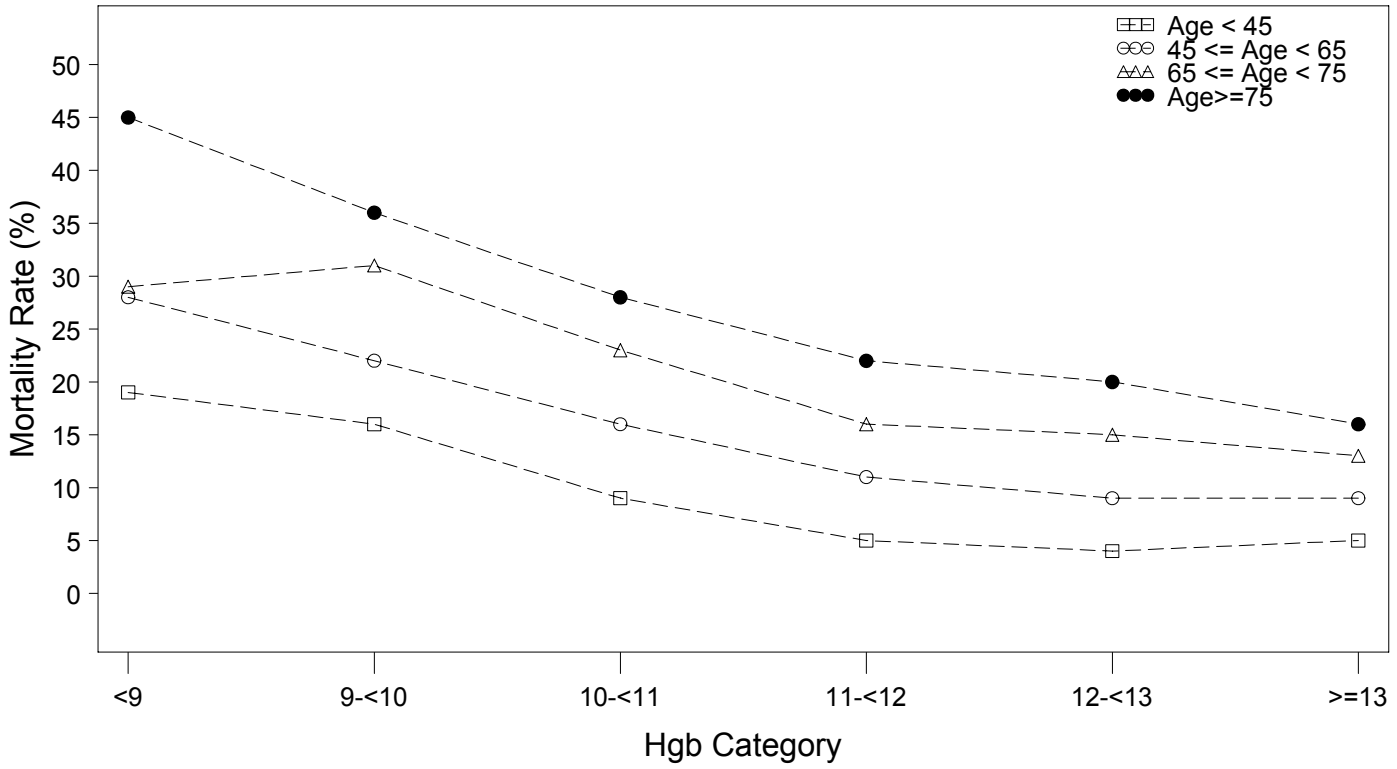
CI=confidence interval; n=number of subjects; no.=number
Adjusted: Cox proportional hazard model including the following covariates: age, prior medical history of congestive heart failure, prior medical history of atrial fibrillation/flutter, baseline National Health and Nutrition Examination Survey I (NHANES) congestive heart failure score ≥3, baseline serum albumin, and baseline percent reticulocyte count.
Source: \\na.jnj.com\OBIusdfsroot\Clinical Affairs Biostats\RO\NEPHROLOGY\PR00-06-014\FDA200706\FINAL

Appendix Table 11. Cumulative Percentage of Patients Achieving Hemoglobin ≥ 11.0 g/dL During 90-day Follow-up by Average Monthly Percentage ESA Dose Change During the Previous 3 Months (FMC-NA, N = 6133)

	Average Monthly Percentage ESA Dose Change During Study Months 4 to 6				
Hb ≥ 11 g/dL by Study Month	≤ 0% (n = 757)	0-12.5% (n = 1429)	> 12.5-25% (n = 1488)	> 25-37.5% (n = 982)	> 37.5% (n = 1477)
7	20.4%	30.7%	34.7%	41.2%	50.3%
8	35.4%	50.3%	55.3%	64.5%	72.5%
9	46.5%	61.2%	69.3%	77.1%	82.2%

Source: \\filesrv04\epi\projects\epidemiology\p07_035_cwc\repository\Project_4.01\Cumulative Hb ge 11

Appendix Figure 1. 12-Month Mortality Rate by Age Groups and Hemoglobin (Hgb) Categories



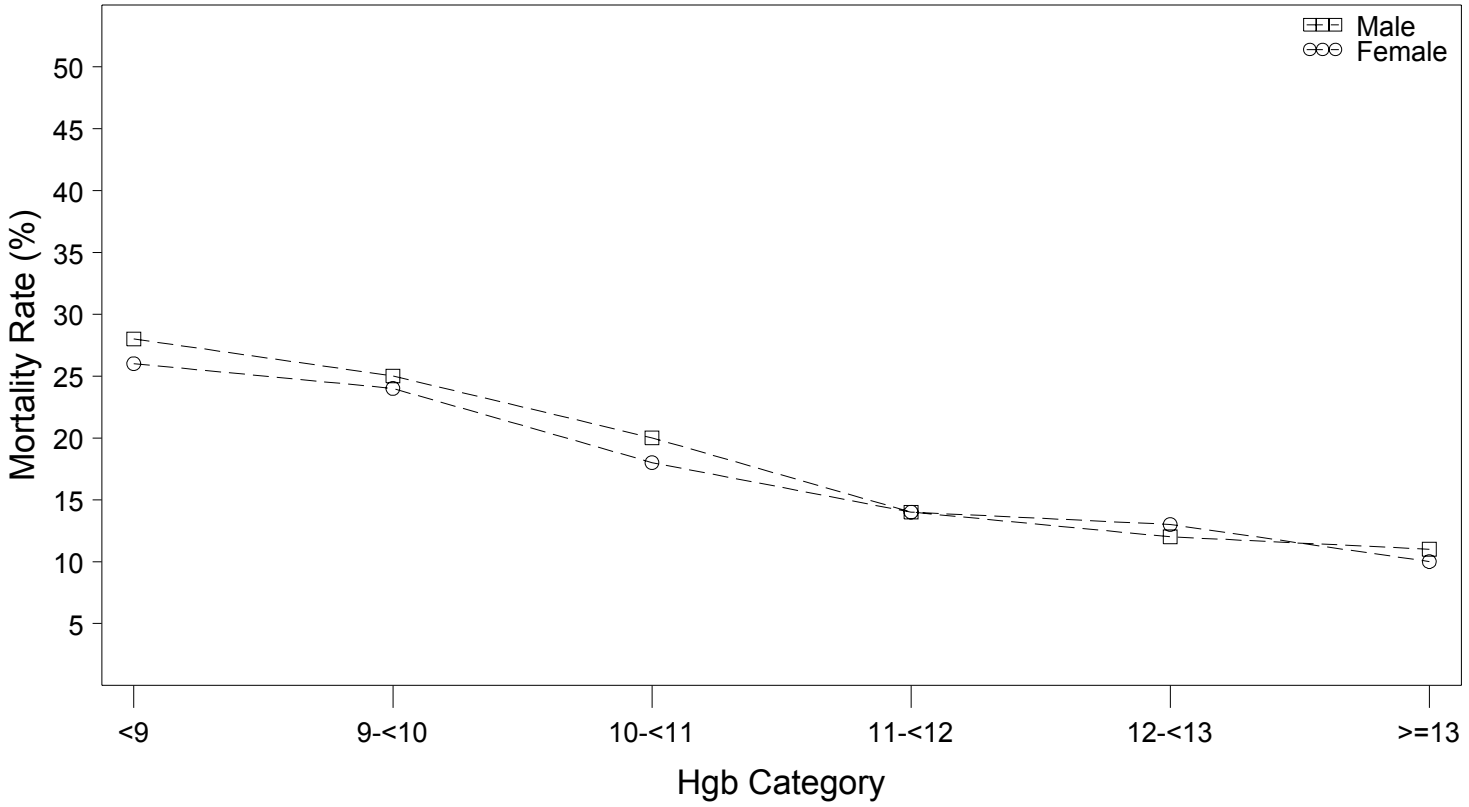
Mortality rate based upon Kaplan-Meier estimates at 12 months after baseline (month 4 to month 6)

Program: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/graphs/blcovariate.sas

Output: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/graphs/output/f5_10_01.cgm

Source: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/statdata/sdf/tmp.sas7bdat (Date Generated: 08JUN2007)

Appendix Figure 2. 12-Month Mortality Rate by Gender and Hemoglobin (Hgb) Categories



Mortality rate based upon Kaplan-Meier estimates at 12 months after baseline (month 4 to month 6)

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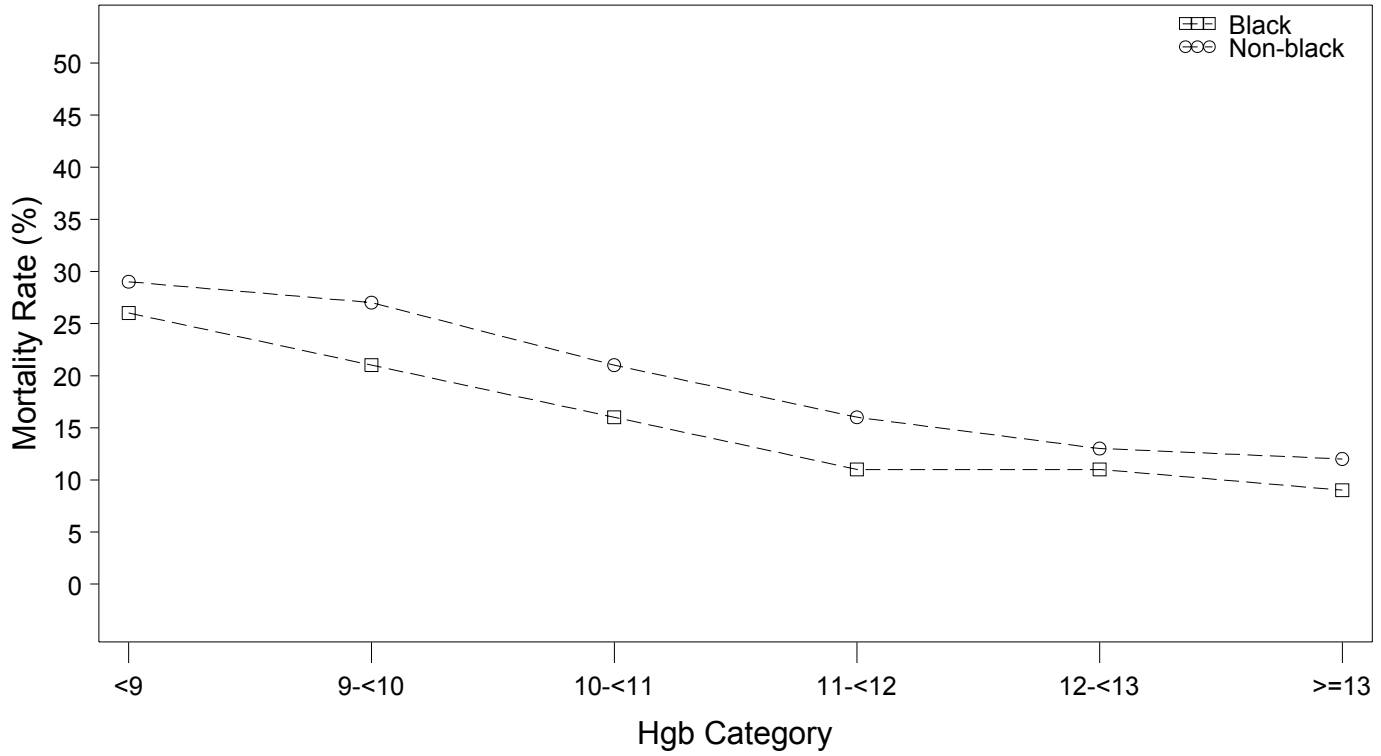
Output: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/graphs/output/f5_10_02.cgm

Source: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/statdata/sdf/tmp.sas7bdat (Date Generated: 08JUN2007)

Appendix Figure 3. 12-Month Mortality Rate by Race and Hemoglobin (Hgb) Categories



Mortality rate based upon Kaplan-Meier estimates at 12 months after baseline (month 4 to month 6)

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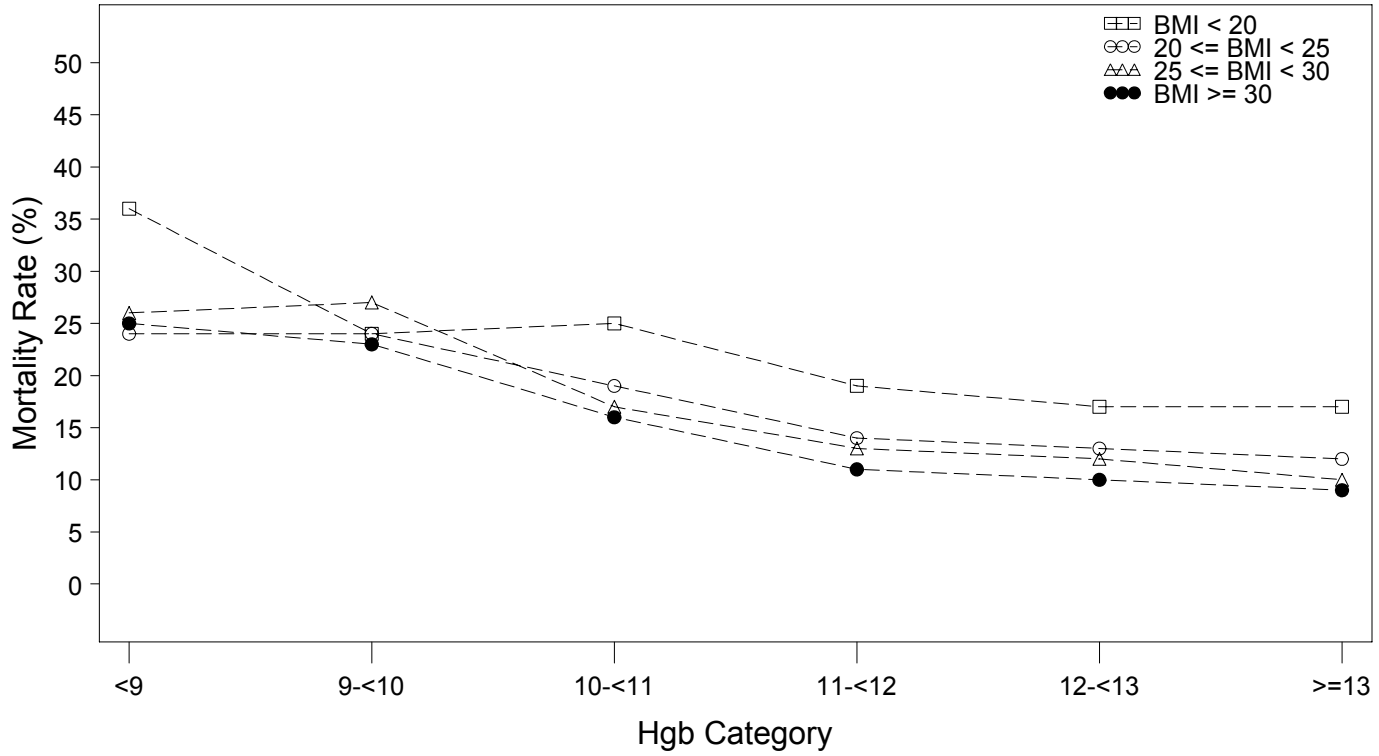
Source: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/statdata/sdf/tmp.sas7bdat (Date Generated: 08JUN2007)

Appendix Figure 4. 12-Month Mortality Rate by Body Mass index (BMI) Groups and Hemoglobin (Hgb) Categories



Mortality rate based upon Kaplan-Meier estimates at 12 months after baseline (month 4 to month 6)

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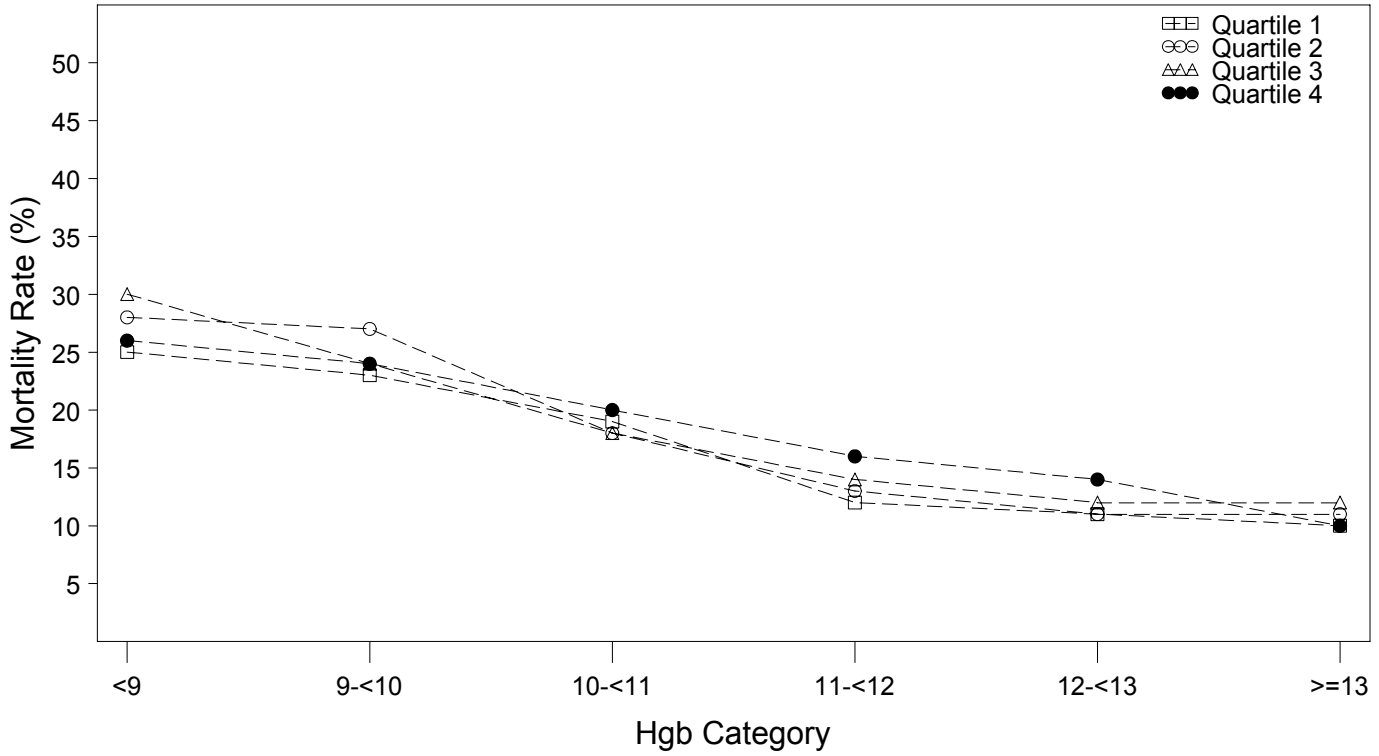
Output: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/graphs/output/f5_10_04.cgm
Source: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/statdata/sdf/tmp.sas7bdat (Date Generated: 08JUN2007)

Appendix Figure 5. 12-Month Mortality Rate and by Hemoglobin (Hgb) Standard Deviation Groups and Hemoglobin Categories



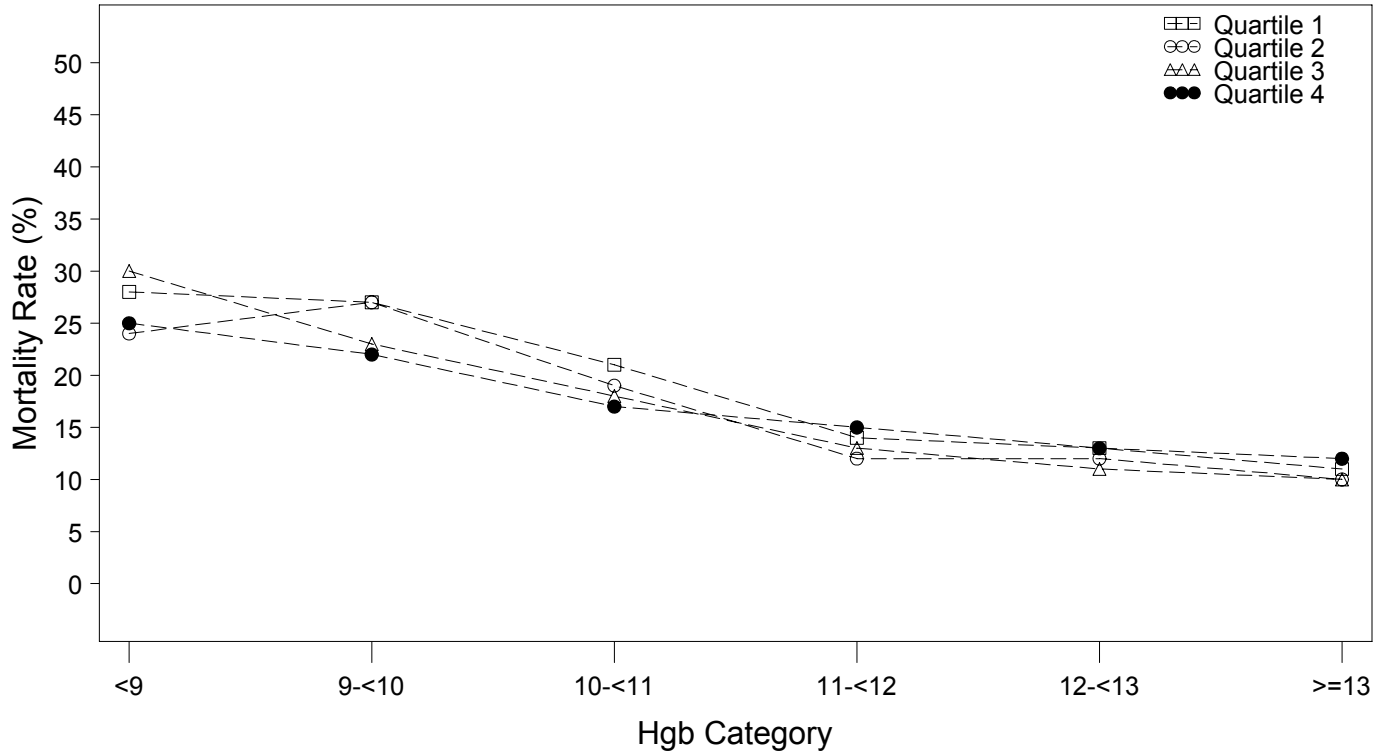
Mortality rate based upon Kaplan-Meier estimates at 12 months after baseline (month 4 to month 6)

Program: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/graphs/blcovariate.sas

Output: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/graphs/output/f5_10_05.cgm

Source: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/statdata/sdf/tmp.sas7bdat (Date Generated: 08JUN2007)

Appendix Figure 6. 12-Month Mortality Rate by Baseline Hemoglobin (Hgb) Slope Groups and Hemoglobin Categories



Mortality rate based upon Kaplan-Meier estimates at 12 months after baseline (month 4 to month 6)

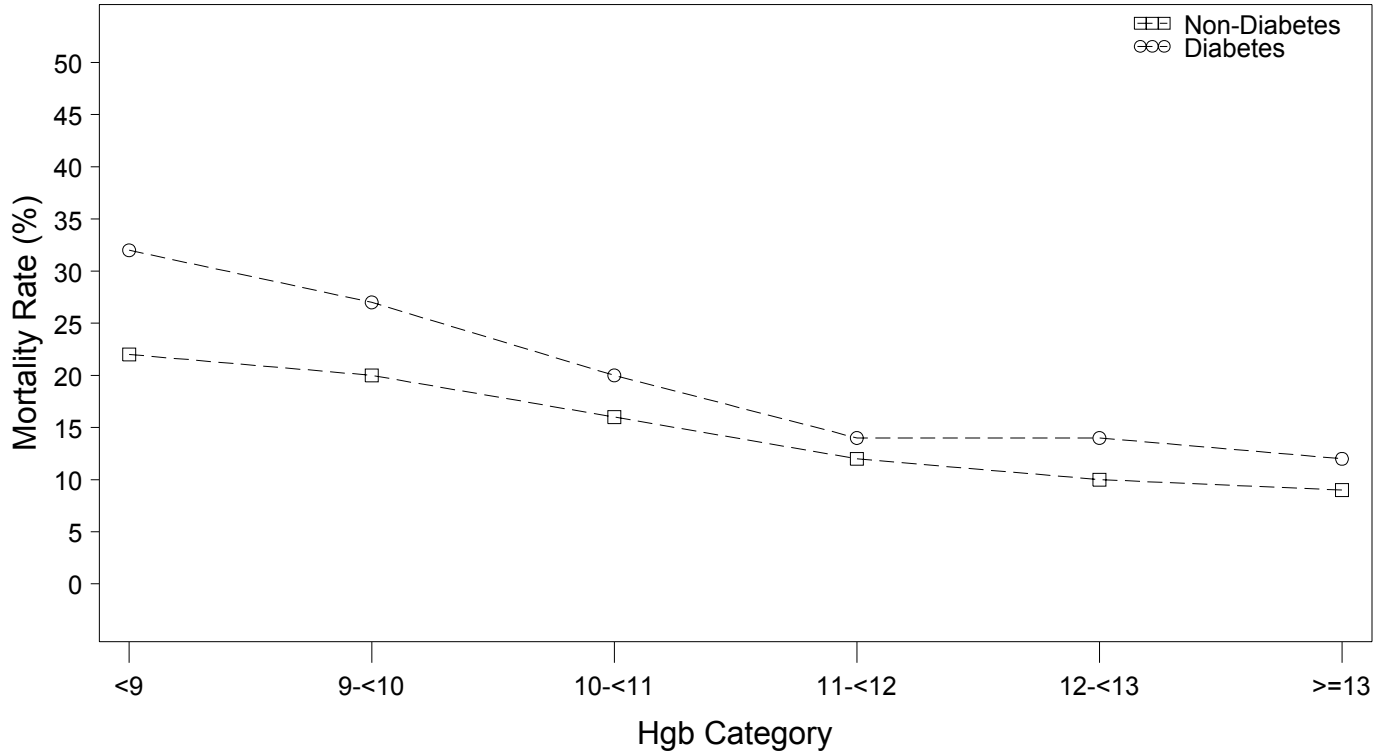
Program: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/graphs/blcovariate.sas

Output: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/graphs/output/f5_10_06.cgm

Source: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/statdata/sdf/tmp.sas7bdat (Date Generated: 08JUN2007)

Baseline hemoglobin slope defined as the regression of hemoglobin on time during the baseline period (g/dL/month)

Appendix Figure 7. 12-Month Mortality Rate by Diabetes Status as a Primary Reason for ESRD and Hemoglobin (Hgb) Categories



Mortality rate based upon Kaplan-Meier estimates at 12 months after baseline (month 4 to month 6)

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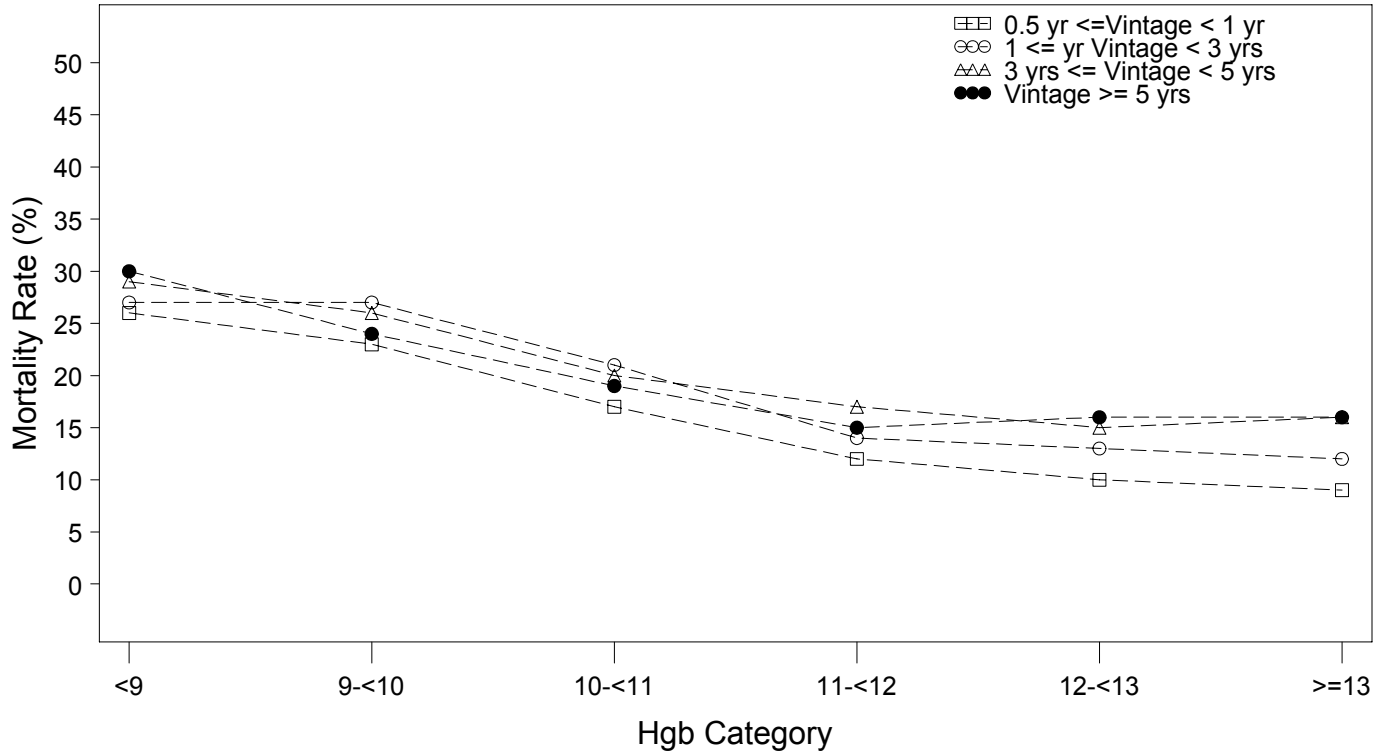
Output: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/graphs/output/f5_10_07.cgm
Source: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/statdata/sdf/tmp.sas7bdat (Date Generated: 08JUN2007)

Appendix Figure 8. 12-Month Mortality Rate by Years on Dialysis (Vintage Years) and Hemoglobin (Hgb) Categories



Mortality rate based upon Kaplan-Meier estimates at 12 months after baseline (month 4 to month 6)

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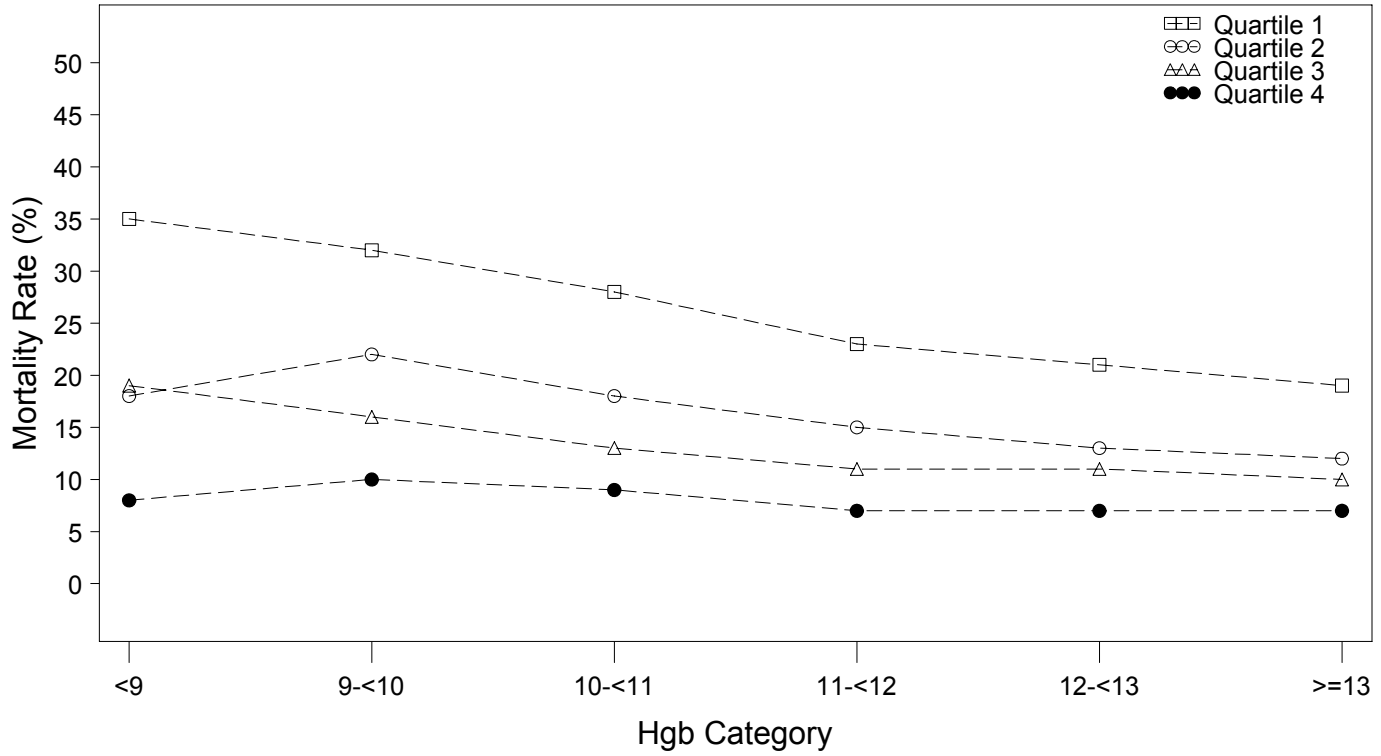
Source: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/statdata/sdf/tmp.sas7bdat (Date Generated: 08JUN2007)

Appendix Figure 9. 12-Month Mortality Rate by Albumin Groups and Hemoglobin (Hgb) Categories



Mortality rate based upon Kaplan-Meier estimates at 12 months after baseline (month 4 to month 6)

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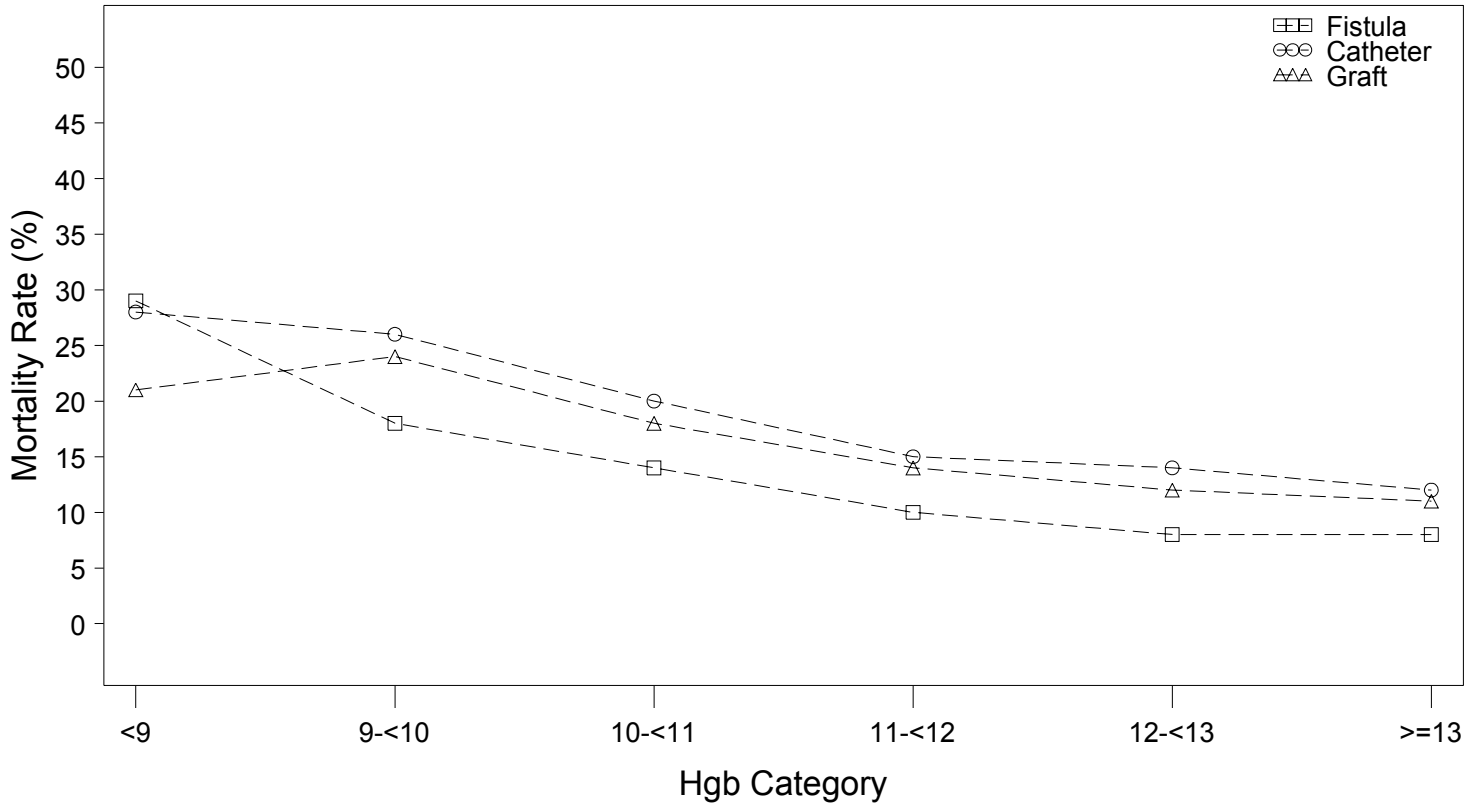
Output: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/graphs/output/f5_10_09.cgm

Source: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/statdata/sdf/tmp.sas7bdat (Date Generated: 08JUN2007)

Appendix Figure 10. 12-Month Mortality Rate by Vascular Access Type and Hemoglobin (Hgb) Categories



Mortality rate based upon Kaplan-Meier estimates at 12 months after baseline (month 4 to month 6)

Program: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/graphs/blcovariate.sas

Output: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/graphs/output/f5_10_10.cgm

Source: /mastat/nesp/neph/confounding_by_indication/analysis/fda_submission/statdata/sdf/tmp.sas7bdat (Date Generated: 08JUN2007)

Appendix 2. Pooled Clinical Trial Analyses

Introduction

Amgen-sponsored Clinical Trials

Forty-six prospective, Amgen-sponsored, single-arm or active-control clinical trials that met the following criteria were pooled at the patient level for analyses:

- phase 2 to 4
- enrolled ≥ 12 adult subjects with CRF either receiving or not receiving dialysis and study duration ≥ 16 weeks (these criteria eliminate small studies with acute dosing [eg, pharmacokinetic studies])
- treatment regimens included either darbepoetin alfa or rHuEPO (eg, epoetin alfa or beta) manufactured using a process approved in at least 1 regulatory region
- final data available and technically feasible to compile into a pooled electronic dataset

Thirty-eight, 2, and 6 of the selected clinical trials, respectively, provide data from subjects receiving darbepoetin alfa, rHuEPO, and both darbepoetin alfa and rHuEPO. Thirty, 13, and 3 of these trials, respectively, provide data from dialysis, nondialysis, and both dialysis and nondialysis CRF subjects. Amgen-sponsored clinical trials included in these analyses are listed in PCT Table 14.

J&J-sponsored Clinical Trials

J&JPRD performed analyses on combined data from prospective clinical studies that it had either conducted or supported. J&JPRD's analyses focused on studies for which it had access to patient-level data available as of 23 July 2007 that could be combined into an electronic dataset. J&JPRD continues to identify appropriate studies for inclusion in future analyses.

The 16 J&JPRD studies identified for this pooled analysis (3 in dialysis and 13 in nondialysis CRF populations) met the following criteria: prospective design, Phase 2 to 4, enrolled 12 or more CRF subjects (nondialysis or dialysis), and treatment with Epoetin alfa (PROCRIT® or EPREX®). The designs of these 16 studies with patient-level data are summarized in PCT Table 15.

Statistical Methods

Amgen-sponsored Clinical Trials

The primary objectives of the exploratory analyses using pooled clinical trial data were to examine the effect of baseline dose, target hemoglobin, and achieved hemoglobin concentration on the clinical outcomes of all cause mortality, composite thromboembolic

events, and heart failure. Analyses were run separately for darbepoetin alfa use for dialysis and nondialysis subjects and rHuEPO use for dialysis subjects.

Cox regression analysis was used to examine the effect of initial on-study absolute ESA dose and hemoglobin target (≤ 12 g/dL or > 12 g/dL) on mortality and each event of interest.

Time-dependent Cox regression was used to estimate the effect of hemoglobin and dose on the risk of mortality and each of the other events of interest. Exposure variables included in the models were achieved hemoglobin concentration (g/dL) over time and ESA dose over time. In addition, models were developed incorporating lags on ESA dose (administered 1 month prior to the event) and hemoglobin concentration (g/dL) (measured 2 months prior to the event).

Crude unadjusted estimates and estimates from full multivariate models including all baseline covariates were calculated. The following baseline covariates were included: age, sex, race/ethnicity, geographic region, dry weight, eGFR, primary cause of renal disease, years on dialysis, dialysis modality, baseline hemoglobin, iron deficiency as determined by TSAT or ferritin, albumin, creatinine, history of diabetes, history of cardiovascular disease, history of peripheral vascular disease, history of hypertension, initial on-study ESA dose, rate of rise criterion in the ESA dosing algorithm, hemoglobin target, and year of study start. Depending on the analyses, some of these variables were included in the models as an exposure variable and not as a covariate.

J&J-sponsored Clinical Trials

The objectives of these exploratory analyses using the combined patient-level data were to examine the association between clinical outcomes of interest (mortality, thromboembolic events, congestive heart failure) and achieved hemoglobin concentration, target hemoglobin, hemoglobin rate of change, and epoetin alfa dose.

A time-dependent Cox regression analysis model was used to estimate the risk of adverse outcomes for each of the clinical outcomes of interest. The time-dependent covariates included were:

- maximal hemoglobin concentration (g/dL) within 1 month before the event of interest
- maximal hemoglobin rate of change (g/dL/week) within the 1 month before the event of interest

- maximal Epoetin alfa dose (units/kg/week) within the 1 month before the event of interest (or at the equivalent time point in follow-up for those who had not experienced an event);
- average cumulative weekly Epoetin alfa dose (units/kg/week) from the start of the study;

In addition, the hemoglobin target (> 12 versus ≤ 12 g/dL) was included in the model as well as treatment phase (maintenance versus initiation, as a fixed covariate for purely initiation/titration or maintenance studies or a time-dependent covariate for the studies that contain both initiation/titration and maintenance phases).

To adjust for potential differences in baseline characteristics among those subjects with different hemoglobin and/or dosing trajectories, the following baseline variables were included in the model as fixed covariates: dialysis requirement, age, sex, body mass index, eGFR, baseline hemoglobin and albumin levels, and history of hypertension, cardiovascular events, and diabetes.

A summary of the results is presented in PCT Table 13.

Achieved Hemoglobin Levels Over Time and Clinical Outcomes

Amgen-sponsored Clinical Trials

The results of pooled analyses across clinical trials with either darbepoetin alfa or rHuEPO consistently show that the risk for mortality, composite thromboembolic events, and heart failure decreases for every 1 g/dL increase in achieved hemoglobin concentration, regardless of dialysis status or ESA administered (PCT Table 1 to PCT Table 3). Similar results were also observed after adjustment for baseline subject characteristics.

J&J-sponsored Clinical Trials

A progressive decrease in mortality risk was observed as maximal hemoglobin concentration within the month prior to the event increased from ≤ 10 to 15 g/dL. The hazard ratio for maximal hemoglobin ≤ 10 g/dL was 2.21 (95% CI: 1.30, 3.74; $p < 0.01$) compared to a reference range of 11.0 to 12.0 g/dL. There appeared to be a greater mortality risk for subjects with hemoglobin rates of rise exceeding 0.75 g/dL/week, as well as for subjects with negative rates of rise (ie, declines) of 0.1 g/dL/week or more, although these findings were not statistically significant.

Although not statistically significant, a progressive decrease in risk for thromboembolic events was also observed as maximal hemoglobin concentration within the month prior to the event increased from ≤ 10 to > 15 g/dL. There was no clear association between maximal hemoglobin rate of change and risk for thromboembolic events.

There appeared to be a decreased risk of congestive heart failure as maximal hemoglobin concentration within the month prior to the event increased from ≤ 10 to 15 g/dL. The hazard ratio exceeded unity for all categories of maximal hemoglobin rate of change compared with the > 0.25 to 0.50 g/dL/week group. The highest risk was observed for the group with a decline of ≥ 0.1 g/dL/week.

Target Hemoglobin (Upper Limit of > 12.0 Compared with ≤ 12.0 g/dL) and Clinical Outcomes

Amgen-sponsored Clinical Trials

No significant difference in mortality risk was observed in studies with darbepoetin alfa administered to a target > 12.0 g/dL compared with a target ≤ 12.0 g/dL, regardless of subject dialysis status (PCT Table 4). Although not conclusive due to wide CIs, point estimates for the hazard ratios suggest an increased mortality risk in studies with rHuEPO administered to a target > 12.0 g/dL compared with a target ≤ 12.0 g/dL (PCT Table 4). This result is largely influenced by the inclusion of the NHCT in this analysis. Similar results were observed after adjustment for baseline subject characteristics.

Comparison of the risk for composite thromboembolic events between target hemoglobin ranges show disparate results depending upon subject dialysis status. A higher risk was observed for studies in which darbepoetin alfa was administered to a hemoglobin target > 12.0 g/dL compared with a target ≤ 12.0 g/dL in nondialysis subjects (hazard ratio [95% CI] 2.00 [1.50, 2.67]) (PCT Table 5). Similar results were observed after adjustment for baseline subject characteristics. Further analyses revealed that these results were primarily driven by increased risks for myocardial infarction/coronary artery disease (hazard ratio [95% CI] 2.23 [1.53, 3.25]) and embolism/thrombosis events (hazard ratio [95% CI] 4.10 [2.25, 7.47]) (data on file, Amgen).

In contrast to the results observed for nondialysis subjects, a lower risk or no difference in risk for thromboembolic events, respectively, was observed for studies in which darbepoetin alfa or rHuEPO was administered to a hemoglobin target > 12.0 g/dL in

dialysis subjects (hazard ratio [95% CI] 0.62 [0.55, 0.69] and 0.98 [0.87, 1.10], respectively) (PCT Table 5). Adjustment for baseline characteristics resulted in a slightly higher hazard ratio, indicating that other factors may be contributing to the risk for clinical outcomes in these subjects and highlight the complexity of relating clinical outcomes to specific study design elements (ie, target hemoglobin) or patient characteristics in these analyses.

Divergent results were also observed between nondialysis and dialysis subjects for the association between target hemoglobin and the risk for heart failure. Similar to the results observed for thromboembolic events, an increased risk for heart failure was observed for studies in which darbepoetin alfa was administered to a hemoglobin target > 12.0 g/dL compared with ≤ 12.0 g/dL in nondialysis subjects (hazard ratio [95% CI] 1.57 [1.13, 2.18]) (PCT Table 6). After adjustment for all covariates, however, the increase in risk was not significant (hazard ratio [95% CI] 1.52 [0.98, 2.34]). In contrast, a lower risk or no increased risk for heart failure was observed for studies in which darbepoetin alfa or rHuEPO was administered to a target hemoglobin concentration > 12.0 g/dL in dialysis subjects (hazard ratio [95% CI] 0.74 [0.58, 0.92] and 0.92 [0.76, 1.12], respectively) (PCT Table 6). Of note, the NHCT was included in the rHuEPO clinical trial analyses.

J&J-sponsored Clinical Trials

There is a suggestion of increased risk for mortality in subjects treated to high hemoglobin targets (> 12 g/dL) compared with those treated to low hemoglobin targets (hazard ratio 1.32 [95% CI: 0.90, 1.94]; p = 0.16). Of note, the CHOIR study was included in these analyses.

There was no apparent increased risk for thromboembolic events or congestive heart failure for the higher- versus lower-hemoglobin target groups; hazard ratio 1.08 (95% CI: 0.85, 1.37; p = 0.54) and 1.19 (95% CI: 0.89, 1.60; p=0.24), respectively.

ESA Dose Over Time and Clinical Outcomes

Amgen-sponsored Clinical Trials

Baseline Dose

The relation between baseline ESA dose and risk for all-cause mortality, composite thromboembolic events (cerebrovascular disorder, myocardial infarction/coronary artery disease, embolism/thrombosis), and heart failure was different for dialysis and

nondialysis subjects. An increased risk (hazard ratios of 1.01 to 1.03) for these clinical outcomes was associated with higher baseline doses of darbepoetin alfa or rHuEPO in dialysis subjects (PCT Table 7 to PCT Table 9). Adjustment for baseline covariates did not attenuate these estimates. However, this analysis is limited by the use of a single baseline measure of ESA dose that does not reflect the effect of ESA dose titration in response to hemoglobin that fluctuates over time.

In nondialysis subjects, higher baseline doses of darbepoetin alfa were not associated with greater risks for mortality, composite thromboembolic events, or heart failure (hazard ratios of 0.98 to 1.00) (PCT Table 7 to PCT Table 9). Similar results were observed after adjustment for baseline patient characteristics.

Dose Over Time

The relation between ESA dose over time and clinical outcomes was explored using time-dependent Cox regression to model the association between ESA dose and clinical outcome allowing hemoglobin levels and subsequent ESA doses to change over time, such that ESA dose was assessed 1-month before death or cardiovascular event, adjusted for the hemoglobin concentration 1 month before the ESA dose.

In dialysis subjects administered higher doses of darbepoetin alfa or rHuEPO, an increased risk for all-cause mortality, composite thromboembolic events, and heart failure was observed (hazard ratios of 1.01 to 1.02) (PCT Table 10 to PCT Table 12). These results are consistent with the results for baseline ESA dose. Similar trends were observed after adjusting for baseline patient characteristics.

In nondialysis subjects increased risk for mortality and heart failure were observed with higher darbepoetin alfa dose (hazard ratio [95% CI]: 1.04 [1.01, 1.07]) (PCT Table 10 and PCT Table 12). Similar to baseline dose, however, higher darbepoetin alfa doses were not associated with an increased risk for composite thromboembolic events (hazard ratio [95% CI]: 1.02 [0.99, 1.05]) (PCT Table 11). Similar results were observed after adjusting for baseline patient characteristics.

<u>J&J-sponsored Clinical Trials</u>

In general, risk of adverse outcomes tended to increase with increasing ESA dose, although dose is highly confounded by hemoglobin responsiveness and target.

For mortality, hazard ratios less than unity were observed for maximal doses (within the 1 month before the event) up to 200 units/kg/week compared with maximal doses

≤ 50 units/kg/week, and a hazard ratio exceeding unity was observed for maximal doses > 200 units/kg/week. Subjects receiving average cumulative weekly doses (from study start to the event) greater than 50 units/kg/week were at greater risk compared with those receiving average cumulative weekly doses ≤ 50 units/kg/week.

For thromboembolic events, hazard ratios exceeding unity were observed for all maximal doses > 50 units/kg/week compared with maximal doses ≤ 50 units/kg/week. These results were not statistically significant and the associations were weak. Subjects receiving average cumulative weekly doses > 50 units/kg/week appeared to be at greater risk compared with those subjects receiving average cumulative weekly doses ≤ 50 units/kg/week.

For congestive heart failure, there appeared to be an increased risk for congestive heart failure at maximal doses > 150 units/kg/week. Hazard ratios exceeding unity were observed for average cumulative doses > 50 units/kg/week, but not statistically significant.

PCT Table 1. Effect of Achieved Hemoglobin Level Over Time on Time to All-cause Mortality by Dialysis Status and ESA Administered (Amgen-sponsored Clinical Trials)

Dialysis Status - ESA Administered	Achieved Hemoglobin (per 1 g/dL increase)			
	n	No. of Events	Hazard Ratio	95% CI
Dialysis - Darbepoetin alfa (N=10005)				
Main effect	10005	755	0.61	0.58, 0.65
Main effects adjusted by				
All covariates	8074	567	0.60	0.56, 0.65
Core covariates	8103	569	0.61	0.56, 0.65
Nondialysis - Darbepoetin alfa (N=3045)				
Main effect	3045	89	0.55	0.47, 0.65
Main effects adjusted by				
All covariates	2694	83	0.49	0.41, 0.58
Core covariates	2711	84	0.49	0.41, 0.58
Dialysis - rHuEPO (N=2253)				
Main effect	2253	502	0.84	0.80, 0.89
Main effects adjusted by				
All covariates	2033	421	0.76	0.72, 0.82
Core covariates	2040	422	0.83	0.78, 0.89

Hazard ratio and 95% CI were obtained from Cox regression
n: number of subjects included in the model
Core covariates: age, sex, race, baseline eGFR (mL/min/1.73m^2), years on dialysis, diabetes, history of myocardial infarction (MI), history of cerebrovascular accident (CVA) (except for rHuEPO trials), history of transient ischemic attack (TIA) (except for rHuEPO trials), history of peripheral vascular disease (PVD), history of hypertension, baseline hemoglobin (g/dL), iron deficiency at baseline, baseline albumin (g/dL), baseline creatinine (mg/dL).
All covariates = core covariates + region, dry weight (kg), primary cause of renal disease, dialysis modality (dialysis subjects only), initial absolute ESA dose, rate of rise consideration in dosing algorithm, year study started.
If the convergence criterion was not met, the hazard ratio and 95% CI estimates will be displayed as 'n/a'.
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PCT Table 2. Effect of Achieved Hemoglobin Level Over Time on Time to Composite of Thromboembolic Event by Dialysis Status and ESA Administered (Amgen-sponsored Clinical Trials)

Dialysis Status - ESA Administered	Achieved Hemoglobin (per 1 g/dL increase)			
	n	No. of Events	Hazard Ratio	95% CI
Dialysis - Darbepoetin alfa (N=10005)				
Main effect	10005	1771	0.76	0.73, 0.79
Main effects adjusted by				
All covariates	8074	1320	0.76	0.73, 0.81
Core covariates	8103	1328	0.76	0.72, 0.80
Nondialysis - Darbepoetin alfa (N=3045)				
Main effect	3045	179	0.78	0.69, 0.88
Main effects adjusted by				
All covariates	2694	170	0.71	0.62, 0.82
Core covariates	2711	172	0.74	0.64, 0.85
Dialysis - rHuEPO (N=2253)				
Main effect	2253	1110	0.87	0.84, 0.91
Main effects adjusted by				
All covariates	2033	976	0.85	0.81, 0.89
Core covariates	2040	980	0.90	0.86, 0.94

Hazard ratio and 95% CI were obtained from Cox regression
n: number of subjects included in the model
Composite cardiovascular event = cerebrovascular disorder, myocardial infarction/coronary artery disease, embolism/thrombosis
Core covariates: age, sex, race, baseline eGFR (mL/min/1.73m^2), years on dialysis, diabetes, history of myocardial infarction (MI), history of cerebrovascular accident (CVA) (except for rHuEPO trials), history of transient ischemic attack (TIA) (except for rHuEPO trials), history of peripheral vascular disease (PVD), history of hypertension, baseline hemoglobin (g/dL), iron deficiency at baseline, baseline albumin (g/dL), baseline creatinine (mg/dL).
All covariates = core covariates + region, dry weight (kg), primary cause of renal disease, dialysis modality (dialysis subjects only), initial absolute ESA dose, rate of rise consideration in dosing algorithm, year study started.
If the convergence criterion was not met, the hazard ratio and 95% CI estimates will be displayed as 'n/a'.
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PCT Table 3. Effect of Achieved Hemoglobin Level Over Time on Time to Heart Failure by Dialysis Status and ESA Administered (Amgen-sponsored Clinical Trials)

Dialysis Status - ESA Administered	Achieved Hemoglobin (per 1 g/dL increase)			
	n	No. of Events	Hazard Ratio	95% CI
Dialysis - Darbepoetin alfa (N=10005)				
Main effect	10005	471	0.65	0.60, 0.70
Main effects adjusted by				
All covariates	8074	372	0.69	0.62, 0.75
Core covariates	8103	375	0.68	0.62, 0.75
Nondialysis - Darbepoetin alfa (N=3045)				
Main effect	3045	133	0.68	0.59, 0.78
Main effects adjusted by				
All covariates	2694	120	0.61	0.53, 0.72
Core covariates	2711	121	0.62	0.53, 0.72
Dialysis - rHuEPO (N=2253)				
Main effect	2253	402	0.82	0.77, 0.88
Main effects adjusted by				
All covariates	2033	343	0.79	0.73, 0.85
Core covariates	2040	344	0.83	0.77, 0.89

Hazard ratio and 95% CI were obtained from Cox regression
n: number of subjects included in the model
Core covariates: age, sex, race, baseline eGFR (mL/min/1.73m^2), years on dialysis, diabetes, history of myocardial infarction (MI), history of cerebrovascular accident (CVA) (except for rHuEPO trials), history of transient ischemic attack (TIA) (except for rHuEPO trials), history of peripheral vascular disease (PVD), history of hypertension, baseline hemoglobin (g/dL), iron deficiency at baseline, baseline albumin (g/dL), baseline creatinine (mg/dL).
All covariates = core covariates + region, dry weight (kg), primary cause of renal disease, dialysis modality (dialysis subjects only), initial absolute ESA dose, rate of rise consideration in dosing algorithm, year study started.
If the convergence criterion was not met, the hazard ratio and 95% CI estimates will be displayed as 'n/a'.
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PCT Table 4. Effect of Hemoglobin Target (> vs ≤ 12.0 g/dL) on Time to All-cause Mortality by Dialysis Status and ESA Administered (Amgen-sponsored Clinical Trials)

Dialysis Status - ESA Administered	Hemoglobin target > 12 g/dL vs. <= 12 g/dL			
	n	No. of Events	Hazard Ratio	95% CI
Dialysis - Darbepoetin alfa (N=10005)				
Main effect	10005	836	0.97	0.81, 1.16
Main effects adjusted by				
All covariates	8074	632	0.91	0.68, 1.21
Core covariates	8103	636	0.94	0.71, 1.24
Nondialysis - Darbepoetin alfa (N=3045)				
Main effect	3045	136	1.03	0.72, 1.48
Main effects adjusted by				
All covariates	2694	122	0.87	0.53, 1.42
Core covariates	2711	124	0.99	0.66, 1.47
Dialysis - rHuEPO (N=2253)				
Main effect	2253	638	1.12	0.96, 1.31
Main effects adjusted by				
All covariates	2033	541	1.14	0.96, 1.36
Core covariates	2040	543	1.17	0.98, 1.39

Hazard ratio and 95% CI were obtained from Cox regression
n: number of subjects included in the model
Core covariates: age, sex, race, baseline eGFR (mL/min/1.73m^2), years on dialysis, diabetes, history of myocardial infarction (MI), history of cerebrovascular accident (CVA) (except for rHuEPO trials), history of transient ischemic attack (TIA) (except for rHuEPO trials), history of peripheral vascular disease (PVD), history of hypertension, baseline hemoglobin (g/dL), iron deficiency at baseline, baseline albumin (g/dL), baseline creatinine (mg/dL).
All covariates = core covariates + region, dry weight (kg), primary cause of renal disease, dialysis modality (dialysis subjects only), initial absolute ESA dose, rate of rise consideration in dosing algorithm, year study started.
If the convergence criterion was not met, the hazard ratio and 95% CI estimates will be displayed as 'n/a'.
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PCT Table 5. Effect of Hemoglobin Target (> vs ≤ 12.0 g/dL) on Time to Composite of Thromboembolic Event by Dialysis Status and ESA Administered (Amgen-sponsored Clinical Trials)

Dialysis Status - ESA Administered	Hemoglobin target > 12 g/dL vs. <= 12 g/dL			
	n	No. of Events	Hazard Ratio	95% CI
Dialysis - Darbepoetin alfa (N=10005)				
Main effect	10005	1782	0.62	0.55, 0.69
Main effects adjusted by				
All covariates	8074	1330	0.94	0.78, 1.14
Core covariates	8103	1338	0.80	0.66, 0.96
Nondialysis - Darbepoetin alfa (N=3045)				
Main effect	3045	199	2.00	1.50, 2.67
Main effects adjusted by				
All covariates	2694	188	1.66	1.16, 2.39
Core covariates	2711	190	1.81	1.32, 2.47
Dialysis - rHuEPO (N=2253)				
Main effect	2253	1120	0.98	0.87, 1.10
Main effects adjusted by				
All covariates	2033	984	1.05	0.92, 1.19
Core covariates	2040	988	1.09	0.96, 1.24

Hazard ratio and 95% CI were obtained from Cox regression
n: number of subjects included in the model
Composite cardiovascular event = cerebrovascular disorder, myocardial infarction/coronary artery disease, embolism/thrombosis
Core covariates: age, sex, race, baseline eGFR (mL/min/1.73m^2), years on dialysis, diabetes, history of myocardial infarction (MI), history of cerebrovascular accident (CVA) (except for rHuEPO trials), history of transient ischemic attack (TIA) (except for rHuEPO trials), history of peripheral vascular disease (PVD), history of hypertension, baseline hemoglobin (g/dL), iron deficiency at baseline, baseline albumin (g/dL), baseline creatinine (mg/dL).
All covariates = core covariates + region, dry weight (kg), primary cause of renal disease, dialysis modality (dialysis subjects only), initial absolute ESA dose, rate of rise consideration in dosing algorithm, year study started.
If the convergence criterion was not met, the hazard ratio and 95% CI estimates will be displayed as 'n/a'.
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PCT Table 6. Effect of Hemoglobin Target (> vs ≤ 12.0 g/dL) on Time to Heart Failure by Dialysis Status and ESA Administered (Amgen-sponsored Clinical Trials)

Dialysis Status - ESA Administered	Hemoglobin target > 12 g/dL vs. <= 12 g/dL			
	n	No. of Events	Hazard Ratio	95% CI
Dialysis - Darbepoetin alfa (N=10005)				
Main effect	10005	473	0.74	0.58, 0.92
Main effects adjusted by				
All covariates	8074	374	1.03	0.74, 1.43
Core covariates	8103	377	0.91	0.66, 1.26
Nondialysis - Darbepoetin alfa (N=3045)				
Main effect	3045	150	1.57	1.13, 2.18
Main effects adjusted by				
All covariates	2694	135	1.52	0.98, 2.34
Core covariates	2711	136	1.67	1.15, 2.41
Dialysis - rHuEPO (N=2253)				
Main effect	2253	408	0.92	0.76, 1.12
Main effects adjusted by				
All covariates	2033	347	0.94	0.75, 1.17
Core covariates	2040	348	0.93	0.75, 1.15

Hazard ratio and 95% CI were obtained from Cox regression
n: number of subjects included in the model
Core covariates: age, sex, race, baseline eGFR (mL/min/1.73m^2), years on dialysis, diabetes, history of myocardial infarction (MI), history of cerebrovascular accident (CVA) (except for rHuEPO trials), history of transient ischemic attack (TIA) (except for rHuEPO trials), history of peripheral vascular disease (PVD), history of hypertension, baseline hemoglobin (g/dL), iron deficiency at baseline, baseline albumin (g/dL), baseline creatinine (mg/dL).
All covariates = core covariates + region, dry weight (kg), primary cause of renal disease, dialysis modality (dialysis subjects only), initial absolute ESA dose, rate of rise consideration in dosing algorithm, year study started.
If the convergence criterion was not met, the hazard ratio and 95% CI estimates will be displayed as 'n/a'.
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PCT Table 7. Effect of Baseline ESA Dose on Time to All-cause Mortality by Dialysis Status and ESA Administered (Amgen-sponsored Clinical Trials)

Dialysis Status - ESA Administered	Baseline ESA Dose (per 5μg/wk darbepoetin alfa or 1000 U/wk rHuEPO)			
	n	No. of Events	Hazard Ratio	95% CI
Dialysis - Darbepoetin alfa (N=10005)				
Main effect	10004	836	1.02	1.01, 1.03
Main effects adjusted by				
All covariates	8074	632	1.03	1.02, 1.04
Core covariates	8102	636	1.03	1.02, 1.04
Nondialysis - Darbepoetin alfa (N=3045)				
Main effect	3045	136	0.99	0.95, 1.04
Main effects adjusted by				
All covariates	2694	122	1.02	0.97, 1.07
Core covariates	2711	124	1.00	0.95, 1.06
Dialysis - rHuEPO (N=2253)				
Main effect	2253	638	1.02	1.01, 1.02
Main effects adjusted by				
All covariates	2033	541	1.01	1.00, 1.02
Core covariates	2040	543	1.01	1.01, 1.02

Hazard ratio and 95% CI were obtained from Cox regression
n: number of subjects included in the model
Core covariates: age, sex, race, baseline eGFR (mL/min/1.73m^2), years on dialysis, diabetes, history of myocardial infarction (MI), history of cerebrovascular accident (CVA) (except for rHuEPO trials), history of transient ischemic attack (TIA) (except for rHuEPO trials), history of peripheral vascular disease (PVD), history of hypertension, baseline hemoglobin (g/dL), iron deficiency at baseline, baseline albumin (g/dL), baseline creatinine (mg/dL).
All covariates = core covariates + region, dry weight (kg), primary cause of renal disease, dialysis modality (dialysis subjects only), hemoglobin target (g/dL), rate of rise consideration in dosing algorithm, year study started.
If the convergence criterion was not met, the hazard ratio and 95% CI estimates will be displayed as 'n/a'.
Output: /tables/output/rtf/t_06_008_003_cox_bsdose_bsdose_death_nesp_d_main.rtf (Date Generated: 15JUN2007 19:37)
/tables/output/rtf/t_06_008_009_cox_bsdose_bsdose_death_nesp_nd_main.rtf (Date Generated: 15JUN2007 19:37)
/tables/output/rtf/t_06_008_015_cox_bsdose_bsdose_death_epo_d_main.rtf (Date Generated: 15JUN2007 19:37)

PCT Table 8. Effect of Baseline ESA Dose on Time to Composite of Thromboembolic Event by Dialysis Status and ESA Administered (Amgen-sponsored Clinical Trials)

Dialysis Status - ESA Administered	Baseline ESA Dose (per 5μg/wk darbepoetin alfa or 1000 U/wk rHuEPO)			
	n	No. of Events	Hazard Ratio	95% CI
Dialysis - Darbepoetin alfa (N=10005)				
Main effect	10004	1782	1.02	1.02, 1.03
Main effects adjusted by				
All covariates	8074	1330	1.01	1.00, 1.02
Core covariates	8102	1338	1.02	1.01, 1.03
Nondialysis - Darbepoetin alfa (N=3045)				
Main effect	3045	199	0.98	0.94, 1.02
Main effects adjusted by				
All covariates	2694	188	0.98	0.93, 1.03
Core covariates	2711	190	0.97	0.93, 1.02
Dialysis - rHuEPO (N=2253)				
Main effect	2253	1120	1.01	1.01, 1.02
Main effects adjusted by				
All covariates	2033	984	1.01	1.00, 1.01
Core covariates	2040	988	1.01	1.00, 1.02

Hazard ratio and 95% CI were obtained from Cox regression
n: number of subjects included in the model
Composite cardiovascular event = cerebrovascular disorder, myocardial infarction/coronary artery disease, embolism/thrombosis
Core covariates: age, sex, race, baseline eGFR (mL/min/1.73m^2), years on dialysis, diabetes, history of myocardial infarction (MI), history of cerebrovascular accident (CVA) (except for rHuEPO trials), history of transient ischemic attack (TIA) (except for rHuEPO trials), history of peripheral vascular disease (PVD), history of hypertension, baseline hemoglobin (g/dL), iron deficiency at baseline, baseline albumin (g/dL), baseline creatinine (mg/dL).
All covariates = core covariates + region, dry weight (kg), primary cause of renal disease, dialysis modality (dialysis subjects only), hemoglobin target (g/dL), rate of rise consideration in dosing algorithm, year study started.
If the convergence criterion was not met, the hazard ratio and 95% CI estimates will be displayed as 'n/a'.
Output: /tables/output/rtf/t_06_008_057_cox_bsdose_bsdose_compte_nesp_d_main.rtf (Date Generated: 15JUN2007 19:37)
/tables/output/rtf/t_06_008_063_cox_bsdose_bsdose_compte_nesp_nd_main.rtf (Date Generated: 15JUN2007 19:37)
/tables/output/rtf/t_06_008_069_cox_bsdose_bsdose_compte_epo_d_main.rtf (Date Generated: 15JUN2007 19:37)

PCT Table 9. Effect of Baseline ESA Dose on Time to Heart Failure by Dialysis Status and ESA Administered (Amgen-sponsored Clinical Trials)

Dialysis Status - ESA Administered	Baseline ESA Dose (per 5μg/wk darbepoetin alfa or 1000 U/wk rHuEPO)			
	n	No. of Events	Hazard Ratio	95% CI
Dialysis - Darbepoetin alfa (N=10005)				
Main effect	10004	473	1.03	1.01, 1.04
Main effects adjusted by				
All covariates	8074	374	1.02	1.00, 1.03
Core covariates	8102	377	1.03	1.01, 1.04
Nondialysis - Darbepoetin alfa (N=3045)				
Main effect	3045	150	1.00	0.96, 1.05
Main effects adjusted by				
All covariates	2694	135	0.98	0.93, 1.03
Core covariates	2711	136	0.98	0.93, 1.03
Dialysis - rHuEPO (N=2253)				
Main effect	2253	408	1.01	1.00, 1.02
Main effects adjusted by				
All covariates	2033	347	1.01	1.00, 1.02
Core covariates	2040	348	1.01	1.00, 1.02

Hazard ratio and 95% CI were obtained from Cox regression
n: number of subjects included in the model
Core covariates: age, sex, race, baseline eGFR (mL/min/1.73m^2), years on dialysis, diabetes, history of myocardial infarction (MI), history of cerebrovascular accident (CVA) (except for rHuEPO trials), history of transient ischemic attack (TIA) (except for rHuEPO trials), history of peripheral vascular disease (PVD), history of hypertension, baseline hemoglobin (g/dL), iron deficiency at baseline, baseline albumin (g/dL), baseline creatinine (mg/dL).
All covariates = core covariates + region, dry weight (kg), primary cause of renal disease, dialysis modality (dialysis subjects only), hemoglobin target (g/dL), rate of rise consideration in dosing algorithm, year study started.
If the convergence criterion was not met, the hazard ratio and 95% CI estimates will be displayed as 'n/a'.
Output: /tables/output/rtf/t_06_008_075_cox_bsdose_bsdose_hf_nesp_d_main.rtf (Date Generated: 15JUN2007 19:37)
/tables/output/rtf/t_06_008_081_cox_bsdose_bsdose_hf_nesp_nd_main.rtf (Date Generated: 15JUN2007 19:37)
/tables/output/rtf/t_06_008_087_cox_bsdose_bsdose_hf_epo_d_main.rtf (Date Generated: 15JUN2007 19:37)

PCT Table 10. Effect of ESA Dose Over Time on Time to All-cause Mortality by Dialysis Status and ESA Administered (Amgen-sponsored Clinical Trials)

Dialysis Status - ESA Administered	ESA Dose Over Time (per 5μg/wk darbepoetin alfa or 1000 U/wk rHuEPO)			
	n	No. of Events	Hazard Ratio	95% CI
Dialysis - Darbepoetin alfa (N=10005)				
Main effect	9308	676	1.02	1.02, 1.03
Main effects adjusted by				
All covariates	7558	512	1.02	1.01, 1.04
Core covariates	7582	515	1.03	1.02, 1.04
Nondialysis - Darbepoetin alfa (N=3045)				
Main effect	2792	81	1.04	1.01, 1.07
Main effects adjusted by				
All covariates	2491	79	1.04	1.01, 1.08
Core covariates	2508	80	1.04	1.01, 1.07
Dialysis - rHuEPO (N=2253)				
Main effect	2113	513	1.01	1.01, 1.01
Main effects adjusted by				
All covariates	1914	433	1.01	1.01, 1.01
Core covariates	1920	435	1.01	1.01, 1.01

Model 2: one month lag from time of event for dose, and two month lag from time of event for Hb, adjusting for no/all/core covariates.
Hazard ratio and 95% C.I. were obtained from Cox regression
n: number of subjects included in the model
Core covariates: age, sex, race, baseline eGFR (mL/min/1.73m^2), years on dialysis, diabetes, history of myocardial infarction (MI), history of cerebrovascular accident (CVA) (except for rHuEPO trials), history of transient ischemic attack (TIA) (except for rHuEPO trials), history of peripheral vascular disease (PVD), history of hypertension, baseline hemoglobin (g/dL), iron deficiency at baseline, baseline albumin (g/dL), baseline creatinine (mg/dL).
All covariates = core covariates + region, dry weight (kg), primary cause of renal disease, dialysis modality (dialysis subjects only), initial absolute ESA dose, hemoglobin target (g/dL), rate of rise consideration in dosing algorithm, year study started.
If the convergence criteria was not met, the hazard ratio and 95% C.I. estimates will be displayed as 'n/a'.
Output:
/tables/output/rtf/t_06_008_001_004_tmcox_doselag1_dose_death_nesp_d_model2_main.rtf
(Date Generated: 20JUN2007 19:26)
/tables/output/rtf/t_06_008_001_022_tmcox_doselag1_dose_death_nesp_nd_model2_main.rtf
(Date Generated: 20JUN2007 19:26)
/tables/output/rtf/t_06_008_001_040_tmcox_doselag1_dose_death_epo_d_model2_main.rtf
(Date Generated: 20JUN2007 19:26)

PCT Table 11. Effect of ESA Dose Over Time on Time to Composite of Thromboembolic Event by Dialysis Status and ESA Administered (Amgen-sponsored Clinical Trials)

Dialysis Status - ESA Administered	ESA Dose Over Time (per 5μg/wk darbepoetin alfa or 1000 U/wk rHuEPO)			
	n	No. of Events	Hazard Ratio	95% CI
Dialysis - Darbepoetin alfa (N=10005)				
Main effect	9307	1295	1.02	1.02, 1.03
Main effects adjusted by				
All covariates	7557	972	1.01	1.00, 1.02
Core covariates	7581	980	1.02	1.01, 1.03
Nondialysis - Darbepoetin alfa (N=3045)				
Main effect	2790	120	1.02	0.99, 1.05
Main effects adjusted by				
All covariates	2490	113	1.03	0.99, 1.07
Core covariates	2507	115	1.02	0.98, 1.05
Dialysis - rHuEPO (N=2253)				
Main effect	2113	925	1.01	1.01, 1.02
Main effects adjusted by				
All covariates	1914	807	1.01	1.00, 1.01
Core covariates	1920	810	1.01	1.01, 1.01

Model 2: one month lag from time of event for dose, and two month lag from time of event for Hb, adjusting for no/all/core covariates.
Hazard ratio and 95% C.I. were obtained from Cox regression
n: number of subjects included in the model
Composite cardiovascular event = cerebrovascular disorder, myocardial infarction/coronary artery disease, embolism/thrombosis
Core covariates: age, sex, race, baseline eGFR (mL/min/1.73m^2), years on dialysis, diabetes, history of myocardial infarction (MI), history of cerebrovascular accident (CVA) (except for rHuEPO trials), history of transient ischemic attack (TIA) (except for rHuEPO trials), history of peripheral vascular disease (PVD), history of hypertension, baseline hemoglobin (g/dL), iron deficiency at baseline, baseline albumin (g/dL), baseline creatinine (mg/dL).
All covariates = core covariates + region, dry weight (kg), primary cause of renal disease, dialysis modality (dialysis subjects only), initial absolute ESA dose, hemoglobin target (g/dL), rate of rise consideration in dosing algorithm, year study started.
If the convergence criteria was not met, the hazard ratio and 95% C.I. estimates will be displayed as 'n/a'.
Output:
/tables/output/rtf/t_06_008_001_166_tmcox_doselag2_dose_compte_nesp_d_model2_main.rtf
(Date Generated: 19JUN2007 20:11)
/tables/output/rtf/t_06_008_001_184_tmcox_doselag2_dose_compte_nesp_nd_model2_main.rtf
(Date Generated: 19JUN2007 20:11)
/tables/output/rtf/t_06_008_001_202_tmcox_doselag2_dose_compte_epo_d_model2_main.rtf
(Date Generated: 19JUN2007 20:11)

PCT Table 12. Effect of ESA Dose Over Time on Time to Heart Failure by Dialysis Status and ESA Administered (Amgen-sponsored Clinical Trials)

Dialysis Status - ESA Administered	ESA Dose Over Time (per 5μg/wk darbepoetin alfa or 1000 U/wk rHuEPO)			
	n	No. of Events	Hazard Ratio	95% CI
Dialysis - Darbepoetin alfa (N=10005)				
Main effect	9307	376	1.02	1.01, 1.03
Main effects adjusted by				
All covariates	7557	293	1.02	1.00, 1.04
Core covariates	7581	295	1.03	1.01, 1.04
Nondialysis - Darbepoetin alfa (N=3045)				
Main effect	2790	97	1.04	1.01, 1.07
Main effects adjusted by				
All covariates	2490	91	1.03	1.00, 1.07
Core covariates	2507	92	1.02	0.99, 1.06
Dialysis - rHuEPO (N=2253)				
Main effect	2113	317	1.01	1.00, 1.01
Main effects adjusted by				
All covariates	1914	274	1.01	1.00, 1.02
Core covariates	1920	274	1.01	1.01, 1.01

Model 2: one month lag from time of event for dose, and two month lag from time of event for Hb, adjusting for no/all/core covariates.
Hazard ratio and 95% C.I. were obtained from Cox regression
n: number of subjects included in the model
Core covariates: age, sex, race, baseline eGFR (mL/min/1.73m^2), years on dialysis, diabetes, history of myocardial infarction (MI), history of cerebrovascular accident (CVA) (except for rHuEPO trials), history of transient ischemic attack (TIA) (except for rHuEPO trials), history of peripheral vascular disease (PVD), history of hypertension, baseline hemoglobin (g/dL), iron deficiency at baseline, baseline albumin (g/dL), baseline creatinine (mg/dL).
All covariates = core covariates + region, dry weight (kg), primary cause of renal disease, dialysis modality (dialysis subjects only), initial absolute ESA dose, hemoglobin target (g/dL), rate of rise consideration in dosing algorithm, year study started.
If the convergence criteria was not met, the hazard ratio and 95% C.I. estimates will be displayed as 'n/a'.
Output: /tables/output/rtf/t_06_008_001_220_tmcox_doselag3_dose_hf_nesp_d_model2_main.rtf (Date Generated: 19JUN2007 11:44)
/tables/output/rtf/t_06_008_001_238_tmcox_doselag3_dose_hf_nesp_nd_model2_main.rtf (Date Generated: 19JUN2007 11:44)
/tables/output/rtf/t_06_008_001_256_tmcox_doselag3_dose_hf_epo_d_model2_main.rtf (Date Generated: 19JUN2007 11:44)

PCT Table 13. Association between Mortality, Thromboembolic Events (TVE), Congestive Heart Failure (CHF) and ESA Dosing and Hemoglobin: Cox Regression with Time Dependent Covariates (J&JPRD-sponsored Clinical Trials)

Variable	Mortality				TVE				CHF			
	Hazards Ratio	Lower 95%CI	Upper 95%CI	P value	Hazards Ratio	Lower 95%CI	Upper 95%CI	P value	Hazards Ratio	Lower 95%CI	Upper 95%CI	P value
Maximal Hb within the past month (g/dL)(a)												
<=10 vs >11-<=12	2.2051	1.2997	3.7413	0.0034	1.3335	0.9335	1.9047	0.1137	1.8295	1.1970	2.7963	0.0053
>10-<=11 vs >11-<=12	1.1000	0.6607	1.8314	0.7140	1.1258	0.8488	1.4931	0.4108	1.3559	0.9582	1.9188	0.0857
>12-<=13 vs >11-<=12	0.6058	0.3538	1.0372	0.0677	1.0622	0.8159	1.3828	0.6541	0.8027	0.5625	1.1455	0.2258
>13-<=15 vs >11-<=12	0.5227	0.3009	0.9080	0.0213	0.9493	0.7143	1.2615	0.7198	0.5262	0.3466	0.7989	0.0026
>15 vs >11-<=12	1.2956	0.4898	3.4269	0.6018	0.7935	0.4147	1.5180	0.4846	0.5362	0.1649	1.7436	0.3003
NA vs >11-<=12	2.5720	1.5289	4.3267	0.0004	1.0486	0.6939	1.5848	0.8217	1.2584	0.7329	2.1606	0.4046
Maximal Hgb rate of change (g/dL/wk) within the past month (b)												
<=-0.10 vs >0.25-<=0.50	1.3753	0.6393	2.9583	0.4149	1.0480	0.6834	1.6071	0.8299	1.6716	0.9668	2.8901	0.0659
>-0.10-<=0.05 vs >0.25-<=0.50	0.7407	0.3447	1.5916	0.4418	0.9763	0.6836	1.3943	0.8951	1.3561	0.8420	2.1841	0.2102
>0.05-<=0.25 vs >0.25-<=0.50	0.7734	0.4266	1.4021	0.3973	0.9254	0.6972	1.2282	0.5913	1.3909	0.9527	2.0307	0.0874
>0.50-<=0.75 vs >0.25-<=0.50	0.9472	0.4762	1.8841	0.8772	1.0373	0.7529	1.4292	0.8227	1.2352	0.7855	1.9424	0.3605
>0.75 vs >0.25-<=0.50	1.4099	0.7621	2.6085	0.2738	1.1830	0.8731	1.6029	0.2782	1.1685	0.7263	1.8800	0.5210
NA >0.25-<=0.50	2.2998	1.3837	3.8224	0.0013	1.0647	0.7823	1.4490	0.6901	1.4569	0.9605	2.2099	0.0766
Maximal ESA dose (IU/kg/wk) within the previous month (c)												
>50-<=100 vs <=50	0.4701	0.2559	0.8636	0.0150	1.0671	0.7957	1.4309	0.6645	0.6169	0.3968	0.9592	0.0320
>100-<=150 vs <=50	0.6408	0.3738	1.0985	0.1056	1.1704	0.8525	1.6069	0.3305	0.7873	0.5077	1.2208	0.2852
>150-<=200 vs <=50	0.7507	0.4214	1.3374	0.3305	1.0786	0.7401	1.5718	0.6938	1.2446	0.7700	2.0118	0.3718
>200 vs <=50	1.0202	0.5680	1.8326	0.9466	1.4239	0.9450	2.1454	0.0911	1.4452	0.8517	2.4524	0.1723
Average cumulative ESA dose from start (IU/kg/wk) (d)												
>50-<=100 vs <=50	2.3130	1.3767	3.8859	0.0015	1.3662	1.0304	1.8114	0.0301	1.1233	0.7502	1.6819	0.5723
>100-<=150 vs <=50	2.9736	1.6523	5.3514	0.0003	1.2422	0.8795	1.7543	0.2183	1.0553	0.6554	1.6993	0.8247
>150-<=200 vs <=50	3.9783	2.0216	7.8288	0.0001	1.6689	1.0972	2.5383	0.0167	1.5112	0.8609	2.6526	0.1503
>200 vs <=50	3.6018	1.5784	8.2195	0.0023	1.3950	0.8246	2.3600	0.2146	1.0612	0.5063	2.2242	0.8750

PCT Table 13. Association between Mortality, Thromboembolic Events (TVE), Congestive Heart Failure (CHF) and ESA Dosing and Hemoglobin: Cox Regression with Time Dependent Covariates (J&JPRD-sponsored Clinical Trials)

Variable	Mortality				TVE				CHF			
	Hazards Ratio	Lower 95%CI	Upper 95%CI	P value	Hazards Ratio	Lower 95%CI	Upper 95%CI	P value	Hazards Ratio	Lower 95%CI	Upper 95%CI	P value
ESA dose and Hgb covariates included as continuous (e)												
Target: >12 g/dL vs <=12	1.3211	0.8980	1.9436	0.1574	1.0766	0.8487	1.3658	0.5430	1.1903	0.8881	1.5953	0.2438
Phase: maintenance vs initiation	1.7541	1.1963	2.5720	0.0040	1.3440	1.0848	1.6651	0.0068	1.0761	0.7937	1.4590	0.6366
Max Hb in past month: linear	0.4545	0.2656	0.7777	0.0040	0.6982	0.4054	1.2026	0.1954	0.8917	0.3809	2.0874	0.7917
Max Hb in past month: quadratic	1.0228	0.9999	1.0462	0.0510	1.0128	0.9902	1.0358	0.2703	0.9934	0.9574	1.0307	0.7237
Max Hb RtR in pv mon (g/dL/wk): linear	1.2717	0.7936	2.0377	0.3178	1.1244	0.8362	1.5117	0.4378	0.7988	0.5877	1.0858	0.1515
Max Hb RtR in pv mon (g/dL/wk): quadratic	0.9839	0.9206	1.0515	0.6321	0.9690	0.9026	1.0402	0.3835	1.0048	0.9917	1.0181	0.4726
Max ESA dose in pv mon (x100 IU/kg/wk): linear	0.9306	0.6728	1.2872	0.6639	1.1049	0.8432	1.4480	0.4695	1.2317	0.8782	1.7275	0.2273
Max ESA dose in pv mon (x100 IU/kg/wk): quadratic	1.0156	0.9705	1.0627	0.5045	1.0029	0.9519	1.0566	0.9137	0.9987	0.9384	1.0630	0.9683
Avg cumulative ESA dose (x100 IU/kg/wk): linear	2.5774	1.3308	4.9917	0.0050	1.2083	0.8141	1.7933	0.3477	1.4172	0.7509	2.6747	0.2820
Avg cumulative ESA dose (x100 IU/kg/wk): quadratic	0.8703	0.7347	1.0309	0.1078	0.9971	0.9060	1.0973	0.9520	0.8945	0.7428	1.0772	0.2396

Hazards ratio: a value of <1 suggests lower risk, and a value of >1 suggests higher risk.

a) The model also included maximal rate of Hgb change in a month (linear+quadratic), maximal weekly ESA dose in a month (linear+quadratic), average cumulative dose in a month (linear+quadratic), maintenance, and the following fixed covariates: target Hgb, dialysis requirement, age, sex, BMI, eGFR, baseline Hgb, albumin, history of hypertension, history of cardiovascular events, and history of diabetes.

b) The model also included maximal Hgb in a month (linear+quadratic), maximal weekly ESA dose in a month (linear+quadratic), average cumulative dose in a month (linear+quadratic), maintenance, and the following fixed covariates: target Hgb, dialysis requirement, age, sex, BMI, eGFR, baseline Hgb, albumin, history of hypertension, history of cardiovascular events, and history of diabetes.

c) The model also included maximal Hgb in a month (linear+quadratic), maximal rate of hgb change in a month (linear+quadratic), average cumulative dose in a month (linear+quadratic), maintenance, and the following fixed covariates: target Hgb, dialysis requirement, age, sex, BMI, eGFR, baseline Hgb, albumin, history of hypertension, history of cardiovascular events, and history of diabetes.

d) The model also included maximal Hgb in a month (linear+quadratic), maximal rate of Hgb in a month (linear+quadratic), maximal weekly ESA dose in a month (linear+quadratic), maintenance, and the following fixed covariates: target Hgb, dialysis requirement, age, sex, BMI, eGFR, baseline Hgb, albumin, history of hypertension, history of cardiovascular events, and history of diabetes.

e) The model also included the following fixed covariates: dialysis requirement, age, sex, BMI, eGFR, baseline Hgb, albumin, history of hypertension, history of cardiovascular events, and history of diabetes.

The analysis database included 16 studies and 5467 ESA-treated patients with 190 on-study deaths, 559 TVEs and 317 CHF events.

Source: O:\COMPOUND\epocrf\crac2007\pgstat\kliu\epo_renal16_timedep_esub.sas

PCT Table 14. Characteristics of the Amgen-Sponsored Clinical Trials Included in Pooled Analyses (with Darbepoetin alfa and rHuEPO)

Study	Study Start	Study Type	Study Phase	Population	Dialysis Type	ESA	Blinding	Rand./ Control	Duration (weeks)	Hb Elig. (g/dL)	Hb Target (g/dL)	Subjects Enrolled	
												Aranesp	rHuEPO
930107	1993	maintenance	3	CRF dialysis	HD	rHuEPO	open label	yes/ active	156-286	9-11	9-11, 13-15	0	1260
20050113	2005	maintenance	3	CRF dialysis	HD	rHuEPO	double blind	yes/ active	28	10-13	10-13	0	229
960246	1997	correction	2	CRF dialysis	PD	Aranesp rHuEPO	open label	yes/ active	≥16	<10	10-13	72	9
970200	1997	maintenance	3	CRF dialysis	HD/PD	Aranesp rHuEPO	open label	yes/ active	52	9.5-12.5	9-13	344	175
970235	1998	maintenance	1/2	CRF dialysis	HD	Aranesp rHuEPO	open label	yes/ active	52	9.5-12.5	9-13	32	15
980117	1998	maintenance	3	CRF dialysis	HD	Aranesp rHuEPO	double blind	yes/ active	28	9.5-12.5	9-13	169	335
980202	1998	correction	2	CRF no dialysis	NA	Aranesp rHuEPO	open label	yes/ active	≥24	<11	11-13	129	37
980211	1998	correction	2	CRF dialysis	HD/PD	Aranesp rHuEPO	open label	yes/ active	20	≤10	11-13	90	31
20010125	2002	maintenance	4	CRF dialysis	HD	Aranesp rHuEPO	double blind	yes/ active	28	9.5-12.5	10-12	200	206
960245	1997	correction	2	CRF dialysis	HD	Aranesp	open label	yes/ active	≥16	<10	10-13	85	0
980140	1998	maintenance	3	CRF dialysis	HD/PD	Aranesp	open label	none	52	9.5-12.5	9-13	703	0
980160	1998	maintenance	3	CRF dialysis	HD/PD	Aranesp	open label	none	192	NA	9-13	812	0
990122	1999	maintenance	2	CRF dialysis	HD/PD	Aranesp	open label	none	24	9.5-12.5	9-13	38	0
990151	2000	correction	2	CRF no dialysis	NA	Aranesp	open label	none	24	<11	11-13	75	0
990164	2000	maintenance	3b	CRF dialysis	HD/PD	Aranesp	open label	none	≥24	10-13	10-13	417	0
990748	2000	maintenance	3b	CRF dialysis	HD/PD	Aranesp	open label	none	≥24	10-13	10-13	341	0

PCT Table 14. Characteristics of the Amgen-Sponsored Clinical Trials Included in Pooled Analyses (with Darbepoetin alfa and rHuEPO)

Study	Study Start	Study Type	Study Phase	Population	Dialysis Type	ESA	Blinding	Rand./ Control	Duration (weeks)	Hb Elig. (g/dL)	Hb Target (g/dL)	Subjects Enrolled	
												Aranesp	rHuEPO
990773	2000	maintenance	3b	CRF dialysis	HD	Aranesp	open label	yes/ active	30	9.5-12	10-12	267	0
990787	2000	maintenance	3b	CRF dialysis	HD	Aranesp	open label	yes/ active	30	9.5-12.5	10-12	280	0
20000111	2000	maintenance	3b	CRF dialysis	HD/PD	Aranesp	open label	none	24	10-13	10-13	1499	0
20000112	2000	maintenance	3b	CRF dialysis	HD/PD	Aranesp	open label	none	24	10-13	10-13	250	0
20000113	2000	maintenance	3b	CRF dialysis	HD/PD	Aranesp	open label	none	24	10-13	10-13	258	0
20000114	2001	maintenance	3b	CRF dialysis	HD/PD	Aranesp	open label	none	24	10-13	10-13	824	0
20000115	2000	maintenance	3b	CRF dialysis	HD/PD	Aranesp	open label	none	24	10-13	10-13	221	0
20000116	2001	maintenance	3b	CRF dialysis	HD/PD	Aranesp	open label	none	24	10-13	10-13	934	0
20000117	2001	maintenance	3b	CRF dialysis	HD/PD	Aranesp	open label	none	24	10-13	10-13	1004	0
20000118	2001	maintenance	3b	CRF dialysis	HD/PD	Aranesp	open label	none	24	10-13	10-13	299	0
20000119	2001	maintenance	3b	CRF dialysis	HD/PD	Aranesp	open label	none	24	10-13	10-13	199	0
20000129	2001	correction	2	CRF no dialysis	NA	Aranesp	open label	none	36	≤10	12-14	15	0
20000144	2000	maintenance	2	CRF dialysis	HD/PD	Aranesp	open label	none	≥40	10-13	10-13	54	0
20000146	2000	correction	2	CRF no dialysis	NA	Aranesp	open label	yes/ SOC	24	≤10	12-13	61	0
20000164	2000	maintenance	3b	CRF	HD/PD	Aranesp	open label	none	78	NA	11-13	22	0
20000165	2001	maintenance	3b	CRF dialysis	HD/PD	Aranesp	open label	none	36	9-13	10-13	80	0

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PCT Table 14. Characteristics of the Amgen-Sponsored Clinical Trials Included in Pooled Analyses (with Darbepoetin alfa and rHuEPO)

Study	Study Start	Study Type	Study Phase	Population	Dialysis Type	ESA	Blinding	Rand./ Control	Duration (weeks)	Hb Elig. (g/dL)	Hb Target (g/dL)	Subjects Enrolled	
												Aranesp	rHuEPO
20000179	2000	maintenance	3b	CRF	HD/PD	Aranesp	open label	none	78	NA	11-13	103	0
20000256	2002	correction/ maintenance	4	CRF no dialysis	NA	Aranesp	open label	none	52	<11	12	374	0
20010212	2002	maintenance	2	CRF no dialysis	NA	Aranesp	open label	none	29	10-12	10-12	97	0
20010215	2002	correction/ maintenance	4	CRF no dialysis	NA	Aranesp	open label	none	52	<11	12	618	0
20010219	2002	maintenance	3	CRF dialysis	HD	Aranesp	double blind	yes/ active	30	10-13	10-13	306	0
20010243	2002	correction/ maintenance	4	CRF no dialysis	NA	Aranesp	open label	none	52	<11	12	443	0
20020147	2002	maintenance	4	CRF no dialysis	NA	Aranesp	open label	none	28	10-12	10-12	116	0
20020380	2003	maintenance	4	CRF no dialysis	NA	Aranesp	open label	none	28	10-12	10-12	304	0
20030112	2003	maintenance	3	CRF no dialysis	NA	Aranesp	open label	none	28	10-13	10-13	66	0
20030153	2004	maintenance	3	CRF no dialysis	NA	Aranesp	open label	none	28	11-13	11-13	150	0
20030237	2004	correction	3	CRF no dialysis	NA	Aranesp	open label	none	18	<11	11-13	128	0
20040104	2005	maintenance	3	CRF dialysis	HD	Aranesp	double blind	yes/ active	28	10-13	10-13	442	0
20040180	2004	maintenance	3	CRF	HD/PD	Aranesp	open label	none	52	11-13	11-13	1116	0
20040202	2004	maintenance	3	CRF dialysis	HD/PD	Aranesp	open label	none	32	11-13	11-13	109	0

PCT Table 15. Overview & Design of Clinical Studies in Nondialysis and Dialysis Patients With CRF Used in the Meta-Analysis (J&JPRD-sponsored Clinical Trials)

No.	Study Designation (year of study start)/Country	Study Design	Entry Hb (Hct)/ Target Hb/(Hct) on Study	EPO Dose Regimen/ Dose Adjustment	No. of Subjects		
					EPO	Placebo	Total
1.	EPO-CAN-10 (1997)/ Canada	Open-label, blinded, randomized, multicenter study to determine whether maintenance of Hb within the normal range, using erythropoietin therapy, delays the progression of LV mass growth	Subjects had either 1) entry Hb of 11 to 13.5 g/dL (men) and 10 to 13.5 g/dL (women) following a progressive decline in Hb of ≥1.0 g/dL over the previous 12 months or 2) entry Hb between 11.5 and 12.5 g/dL (men) and 11 and 12 g/dL (women)/target Hb 12 to 14 g/dL (± 0.5 g/dL)	2,000 IU s.c. QW Subjects randomly assigned to the treatment arm received EPREX as needed to maintain Hb in the target range of 12 to 14 g/dL. Subjects randomly assigned to the control arm did not receive additional treatment for a progressive decline in Hb unless their Hb decreased to ≤9.0 g/dL at which point EPREX could be administered to maintain their Hb between 9.0 and 10.5 g/dL. Hb was not to exceed 14 g/dL.	172	NA	172

Hb=hemoglobin; Hct=hematocrit; EPO=erythropoietin; s.c.=subcutaneous; LV=left ventricular; QW=weekly; NA=not applicable or not available; No.=number

(Continued)

PCT Table 15. Overview & Design of Clinical Studies in Nondialysis and Dialysis Patients With CRF Used in the Meta-Analysis (J&JPRD-sponsored Clinical Trials)

No.	Study Designation (year of study start)/Country	Study Design	Entry Hb (Hct)/ Target Hb/(Hct) on Study	EPO Dose Regimen/ Dose Adjustment	No. of Subjects		
					EPO	Placebo	Total
2.	EPOCKD2001 (2005)/NA	Open-label, randomized, multicenter study to compare change in Hb from baseline to the end of the study between the Q2W and the Q4W dosing regimens in subjects with anemia of chronic kidney disease initiated on PROCRIT	Hb <11 g/dL/ Hb 12 g/dL	Group 1: PROCRIT 10,000 IU s.c. QW Group 2: PROCRIT 20,000 IU s.c Q2W Group 3: PROCRIT 20,000 IU s.c Q4W Group 4: PROCRIT 40,000 IU s.c Q4W No dose adjustments prior to Week 5. Dose increase criteria: received same dose for consecutive visits (Group 1-4 QW visits, Group 2-2QW visits); Hb failed to increase by more than 0.5 g/dL over preceding 4 weeks; subject Hb <11 g/dL over each of preceding 4 weeks. Group 1: increased by 2,500 IU to 12,500 IU QW-if met again further increase by 2,500 IU. Maximum dose: 20,000 IU QW Group 2: increased by 5,000 IU to 25,000 IU Q2W-if met again further increase by 5,000 IU. Maximum dose: 40,000 IU Q2W Group 3: increased by 5,000 IU to 25,000 IU Q4W-if met again further increase by 5,000 IU. Maximum dose: 35,000 IU Q4W Group 4: increased by 10,000 IU to 50,000 IU Q4W-if met again further increase by 10,000 IU. Maximum dose: 70,000 IU Q4W Dose Withheld: Hb greater than 12 g/dL (anytime since last dose); cumulative Hb increase of greater than 1.0 g/dL on the last 1 or 2 consecutive weeks (Group 2-over the last 3-week interval, Group 3 and 4-over the last 5-week interval). All subjects will continue weekly visits after a dose is withheld. Dose restart after Hb >12 g/dL: Hb ≤12 g/dL but ≥11 g/dL resume dose (Group 1-2,500 IU, Group 2-5,000 IU, Group 3-5,000 IU, Group 4-10,000 IU) below dose subject received at dose hold Hb <11 g/dL: dose resumed at same dose subject received at time of dose hold Dose restart after Hb rise of greater than 1.0 g/dL: restart using same dose regime as Hb >12 g/dL. If criteria met again further decrease dose (Group 1-2,500 IU, Group 2-5,000 IU, Group 3-5,000 IU, Group 4-10,000 IU).	259 to be enrolled	NA	259 to be enrolled

Hb=hemoglobin; Hct=hematocrit; EPO=erythropoietin; s.c.=subcutaneous; QW=weekly; Q2W=every 2 weeks; Q4W=every 4 weeks; NA=not applicable or not available; No.=number

(Continued)

PCT Table 15. Overview & Design of Clinical Studies in Nondialysis and Dialysis Patients With CRF Used in the Meta-Analysis (J&JPRD-sponsored Clinical Trials)

No.	Study Designation (year of study start)/Country	Study Design	Entry Hb (Hct)/ Target Hb/(Hct) on Study	EPO Dose Regimen/ Dose Adjustment	No. of Subjects EPO	Placebo	Total
3.	EPO-INT-14 (1998)/Europe/ Brazil/Israel	Open-label, randomized, prospective, multicenter study to evaluate the effect of normalization of Hb concentration with r-HuEPO on the exercise capacity, left ventricular mass, maximum oxygen uptake, and quality of life in subjects with early chronic renal failure (predialysis).	Hb ≤11 g/dL/ Lower target group: Hb 9 to 11 g/dL; Higher target group: Hb 13 to 15 g/dL	Baseline Period: All subjects continued on their prestudy dosing regimens of epoetin alfa. Subjects who had been receiving epoetin beta were switched to an equivalent regimen of epoetin alfa. Titration (higher target group): For subjects with no prior epoetin alfa treatment: began with a dose of 25 to 50 IU/kg, 1 to 3 times a week, and was titrated upward slowly. For subjects already receiving epoetin alfa: began at 1.5 times the total weekly dose administered during the baseline period. If Hb did not increase ≥1 g/dL, increase weekly dose by 25 IU/kg at monthly intervals for 3 to 6 months, until the target Hb is 13 to 15 g/dL. Reduce weekly dose by approximately 25% if Hb rises by more than 2 g/dL or 1.24 mmol/L in a month. Continue each reduced dose for at least 2 weeks before making further dose reductions.	229	NA	229
4.	G86-053 (1987)/United States	Open-label, multicenter study of r-HuEPO as maintenance therapy in the treatment of anemia in subjects with pre-dialysis, end-stage renal disease. Subjects must have completed Study G86-011.	Hct not specified / Hct 40% (men), 37% (women)	For subjects who received r-HuEPO in Study G86-011, the starting dose of r-HuEPO was based on the Hct response in Study G86-011. For subjects who received placebo in Study G86-011, the starting dose was based on their hematologic response and dosage group assignment in Study G86-011 (either 50, 100, or 150 IU/kg, i.v., t.i.w.). r-HuEPO was administered i.v., t.i.w. until the target Hct values were met, then the route of administration was changed to s.c., t.i.w. for the remainder of the 6-month study. The dosage was to remain the same if Hct had increased by 2 percentage points in the past month but was still below the target values of 40% for males and 37% for females. The dosage was increased by 50 IU/kg if the Hct had not increased by 2 percentage points in the past month and did not attain target values. The dosage was reduced by 50 IU/kg if the Hct reached or exceeded the target values of 40% for males and 37% for females. The maximum dosage was not to exceed 300 IU/kg t.i.w.	105	NA	105

Hb=hemoglobin; Hct=hematocrit; EPO=erythropoietin; r-HuEPO = recombinant human erythropoietin; s.c.=subcutaneous; i.v.=intravenous; NA=not applicable or not available; t.i.w.=3 times weekly; No.=number

(Continued)

PCT Table 15. Overview & Design of Clinical Studies in Nondialysis and Dialysis Patients With CRF Used in the Meta-Analysis (J&JPRD-sponsored Clinical Trials)

No.	Study Designation (year of study start)/Country	Study Design	Entry Hb (Hct)/ Target Hb/(Hct) on Study	EPO Dose Regimen/ Dose Adjustment	No. of Subjects		
					EPO	Placebo	Total
5.	N93-063 (1994)/United States	Open-label, randomized, multicenter study to compare the safety and efficacy of t.i.w. versus QW s.c. dosing of PROCRIT for anemia of chronic renal failure in predialysis subjects.	Hb 10 to 12 g/dL/ Hb ±1 g/dL from the prestudy screening Hb for first 4 weeks and ±1 g/dL from the last baseline Hb for remaining 16 weeks of study	4,000 IU/mL s.c. Subjects initially received PROCRIT s.c., t.i.w. for 4 weeks to maintain a stable baseline Hb (±1 g/dL from the prestudy screening Hb). Subjects who exhibited a stable Hb and had all laboratory tests within the reference range for predialysis chronic renal failure subjects were randomized to receive additional PROCRIT therapy either t.i.w. or QW for an additional 16 weeks. The starting weekly dose was calculated at 3 times the subject's most recent baseline dose. If the Hb rose or fell too rapidly, i.e., ≥1 g/dL change from baseline or >1 g/dL increase per 2 week period, the dose could be increased or decreased by approximately 25% compared to the last baseline Hb result.	53/90 at termination of study[a]	NA	53
6.	PR00-06-009 (NA)/United States	Open-label, prospective, multicenter, nonrandomized 16-week study to evaluate the efficacy and safety of QW epoetin alfa to correct anemia in a large, outpatient population with chronic kidney disease	Hb ≤10 g/dL Hb ≤13 g/dL	Single-arm 10,000 IU QW s.c. Increase to 20,000 IU QW at Week 5 if Hb did not increase ≥1 g/dL Subsequent increase at investigator discretion. Hold dose if Hb >13g/dL; resume at 50% of previous dose once Hb is ≤12 g/dL. Reduce dose by 50% if Hb increases by >1.3 g/dL in any 2-week period.	1,557	NA	1,557
7.	PR00-06-014 (2002)/United States	Prospective, open-label, randomized, multi-center study in subjects with chronic kidney disease to compare the composite cardiovascular event rates for chronic kidney disease subjects randomized to a target Hb level of 13.5 g/dL (Group A: high Hb arm) versus a target Hb level of 11.3 g/dL (Group B: low Hb arm)	Hb <11 g/dL/ Hb: Group A: 13.5 g/dL Group B: 11.3 g/dL	Group A: 10,000 IU s.c. QW Group B: 10,000 IU s.c. QW No dose adjustments were made for the first 3 doses of PROCRIT. For all subjects, beginning with the fourth weekly dose, PROCRIT dosing was adjusted based on an assessment of the prior 2 Hb values. The maximum dose permitted was 20,000 IU.	1,432	NA	1,432

Hb=hemoglobin; Hct=hematocrit; EPO=erythropoietin; s.c.=subcutaneous; t.i.w.=3 times weekly; QW=once weekly; NA=not applicable or not available; No.=number

[a] The study was terminated early after the enrollment of 53 subjects due to difficulty in subject accrual. It was found that clinical practice was changing to include the weekly dosing regimen, thus eliminating many prospective subjects

(Continued)

PCT Table 15. Overview & Design of Clinical Studies in Nondialysis and Dialysis Patients With CRF Used in the Meta-Analysis (J&JPRD-sponsored Clinical Trials)

No.	Study Designation (year of study start)/Country	Study Design	Entry Hb (Hct)/ Target Hb/(Hct) on Study	EPO Dose Regimen/ Dose Adjustment	No. of Subjects EPO	Placebo	Total
8.	PR01-06-021 (2002)/United States	Open-label, randomized, multi-center study of subjects with anemia due to chronic kidney disease to evaluate the safety and efficacy of PROCRIT dosing up Q4W	Hb ≥11 g/dL/ Hb ≤13 g/dL	Group 1: PROCRIT 10,000 IU s.c. QW Group 2: PROCRIT 20,000 IU s.c. Q2W Group 3: PROCRIT 30,000 IU s.c. Q3W Group 4: PROCRIT 40,000 IU s.c. Q4W If the Hb was >13.0 g/dL on 2 consecutive evaluations, PROCRIT therapy was held until dosing week at which the Hb level decreased to 12.0 g/dL or less. PROCRIT therapy was then resumed with a reduction in dose to 50% of the most current dose for the remainder of the study. The dose of PROCRIT was also reduced by 50% of the most current dose for the remainder of the study if there was an increase in Hb of >1.3 g/dL in a 2-week period. Dose escalations were not permitted at any time.	519	NA	519
9.	PR03-06-001 (2004)/United States	Open-label, multicenter single-arm study in non-dialysis subjects with anemia of chronic kidney disease to evaluate Hb response after initiation of PROCRIT Q2W	Hb <11 g/dL/ Hb 11 to 12 g/dL	20,000 IU Q2W s.c. Dose titration was not allowed prior to Week 5. Dose could be up-titrated if: the subject received the same dose at 2 consecutive visits; Hb failed to increase by more than 0.5 g/dL during the preceding 4 weeks, and the subject's Hb was not within target range. Dose was increased by 5,000 IU as frequently as Q4W with a maximum dose of 40,00 IU Q2W. Dose was held if: Hb rose above 12 g/dL and/or cumulative Hb increase of greater than 1.0 g/dL over any 1 or 2 week period. Drug restart after Hb >12 g/dL: Hb ≤12 g/dL but ≥11 g/dL: Q2W dose resumed at 2500 IU below dose received at time of dose hold Hb <11 g/dL: Q2W dose resumed at dose subject receiving at time of dose hold Drug restart after Hb rise greater than 1.0 g/dL: dose resumes at 2500 IU below dose subject received at time of dose hold	67	NA	67

Hb=hemoglobin, Hct=hematocrit; EPO=erythropoietin; s.c.=subcutaneous; QW=weekly; Q2W=every 2 weeks; Q3W=every 3 weeks; Q4W=every 4 weeks; NA=not applicable or not available; No.=number

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PCT Table 15. Overview & Design of Clinical Studies in Nondialysis and Dialysis Patients With CRF Used in the Meta-Analysis (J&JPRD-sponsored Clinical Trials)

No.	Study Designation (year of study start)/Country	Study Design	Entry Hb (Hct)/ Target Hb/(Hct) on Study	EPO Dose Regimen/ Dose Adjustment	No. of Subjects		
					EPO	Placebo	Total
10.	EPO-INT-37 (1998)/Europe	Phase 4, open-label multicenter, study to assess the effect of increasing the maintenance hemoglobin level of hemodialysis subjects from ≤10/dL (6.2 mmol/L) to 12 g/dL (7.4 mmol/L) with epoetin alfa treatment	Hb ≤10 g/dL/ Hb 12 g/dL	During the titration phase (2 to 4 months), subjects were to have their Hb titrated up to reach a level of 12±0.5 g/dL (7.4±0.31 mmol/L). Subjects without previous r-HuEPO treatment were to be started at a dose of 50 to 100 IU/kg 3 times weekly. Depending on their Hb response, the dose of epoetin alfa was to be increased by 25 IU/kg/week at 4-week intervals until the target Hb level of 11.5 to 12.5 g/dL was reached within 2 to 4 months. Subjects already on epoetin alfa during the baseline period were to be started at 1.25 times the baseline dose. This dose was to be increased by increments of 25 IU/kg/week at 4-week intervals until the target Hb of 12±0.5 g/dL (7.4±0.31 mmol/L) was reached within 2 to 4 months. For subjects on the same dose of epoetin alfa for at least 4 weeks who showed insufficient response (defined as a rise in Hb of <1 g/dL or 0.31 mmol/L within the preceding 2 weeks), the total weekly dose of epoetin alfa was to be increased by another 25/IU/kg. Hb was not allowed to increase more rapidly than 1 g/dL in any 2 consecutive weeks. If this occurred, the total weekly dose of epoetin alfa was to be reduced immediately by 25 IU/kg/week. This dose reduction of 25 IU/kg/week was to be maintained for at least 2 more weeks before further dose changes were made. During the maintenance phase of 9 months, once the target range of Hb of 12±0.5 g/dL (7.4±0.31 mmol/L) was reached, the weekly epoetin alfa dose was to be individually adjusted to maintain the Hb at that level.	132	NA	132

Hb=hemoglobin; Hct=hematocrit; EPO=erythropoietin; r-HuEPO = recombinant human erythropoietin; NA=not applicable or not available; No.=number

(Continued)

PCT Table 15. Overview & Design of Clinical Studies in Nondialysis and Dialysis Patients With CRF Used in the Meta-Analysis (J&JPRD-sponsored Clinical Trials)

No.	Study Designation (year of study start)/Country	Study Design	Entry Hb (Hct)/ Target Hb/(Hct) on Study	EPO Dose Regimen/ Dose Adjustment	No. of Subjects		
					EPO	Placebo	Total
11.	EPO-INT-68 (2000)/Europe and Canada	Randomized, multicenter, double-blind, parallel-group study to assess the effect of 2 Hb target ranges in subjects with end-stage renal disease who had been receiving hemodialysis for 3 to 18 months.	Hb 8 to 12 g/dL/ lower Hb target group: Hb 9.5 to 11.5 g/dL; higher Hb target group: Hb 13.5 to 14.5 g/dL	Study drug was originally to be administered s.c. or i.v. Following protocol Amendment INT-3 (22 August 2002), study drug was only given i.v. Subjects receiving a commercial EPO product and assigned to the lower Hb target group: study drug dosage titrated as required to attain Hb within the target of 9.5 to 11.5 g/dL. Subjects receiving a commercial EPO product and assigned to the higher Hb target group: study drug dose increased by 25 IU/kg. Subsequent dose increases of 25 IU/kg or 25% of the previous dose (whichever was greater) were to occur, if required, no less than 4 weeks apart until the subjects attained a Hb within the target range of 13.5 to 14.5 g/dL. Subjects not receiving a commercial EPO product at the time of randomization: study drug if required to raise their Hb to the assigned target range (i.e., all subjects assigned to the higher Hb target group; if required for subjects assigned to the lower Hb target group). When required, these subjects were started at a dosage of 50 IU/kg t.i.w., with subsequent dose increases as described previously (25 IU/kg or 25% of the previous dose). In general, Hb concentration was to increase between 0.5 and 1.0 g/dL within any 2-week period during the titration period until the target Hb was reached, and Hb was not to exceed the upper limit of the target range. Dose increases or decreases (reduction by 25% of the previous dose) were implemented for subjects with Hb rates of rise or absolute Hb concentrations outside these limits. If a subject assigned to the higher Hb target had a Hb >15 g/dL, study drug was withheld until the concentration fell to ≤14.5 g/dL, at which time study drug was restarted at a reduced dose.	596 (300 lower Hb target; 296 higher Hb target)	NA	596

Hb=hemoglobin; Hct=hematocrit; EPO=erythropoietin; t.i.w.=3 times weekly; s.c.=subcutaneous; i.v.=intravenous; NA=not applicable or not available
No.=number

(Continued)

PCT Table 15. Overview & Design of Clinical Studies in Nondialysis and Dialysis Patients With CRF Used in the Meta-Analysis (J&JPRD-sponsored Clinical Trials)

No.	Study Designation (year of study start)/Country	Study Design	Entry Hb (Hct)/ Target Hb/(Hct) on Study	EPO Dose Regimen/ Dose Adjustment	No. of Subjects		
					EPO	Placebo	Total
12.	EPO-CAN-13 (1997)/Canada	Open-label, randomized, prospective, 2-center study to determine the long-term effect of 3 dosages of i.v. iron on epoetin alfa dosage and iron indices in subjects on chronic hemodialysis	Hb 10.0 to 12.0 g/dL for 2 months prior to randomization / Hb 10.5 to 11.5 g/dL	Subjects randomly assigned to receive 25, 50, or 100 mg iron dextran QW for 1 year. If serum ferritin exceeded 750 µg/L, serum ferritin was monitored every month instead of every second month until level fell below 500 µg/L. Intravenous iron therapy was held if serum ferritin exceeded 1,000 µg/L and was restarted at 50% of the previous dose when serum ferritin fell to <500 µg/L. Subjects received EPREX s.c. or i.v. twice weekly at the first and third treatments or t.i.w. Dose was adjusted to maintain Hb within target range of 10.5 to 11.5 g/dL. If Hb fell below 10.5 g/dL, dose was increased by 1,000 or 1,500 IU per week; if Hb exceeded 11.5 g/dL, dose was reduced by 1,000 or 1,500 IU per week.	77	NA	77
13.	G86-011 (1986)/United States	Double-blind, placebo-controlled, parallel-group, multicenter study to determine the safety, efficacy, and PK profile of epoetin alfa 50, 100, and 150 IU/kg i.v. t.i.w. versus placebo, and to determine if treatment with epoetin alfa stimulates erythropoiesis in anemic predialysis subjects with end-stage renal disease	Entry Hb: ≤13 g/dL (men) and ≤11 g/dL (women) Entry Hct: ≤38% (men) and ≤32% (women) / Target Hct: >2 percentage points above lower limit of normal range	50, 100, or 150 IU/kg i.v. or placebo t.i.w. for a maximum of 9 weeks At the completion of the double-blind portion of the study, or whenever a subject's Hct exceeded the lower limit of the normal range by 2 percentage points (men, 40%; women, 37%), subjects could be entered into a 6-month maintenance study (G86-053).	86	31	117
14.	G86-125 (1987)/The Netherlands and Belgium	Open-label, parallel-group, randomized, 2-center study to examine the erythropoietic efficacy and safety of epoetin alfa 50, 100, and 150 IU/kg i.v., t.i.w. in predialysis subjects with end-stage renal disease	Entry Hb: ≤13 g/dL (men) and ≤11 g/dL (women) Entry Hct: ≤38% (men) and ≤32% (women) / Target Hct: >2 percentage points above lower limit of normal range	50, 100, or 150 IU/kg i.v. t.i.w. for 8 weeks, or until Hct exceeded the lower limit of the normal laboratory range by 2 percentage points, whichever occurred first. Three additional doses, if needed, were administered during Week 9 to allow maintenance on epoetin alfa prior to entry into a long-term maintenance study (G86-108).	24	NA	24

Hb=hemoglobin; Hct=hematocrit; EPO=erythropoietin; PK=pharmacokinetic; QW=weekly; t.i.w.=3 times weekly; s.c.=subcutaneous; i.v.=intravenous; NA=not applicable or not available
No.=number

(Continued)

PCT Table 15. Overview & Design of Clinical Studies in Nondialysis and Dialysis Patients With CRF Used in the Meta-Analysis (J&JPRD-sponsored Clinical Trials)

No.	Study Designation (year of study start)/Country	Study Design	Entry Hb (Hct)/ Target Hb/(Hct) on Study	EPO Dose Regimen/ Dose Adjustment	No. of Subjects		
					EPO	Placebo	Total
15.	H87-054 (1987)/United States	Double-blind, placebo-controlled, parallel-group, multicenter study to determine the safety and efficacy of epoetin alfa 100 IU/kg s.c., t.i.w. for up to 12 weeks versus placebo in predialysis subjects with anemia associated with chronic renal failure	Entry Hct ≤30% Target Hct 38% to 40%	100 IU/kg or placebo t.i.w. for 12 weeks or until Hct reached 38% to 40%, whichever came first. Subjects received elemental iron (up to 200 mg daily) if serum iron fell below 50 mg/dL or if the ratio of iron to TIBC fell below 20%, and discontinued iron if serum iron exceeded 150 mg/dL.	45	48	93
16.	EPO-AUS-14 (date unknown)/ Australia and New Zealand	Open-label, randomized, prospective, multicenter study to assess the impact of early correction of anemia on left ventricular mass, using epoetin alfa, in subjects with chronic renal failure	Entry Hb between 11.0 and 13.0 g/dL (males) and 11.0 and 12.0 g/dL (females) Target Hb: Group A: 12 to 13 g/dL; Group B: 9 to 10 g/dL	Subjects were randomly assigned to 1 of 2 treatment groups. Subjects in Group A received epoetin alfa s.c. QW in order to maintain Hb between 12.0 and 13.0 g/dL throughout the entire study period (up to 2 years after enrollment and/or the onset of renal replacement therapy). Epoetin alfa was initiated in subjects in Group B if Hb was <9.0 g/dL for 2 consecutive visits 2 months apart, or <8.0 g/dL at any visit without cause other than chronic kidney disease. Hb was then maintained between 9.0 and 10.0 g/dL for the remainder of the study period.	155	NA	155

Hb=hemoglobin; Hct=hematocrit; EPO=erythropoietin; TIBC=total iron-binding capacity; QW=weekly; t.i.w.=3 times weekly; s.c.=subcutaneous; NA=not applicable or not available
No.=number

Appendix 3. Kidney Disease Questionnaire (KDQ) - Instrument Development and Psychometric Properties

The KDQ is a 26-item quality of life measure for patients with kidney disease. It consists of 5 scales: physical, fatigue, depression, relationships with others, and frustration. Each question is scored using a 7-point Likert scale, with 1 corresponding to severe problems and 7 corresponding to no problems. Mean dimension scores are the mean of all items within that dimension. Higher scores for all dimensions and overall score reflect better quality of life (Laupacis et al, 1991a; Laupacis et al, 1991b; Laupacis, 1990). The item pool was developed through interviews with patients and clinicians and reduced with input from 50 hemodialysis patients.

KDQ Reliability: Cronbach's alpha coefficients have not been reported for the 5 domains. The reproducibility of the KDQ was tested in subjects receiving placebo assessed 2 months apart. The intra-class correlation coefficients were 0.85 (physical), 0.85 (fatigue), 0.96 (relationships), 0.98 (depression) and 0.96 (frustration). (Laupacis et al, 1992).

KDQ Construct Validity: Correlations between dimensions of the KDQ and other outcome measures are in the expected direction (Laupacis et al, 1992). The Physical Symptoms dimension of the KDQ was significantly correlated with the Physical SIP domain (-0.31, $p < 0.01$) and the KDQ Fatigue dimension was also significantly correlated with the Physical SIP domain (-0.38, $p < 0.001$). Furthermore, the correlation of the other KDQ dimensions was lower with SIP Physical Symptoms than the KDQ Physical and Fatigue dimensions. The KDQ Physical and Fatigue dimensions also had significant correlations with the results of a stress test (0.27 and 0.29, $p < 0.01$), whereas other dimensions of the KDQ did not have a significant correlation with a stress test. The SIP Psychological items correlate more highly with of the KDQ Relationships, Depression and Frustration dimensions than the KDQ physical items. Kutlay et al (2003) used the KDQ to evaluate the validity of the NHP in an ESRD population and reported that the KDQ physical symptoms dimension and fatigue dimension strongly correlated ($r > 0.7$) with the energy dimension of the NHP. Neto et al (2000) evaluated the validity of SF-36 in ESRD patients at the initiation of maintenance dialysis treatment and reported that the SF-36 physical function scale correlated significantly ($r > 0.5$) with KDQ physical symptoms dimension.

KDQ Interpretation: The Canadian Erythropoietin Study Group (1990) report that a 0.5 point change in mean score in each KDQ dimension represents a minimally clinically important difference, and a mean change of 1.0 represents a large clinical change.

Appendix 4. Methods for Analyses of Observational Data and Data from the NHCT by Amgen

Association Between rHuEPO Use and Ischemic Cardiovascular Events in Nondialysis Patients (Ingenix Data)

This retrospective cohort analysis estimated the association between ESA use and risk of ischemic cardiovascular events among nondialysis CRF patients with anemia. Patients in the Ingenix database who were 40 to 64 years of age, had a diagnosis of CRF and an eGFR < 60 mL/min/1.73 m^2 recorded between May 2000 and March 2006, and had a diagnosis of anemia one month before, or up to 12 months after the CRF diagnosis were selected (N = 4,752). The date of the CRF or anemia diagnosis, whichever occurred later, was assigned as the index date. Patient characteristics, comorbid conditions and ESA use were assessed during the 6 month (entry) period prior to the index date. Patients with cancer, myocardial infarction (MI), stroke, or who received previous dialysis services were excluded.

The primary outcome is the occurrence of an ischemic cardiovascular (CV) event defined as myocardial infarction based on presence of ICD-9-CM codes 410.x, 411.x or ischemic stroke (ICD-9-CM codes 433.x1, 434.x1, or 436). The primary exposure is ESA use during the entry period. Covariates assessed included age, gender, geographic region, comorbid conditions, medications, physician (nephrologist, oncologist, hematologist) visits, hospitalizations and laboratory values (albumin, serum creatinine, hemoglobin, ferritin). Person-time at risk was calculated as time from the index date to the first of CV event, transition to ESRD, loss to follow-up, or 365 days. Incidence rates were calculated as the number of incident events divided by the relevant person years of follow-up. Cox proportional hazards regression modeling estimated the hazard ratio and 95% confidence intervals for the association between exposure and outcome, adjusting for differences in baseline patient characteristics.

Achieved Hemoglobin Concentration, Patient Characteristics and Mortality (FMC-NA Data)

Data from the FMC-NA database were used to examine the association between achieved hemoglobin levels and mortality over a 12-month period across levels of baseline patient characteristics. Patients were included in this analysis project if they

completed a 6-month entry period and had at least 1 hemoglobin concentration within the last 3 months of the entry period (N=39,916). The outcome measure was time to death. Patients were followed from the end of the entry period until the earliest of date of death, lost to follow-up (eg, renal transplant, transition to peritoneal dialysis), or 30 June 2002. The maximum duration of follow-up is 18 months. Baseline hemoglobin concentrations were the average of all hemoglobin concentrations measured during the last 3 months of the entry period. The achieved baseline hemoglobin concentration was categorized into mutually exclusive categories of < 9, ≥ 9 to <10, ≥ 10 to < 11, ≥ 11 to < 12, ≥ 12 to < 13, and ≥ 13 g/dL. Covariates were assessed during months 4 to 6 were defined as the baseline period and included age (year; < 45, 45-< 65, 65-< 75, ≥ 75), gender, race (non-black, black), BMI (kg/m2; < 20, 20-< 25, 25-< 30, ≥ 30), hemoglobin variability, baseline hemoglobin slope defined as the regression of hemoglobin on time during the baseline period (g/dL/month; quartiles of the distribution), diabetes as the primary cause of ESRD, length of time on dialysis (vintage) (year; < 1, 1-< 3, 3-< 5, ≥ 5), albumin (g/dL; quartiles of the distribution) and vascular access type (fistula, graft, catheter).

The mortality relationship between achieved hemoglobin and covariates was assessed using separate Cox proportional hazards models for each covariate. For each model, the hemoglobin concentration category, the covariate category, and their interaction were included as predictors. In addition, separate Cox proportional hazards models were run for each covariate category comparing mortality rates between hemoglobin categories, with hemoglobin ≥ 11 to < 12 g/dL as the reference group. The 12-month mortality rates based on Kaplan-Meier estimates were calculated and plotted, and stratified by each combination of covariate category and achieved hemoglobin concentration category.

Gilbertson et al, 2007 - Hemoglobin Level Variability: Associations With Mortality

Hemodialysis patients (N = 159,720) from a Medicare claims database who had Medicare as a primary payer and had outpatient epoetin alfa claims in each of the first 6 months of 2004 (exposure assessment period) were identified. Patients were followed from the first day after the end of the exposure assessment period until the first of date of death, loss to follow-up, or 31 December 2004.

Monthly hemoglobin values, ascertained from epoetin claims, were categorized as low

(<11 g/dL), within 11.0 to < 12.5 g/dL, and high (> 12.5 g/dL). Six hemoglobin variability groups were defined based on the lowest and highest categories seen during the 6-month observation period: persistently low (< 11.0 g/dL), persistently within 11.0 to < 12.5 g/dL, persistently high (≥ 12.5 g/dL), variability at the low end (cycled between <11 and 11-<12.5 g/dL), variability at the high end (cycled between 11-<12.5 and >12.5 g/dL), and variability between low and high hemoglobin values (fluctuated between < 11.0 and ≥ 12.5 g/dL).

Patient comorbid conditions were identified during the 6-month exposure window using ICD-9 CM codes from Medicare Part A institutional and Part B physician/supplier claims. Additional data were obtained from the Medicare Inpatient Standard Analytical File (hospital admissions), Centers for Medicare & Medicaid Services Medical Evidence Report (CMS-2728) (demographic data), and CMS ESRD Death Notification (CMS-2746) (mortality).

Mortality rates were calculated for the 6 hemoglobin variability categories.
Cox proportional hazards regression was used to estimate hazard ratios and 95% confidence intervals for the association between hemoglobin categories and mortality, adjusting for demographic and comorbidity characteristics. The persistently within 11 to 12.5 g/dL category was the reference group for all analyses. Adjustment was made for age, race, gender, hospital admissions during the entry period, and comorbid conditions.

Association Between rHuEPO Use and Mortality Among Hemodialysis Patients (FMC-NA Data)

The objective of this retrospective cohort analysis was to examine the influence of exposure history and other confounding variables on the observed association of rHuEPO use with mortality. Patients (N = 23,804) in the FMC-NA database were included in this analysis if they had at least 6 consecutive months of ESA use or hemoglobin data between 01 July 2000 and 30 June 2001 (entry period), and survived into the follow-up period. A 6-month entry period was used to identify comorbidities using hospitalization data. The last day of the entry period was assigned as the index date. The primary outcome was all-cause mortality assessed during a 90-day follow-up period. Current ESA dose was defined as the mean dose per administration (units) in month 6 of the entry period and was categorized into quartiles (< 2708, 2708 - 5000, 5001 - 8800, and > 8800 units) based on the observed distribution of the data. Previous

ESA use (ESA exposure history) was assessed as the mean dose per administration during months 1 through 5 of the entry period. Two hemoglobin measures were calculated, one for month 6 and another for months 1 to 5. For both measures, the mean was calculated over all available measurements during the respective time period. Person-time at risk was defined as the time from the index date until the first of date of death, loss to follow-up, or 90 days.

Covariates assessed include patient demographic characteristics (age, sex, race, diabetes as the cause of ESRD, length of time on dialysis), medical history (number of hospitalizations, mean length of hospital stay), laboratory values (albumin, calcium, ferritin, parathyroid hormone, phosphorus, transferrin saturation), and dialysis care characteristics (vascular access type, urea reduction ratio, number of unexcused missed visits).

Cox proportional hazards regression estimated hazard ratios and 95% confidence intervals for the association between current ESA dose and 90-day mortality, adjusting for candidate confounding variables in two sets of analyses. The first assessed the effect of current ESA dose on 90-day mortality using three levels of adjustment: (i) no adjustment, (ii) adjustment for candidate confounders captured in USRDS data (USRDS adjusted), and (iii) adjustment for those candidate confounders captured in USRDS plus additional confounders available in FMC-NA data (fully adjusted). The second set of analyses replicated the stepped approach employed in the first analysis, but additionally adjusted for previous ESA exposure and hemoglobin levels (during months 1 to 5) at each step.

Kilpatrick et al, 2007 - Epoetin alfa Responsiveness Predicts Survival in the Normalization Arm of the Normal Hematocrit Cardiac Trial

Data from hemodialysis patients randomized to the normalization arm (targeted to achieve and maintain a hematocrit of 42% ± 3%) of the Normal Hematocrit Cardiac Trial (Besarab et al, 1998) were used. The initial total weekly Epoetin alfa dose for these subjects was to be 50% greater than the dose received in the week preceding randomization (baseline dose). Baseline data consisted of subject information collected before randomization; a subject's index date was defined as the date of randomization. Of the 618 subjects in the normalization arm, 560 had sufficient Epoetin alfa dose and hematocrit data needed to construct an erythropoietin-response index. Because

responsiveness was to be evaluated within a cohort of patients receiving a uniform dose increase, subjects were excluded if they were not administered Epoetin alfa during the week prior to randomization (N = 32) or had an initial post-randomization dose increase < 30% (N = 124) or > 70% (N = 83) from baseline, leaving 321 subjects available for analysis.

A prospective measure of responsiveness (erythropoietin-response index) was developed that evaluated change in hematocrit resulting from an Epoetin alfa dose increase that was both relatively uniform (as a percentage) and not clinically indicated. For each subject, erythropoietin response was defined as the ratio of weekly hematocrit change per Epoetin alfa dose increase (1000 units per week). The denominator, the absolute Epoetin alfa dose increase (corresponding to a relative increase of 30% to 70% from baseline), was calculated as the change in weekly Epoetin alfa dose from baseline to the first on-study week. The numerator was the change in weekly hematocrit modeled as the slope parameter obtained from a simple linear regression of each subject's average weekly hematocrit over the first 3 weeks post randomization. The erythropoietin-response index distribution was also categorized into quartiles.

The study end point was all-cause mortality from the index date until the first of date of death, transplantation, loss to follow-up, or 365 days. The association between the erythropoietin-response index and 1-year mortality was assessed using Cox proportional hazard modeling incorporating 3 levels of adjustment: 1) unadjusted models included the index measure and baseline Epoetin alfa dose; 2) case-mix models also included age, gender, race, diabetes mellitus, dialysis vintage (difference in days from the first reported dialysis date to the date of study randomization), and vascular access type; and 3) fully-adjusted models included the previous covariates plus lymphocytes, albumin, transferrin saturation, ferritin, body mass index, Kt/V, and New York Heart Association class.

rHuEPO Dose and Mortality in Hyporesponsive Hemodialysis Patients

Data from FMC-NA were used to evaluate, among hemodialysis patients with persistently low hemoglobin levels (hemoglobin < 11 g/dL), the association between rHuEPO dose changes and (i) achievement of hemoglobin values greater than or equal to 11 g/dL, and (ii) risk of death. Hemodialysis patients included in the analysis (N = 6133) had at least six consecutive months with data between July 2000 and

June 2001 (entry period), non-missing ESA dose data and monthly hemoglobin levels in each of the 6 months during the entry period, and hemoglobin levels <11 g/dL in each of the last 3 months of the entry period (months 4-6). The last day of the entry period was assigned as the index date. The "at-risk" time for study follow-up began the first day after the end of the entry period. Baseline covariates were assessed during the last 3 months of the entry period.

The primary outcomes of interest were achievement of hemoglobin values ≥ 11 g/dL or values ≥ 12 g/dL within 3 months following the entry period, and mortality within 6 months following the entry period. Average per administration ESA dose was determined for each month during the entry period with baseline ESA dose defined as the average per administration dose in month 3. For each individual, a regression line of ESA dose versus time was fitted to estimate the average monthly ESA dose. Dose change over months 4 to 6 was calculated as the geometric mean of the monthly dose changes. The slope of the dose change was categorized based on 12.5% intervals (≤ 0%, > 0 - 12.5%, > 12.5 - 25%, > 25 - 37.5%, and > 37.5%).

Covariates were assessed during the entry period and included age, gender, race, body mass index, diabetes as the primary cause of ESRD, vascular access type, blood pressure, dialysis adequacy, urea reduction ratio, hospitalizations, number of unexcused dialysis treatments, and laboratory values (albumin, ferritin, transferrin saturation, hemoglobin in months 4 - 6 (g/dL; < 9, 9 - < 9.5, 9.5 - < 10.0, 10.0 - < 10.5, ≥ 10.5, missing), and hemoglobin in month 7 (g/dL; < 11, 11 - 12, > 12).

Patients were followed from the index date to the first of date of death, loss-to-follow-up, or 180 days. Changes in hemoglobin over the first three months of follow up (study months 7 to 9) were assessed according to categories of the dose change slopes. Times to achievement of hemoglobin concentrations ≥ 11 g/dL and ≥ 12 g/dL were compared across each of the ESA dose change slope categories using a log-rank test. Crude mortality rates and 95% confidence intervals were calculated by dose change groups overall, and stratified by baseline characteristics. Cox proportional hazard regression estimated the hazard ratio and 95% confidence interval for the association between categories of dose change and 6-month mortality, adjusting for all potential confounding variables. Additional analyses evaluated the effect of dose change on mortality hazard, controlling for hemoglobin concentration during study month 7 (the

month following the 3-month period of hemoglobin < 11 g/dL) as well as the effect of hemoglobin change on death after accounting for previous dose change.

Appendix 5. United States Prescribing Information for EPOGEN®/PROCRIT® and Aranesp®

EPOGEN®
(Epoetin alfa)
FOR INJECTION

WARNINGS: Erythropoiesis-Stimulating Agents

Use the lowest dose of EPOGEN® that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion (see DOSAGE AND ADMINISTRATION).

EPOGEN® and other erythropoiesis-stimulating agents (ESAs) increased the risk for death and for serious cardiovascular events when administered to target a hemoglobin of greater than 12 g/dL (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events).

Cancer Patients: Use of ESAs

- **shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a hemoglobin of greater than 12 g/dL;**
- **shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to target a hemoglobin of greater than 12 g/dL;**
- **increased the risk of death when administered to target a hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for this population.**

(See WARNINGS: Increased Mortality and/or Tumor Progression)

Patients receiving ESAs pre-operatively for reduction of allogeneic red blood cell transfusions: A higher incidence of deep venous thrombosis was documented in patients receiving EPOGEN® who were not receiving prophylactic anticoagulation. Antithrombotic prophylaxis should be strongly considered when EPOGEN® is used to reduce allogeneic red blood cell transfusions (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events).

DESCRIPTION

Erythropoietin is a glycoprotein which stimulates red blood cell production. It is produced in the kidney and stimulates the division and differentiation of committed erythroid progenitors in the bone marrow. EPOGEN® (Epoetin alfa), a 165 amino acid glycoprotein manufactured by recombinant DNA technology, has the same biological effects as endogenous erythropoietin.[1] It has a molecular weight of 30,400 daltons and is produced by mammalian cells into which the human erythropoietin gene has been introduced. The product contains the identical amino acid sequence of isolated natural erythropoietin.

EPOGEN® is formulated as a sterile, colorless liquid in an isotonic sodium chloride/sodium citrate buffered solution or a sodium chloride/sodium phosphate buffered solution for intravenous (IV) or subcutaneous (SC) administration.

Single-dose, Preservative-free Vial: Each 1 mL of solution contains 2000, 3000, 4000 or 10,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 5.8 mg sodium citrate, 5.8 mg sodium chloride, and

0.06 mg citric acid in Water for Injection, USP (pH 6.9 ± 0.3). This formulation contains no preservative.

Single-dose, Preservative-free Vial: 1 mL (40,000 Units/mL). Each 1 mL of solution contains 40,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 1.2 mg sodium phosphate monobasic monohydrate, 1.8 mg sodium phosphate dibasic anhydrate, 0.7 mg sodium citrate, 5.8 mg sodium chloride, and 6.8 mcg citric acid in Water for Injection, USP (pH 6.9 ± 0.3). This formulation contains no preservative.

Multidose, Preserved Vial: 2 mL (20,000 Units, 10,000 Units/mL). Each 1 mL of solution contains 10,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 1.3 mg sodium citrate, 8.2 mg sodium chloride, 0.11 mg citric acid, and 1% benzyl alcohol as preservative in Water for Injection, USP (pH 6.1 ± 0.3).

Multidose, Preserved Vial: 1 mL (20,000 Units/mL). Each 1 mL of solution contains 20,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 1.3 mg sodium citrate, 8.2 mg sodium chloride, 0.11 mg citric acid, and 1% benzyl alcohol as preservative in Water for Injection, USP (pH 6.1 ± 0.3).

CLINICAL PHARMACOLOGY

Chronic Renal Failure Patients

Endogenous production of erythropoietin is normally regulated by the level of tissue oxygenation. Hypoxia and anemia generally increase the production of erythropoietin, which in turn stimulates erythropoiesis.[2] In normal subjects, plasma erythropoietin levels range from 0.01 to 0.03 Units/mL and increase up to 100- to 1000-fold during hypoxia or anemia.[2] In contrast, in patients with chronic renal failure (CRF), production of erythropoietin is impaired, and this erythropoietin deficiency is the primary cause of their anemia.[3,4]

Chronic renal failure is the clinical situation in which there is a progressive and usually irreversible decline in kidney function. Such patients may manifest the sequelae of renal dysfunction, including anemia, but do not necessarily require regular dialysis. Patients with end-stage renal disease (ESRD) are those patients with CRF who require regular dialysis or kidney transplantation for survival.

EPOGEN® has been shown to stimulate erythropoiesis in anemic patients with CRF, including both patients on dialysis and those who do not require regular dialysis.[4-13] The first evidence of a response to the three times weekly (TIW) administration of EPOGEN® is an increase in the reticulocyte count within 10 days, followed by increases in the red cell count, hemoglobin, and hematocrit, usually within 2 to 6 weeks.[4,5] Because of the length of time required for erythropoiesis — several days for erythroid progenitors to mature and be released into the circulation — a clinically significant increase in hematocrit is usually not observed in less than 2 weeks and may require up to 6 weeks in some patients. Once the hematocrit reaches the suggested target range (30% to 36%), that level can be sustained by EPOGEN® therapy in the absence of iron deficiency and concurrent illnesses.

The rate of hematocrit increase varies between patients and is dependent upon the dose of EPOGEN®, within a therapeutic range of approximately 50 to 300 Units/kg TIW.[4] A greater biologic response is not observed at doses exceeding 300 Units/kg TIW.[6] Other factors affecting the rate and extent of response include availability of iron stores, the baseline hematocrit, and the presence of concurrent medical problems.

Zidovudine-treated HIV-infected Patients

Responsiveness to EPOGEN® in HIV-infected patients is dependent upon the endogenous serum erythropoietin level prior to treatment. Patients with endogenous serum erythropoietin levels ≤ 500 mUnits/mL, and who are receiving a dose of zidovudine ≤ 4200 mg/week, may respond to EPOGEN® therapy. Patients with endogenous serum erythropoietin levels > 500 mUnits/mL do not appear to respond to EPOGEN® therapy. In a series of four clinical trials involving 255 patients, 60% to

80% of HIV-infected patients treated with zidovudine had endogenous serum erythropoietin levels ≤ 500 mUnits/mL.

Response to EPOGEN® in zidovudine-treated HIV-infected patients is manifested by reduced transfusion requirements and increased hematocrit.

Cancer Patients on Chemotherapy

A series of clinical trials enrolled 131 anemic cancer patients who received EPOGEN® TIW and who were receiving cyclic cisplatin- or non cisplatin-containing chemotherapy. Endogenous baseline serum erythropoietin levels varied among patients in these trials with approximately 75% (n = 83/110) having endogenous serum erythropoietin levels ≤ 132 mUnits/mL, and approximately 4% (n = 4/110) of patients having endogenous serum erythropoietin levels > 500 mUnits/mL. In general, patients with lower baseline serum erythropoietin levels responded more vigorously to EPOGEN® than patients with higher baseline erythropoietin levels. Although no specific serum erythropoietin level can be stipulated above which patients would be unlikely to respond to EPOGEN® therapy, treatment of patients with grossly elevated serum erythropoietin levels (eg, > 200 mUnits/mL) is not recommended.

Pharmacokinetics

In adult and pediatric patients with CRF, the elimination half-life of plasma erythropoietin after intravenously administered EPOGEN® ranges from 4 to 13 hours.[14-16] The half-life is approximately 20% longer in CRF patients than that in healthy subjects. After SC administration, peak plasma levels are achieved within 5 to 24 hours. The half-life is similar between adult patients with serum creatinine level greater than 3 and not on dialysis and those maintained on dialysis. The pharmacokinetic data indicate no apparent difference in EPOGEN® half-life among adult patients above or below 65 years of age.

The pharmacokinetic profile of EPOGEN® in children and adolescents appears to be similar to that of adults. Limited data are available in neonates.[17] A study of 7 preterm very low birth weight neonates and 10 healthy adults given IV erythropoietin suggested that distribution volume was approximately 1.5 to 2 times higher in the preterm neonates than in the healthy adults, and clearance was approximately 3 times higher in the preterm neonates than in the healthy adults.[42]

The pharmacokinetics of EPOGEN® have not been studied in HIV-infected patients.

A pharmacokinetic study comparing 150 Units/kg SC TIW to 40,000 Units SC weekly dosing regimen was conducted for 4 weeks in healthy subjects (n = 12) and for 6 weeks in anemic cancer patients (n = 32) receiving cyclic chemotherapy. There was no accumulation of serum erythropoietin after the 2 dosing regimens during the study period. The 40,000 Units weekly regimen had a higher C_{max} (3- to 7-fold), longer T_{max} (2- to 3-fold), higher $AUC_{0\text{-}168h}$ (2- to 3-fold) of erythropoietin and lower clearance (50%) than the 150 Units/kg TIW regimen. In anemic cancer patients, the average $t_{1/2}$ was similar (40 hours with range of 16 to 67 hours) after both dosing regimens. After the 150 Units/kg TIW dosing, the values of T_{max} and clearance are similar (13.3 ± 12.4 vs. 14.2 ± 6.7 hours, and 20.2 ± 15.9 vs. 23.6 ± 9.5 mL/h/kg) between Week 1 when patients were receiving chemotherapy (n = 14) and Week 3 when patients were not receiving chemotherapy (n = 4). Differences were observed after the 40,000 Units weekly dosing with longer T_{max} (38 ± 18 hours) and lower clearance (9.2 ± 4.7 mL/h/kg) during Week 1 when patients were receiving chemotherapy (n = 18) compared with those (22 ± 4.5 hours, 13.9 ± 7.6 mL/h/kg) during Week 3 when patients were not receiving chemotherapy (n = 7).

The bioequivalence between the 10,000 Units/mL citrate-buffered Epoetin alfa formulation and the 40,000 Units/mL phosphate-buffered Epoetin alfa formulation has been demonstrated after SC administration of single 750 Units/kg doses to healthy subjects.

INDICATIONS AND USAGE

Treatment of Anemia of Chronic Renal Failure Patients

EPOGEN® is indicated for the treatment of anemia associated with CRF, including patients on dialysis (ESRD) and patients not on dialysis. EPOGEN® is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients.

Non-dialysis patients with symptomatic anemia considered for therapy should have a hemoglobin less than 10 g/dL.

EPOGEN® is not intended for patients who require immediate correction of severe anemia. EPOGEN® may obviate the need for maintenance transfusions but is not a substitute for emergency transfusion.

Prior to initiation of therapy, the patient's iron stores should be evaluated. Transferrin saturation should be at least 20% and ferritin at least 100 ng/mL. Blood pressure should be adequately controlled prior to initiation of EPOGEN® therapy, and must be closely monitored and controlled during therapy.

EPOGEN® should be administered under the guidance of a qualified physician (see DOSAGE AND ADMINISTRATION).

Treatment of Anemia in Zidovudine-treated HIV-infected Patients

EPOGEN® is indicated for the treatment of anemia related to therapy with zidovudine in HIV-infected patients. EPOGEN® is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients. EPOGEN® is not indicated for the treatment of anemia in HIV-infected patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding, which should be managed appropriately.

EPOGEN®, at a dose of 100 Units/kg TIW, is effective in decreasing the transfusion requirement and increasing the red blood cell level of anemic, HIV-infected patients treated with zidovudine, when the endogenous serum erythropoietin level is $\leq$ 500 mUnits/mL and when patients are receiving a dose of zidovudine $\leq$ 4200 mg/week.

Treatment of Anemia in Cancer Patients on Chemotherapy

EPOGEN® is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. EPOGEN® is indicated to decrease the need for transfusions in patients who will be receiving concomitant chemotherapy for a minimum of 2 months. EPOGEN® is not indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding, which should be managed appropriately.

Reduction of Allogeneic Blood Transfusion in Surgery Patients

EPOGEN® is indicated for the treatment of anemic patients (hemoglobin > 10 to $\leq$ 13 g/dL) scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions.[18-20] EPOGEN® is indicated for patients at high risk for perioperative transfusions with significant, anticipated blood loss. EPOGEN® is not indicated for anemic patients who are willing to donate autologous blood (see BOXED WARNINGS and DOSAGE AND ADMINISTRATION).

CLINICAL EXPERIENCE: RESPONSE TO EPOGEN®

Chronic Renal Failure Patients

Response to EPOGEN® was consistent across all studies. In the presence of adequate iron stores (see IRON EVALUATION), the time to reach the target hematocrit is a function of the baseline hematocrit and the rate of hematocrit rise.

The rate of increase in hematocrit is dependent upon the dose of EPOGEN® administered and individual patient variation. In clinical trials at starting doses of 50 to 150 Units/kg TIW, adult patients responded with an average rate of hematocrit rise of:

Starting Dose	Hematocrit Increase	
(TIW IV)	Points/Day	Points/2 Weeks
50 Units/kg	0.11	1.5
100 Units/kg	0.18	2.5
150 Units/kg	0.25	3.5

Over this dose range, approximately 95% of all patients responded with a clinically significant increase in hematocrit, and by the end of approximately 2 months of therapy virtually all patients were transfusion-independent. Changes in the quality of life of adult patients treated with EPOGEN® were assessed as part of a phase 3 clinical trial.[5,8] Once the target hematocrit (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 (VO_2 max), energy, and strength with a significant reduction in aching, dizziness, anxiety, shortness of breath, muscle weakness, and leg cramps.[8,21]

Adult Patients on Dialysis: Thirteen clinical studies were conducted, involving IV administration to a total of 1010 anemic patients on dialysis for 986 patient-years of EPOGEN® therapy. In the three largest of these clinical trials, the median maintenance dose necessary to maintain the hematocrit between 30% to 36% was approximately 75 Units/kg TIW. In the US multicenter phase 3 study, approximately 65% of the patients required doses of 100 Units/kg TIW, or less, to maintain their hematocrit at approximately 35%. Almost 10% of patients required a dose of 25 Units/kg, or less, and approximately 10% required a dose of more than 200 Units/kg TIW to maintain their hematocrit at this level.

A multicenter unit dose study was also conducted in 119 patients receiving peritoneal dialysis who self-administered EPOGEN® subcutaneously for approximately 109 patient-years of experience. Patients responded to EPOGEN® administered SC in a manner similar to patients receiving IV administration.[22]

Pediatric Patients on Dialysis: One hundred twenty-eight children from 2 months to 19 years of age with CRF requiring dialysis were enrolled in 4 clinical studies of EPOGEN®. The largest study was a placebo-controlled, randomized trial in 113 children with anemia (hematocrit $\leq$ 27%) undergoing peritoneal dialysis or hemodialysis. The initial dose of EPOGEN® was 50 Units/kg IV or SC TIW. The dose of study drug was titrated to achieve either a hematocrit of 30% to 36% or an absolute increase in hematocrit of 6 percentage points over baseline.

At the end of the initial 12 weeks, a statistically significant rise in mean hematocrit (9.4% vs 0.9%) was observed only in the EPOGEN® arm. The proportion of children achieving a hematocrit of 30%, or an

increase in hematocrit of 6 percentage points over baseline, at any time during the first 12 weeks was higher in the EPOGEN® arm (96% vs 58%). Within 12 weeks of initiating EPOGEN® therapy, 92.3% of the pediatric patients were transfusion-independent as compared to 65.4% who received placebo. Among patients who received 36 weeks of EPOGEN®, hemodialysis patients required a higher median maintenance dose (167 Units/kg/week [n = 28] vs 76 Units/kg/week [n = 36]) and took longer to achieve a hematocrit of 30% to 36% (median time to response 69 days vs 32 days) than patients undergoing peritoneal dialysis.

Patients With CRF Not Requiring Dialysis

Four clinical trials were conducted in patients with CRF not on dialysis involving 181 patients treated with EPOGEN® for approximately 67 patient-years of experience. These patients responded to EPOGEN® therapy in a manner similar to that observed in patients on dialysis. Patients with CRF not on dialysis demonstrated a dose-dependent and sustained increase in hematocrit when EPOGEN® was administered by either an IV or SC route, with similar rates of rise of hematocrit when EPOGEN® was administered by either route. Moreover, EPOGEN® doses of 75 to 150 Units/kg per week have been shown to maintain hematocrits of 36% to 38% for up to 6 months.[23-24]

Zidovudine-treated HIV-infected Patients

EPOGEN® has been studied in four placebo-controlled trials enrolling 297 anemic (hematocrit < 30%) HIV-infected (AIDS) patients receiving concomitant therapy with zidovudine (all patients were treated with Epoetin alfa manufactured by Amgen Inc). In the subgroup of patients (89/125 EPOGEN® and 88/130 placebo) with prestudy endogenous serum erythropoietin levels ≤ 500 mUnits/mL, EPOGEN® reduced the mean cumulative number of units of blood transfused per patient by approximately 40% as compared to the placebo group.[24] Among those patients who required transfusions at baseline, 43% of patients treated with EPOGEN® versus 18% of placebo-treated patients were transfusion-independent during the second and third months of therapy. EPOGEN® therapy also resulted in significant increases in hematocrit in comparison to placebo. When examining the results according to the weekly dose of zidovudine received during month 3 of therapy, there was a statistically significant ($p < 0.003$) reduction in transfusion requirements in patients treated with EPOGEN® (n = 51) compared to placebo treated patients (n = 54) whose mean weekly zidovudine dose was ≤ 4200 mg/week.[25]

Approximately 17% of the patients with endogenous serum erythropoietin levels ≤ 500 mUnits/mL receiving EPOGEN® in doses from 100 to 200 Units/kg TIW achieved a hematocrit of 38% without administration of transfusions or significant reduction in zidovudine dose. In the subgroup of patients whose prestudy endogenous serum erythropoietin levels were > 500 mUnits/mL, EPOGEN® therapy did not reduce transfusion requirements or increase hematocrit, compared to the corresponding responses in placebo-treated patients.

In a 6 month open-label EPOGEN® study, patients responded with decreased transfusion requirements and sustained increases in hematocrit and hemoglobin with doses of EPOGEN® up to 300 Units/kg TIW.[25-27]

Responsiveness to EPOGEN® therapy may be blunted by intercurrent infectious/inflammatory episodes and by an increase in zidovudine dosage. Consequently, the dose of EPOGEN® must be titrated based on these factors to maintain the desired erythropoietic response.

Cancer Patients on Chemotherapy

Adult Patients

Three-Times Weekly (TIW) Dosing

EPOGEN® administered TIW has been studied in a series of six placebo-controlled, double-blind trials that enrolled 131 anemic cancer patients receiving EPOGEN® or matching placebo. Across all studies, 72 patients were treated with concomitant non cisplatin-containing chemotherapy regimens and 59 patients were treated with concomitant cisplatin-containing chemotherapy regimens. Patients were randomized to EPOGEN® 150 Units/kg or placebo subcutaneously TIW for 12 weeks in each study.

The results of the pooled data from these six studies are shown in the table below. Because of the length of time required for erythropoiesis and red cell maturation, the efficacy of EPOGEN® (reduction in proportion of patients requiring transfusions) is not manifested until 2 to 6 weeks after initiation of EPOGEN®.

Proportion of Patients Transfused During Chemotherapy (Efficacy Population[a])

Chemotherapy Regimen	On Study[b]		During Months 2 and 3[c]	
	EPOGEN®	Placebo	EPOGEN®	Placebo
Regimens without cisplatin	44% (15/34)	44% (16/36)	21% (6/29)	33% (11/33)
Regimens containing cisplatin	50% (14/28)	63% (19/30)	23% (5/22)[d]	56% (14/25)
Combined	47% (29/62)	53% (35/66)	22% (11/51)[d]	43% (25/58)

[a] Limited to patients remaining on study at least 15 days (1 patient excluded from EPOGEN®, 2 patients excluded from placebo).

[b] Includes all transfusions from day 1 through the end of study.

[c] Limited to patients remaining on study beyond week 6 and includes only transfusions during weeks 5-12.

[d] Unadjusted 2-sided $p < 0.05$

Intensity of chemotherapy in the above trials was not directly assessed, however the degree and timing of neutropenia was comparable across all trials. Available evidence suggests that patients with lymphoid and solid cancers respond similarly to EPOGEN® therapy, and that patients with or without tumor infiltration of the bone marrow respond similarly to EPOGEN® therapy.

Weekly (QW) Dosing

EPOGEN® was also studied in a placebo-controlled, double-blind trial utilizing weekly dosing in a total of 344 anemic cancer patients. In this trial, 61 (35 placebo arm and 26 in the EPOGEN® arm) patients were treated with concomitant cisplatin containing regimens and 283 patients received concomitant chemotherapy regimens that did not contain cisplatinum. Patients were randomized to EPOGEN® 40,000 Units weekly (n = 174) or placebo (n = 170) SC for a planned treatment period of 16 weeks. If hemoglobin had not increased by > 1 g/dL, after 4 weeks of therapy or the patient received RBC transfusion during the first 4 weeks of therapy, study drug was increased to 60,000 Units weekly. Forty-three percent of patients in the Epoetin alfa group required an increase in EPOGEN® dose to 60,000 Units weekly. [25]

Results demonstrated that EPOGEN® therapy reduced the proportion of patients transfused in day 29 through week 16 of the study as compared to placebo. Twenty-five patients (14%) in the EPOGEN® group received transfusions compared to 48 patients (28%) in the placebo group ($p = 0.0010$) between day 29 and week 16 or the last day on study.

Comparable intensity of chemotherapy for patients enrolled in the two study arms was suggested by similarities in mean dose and frequency of administration for the 10 most commonly administered chemotherapy agents, and similarity in the incidence of changes in chemotherapy during the trial in the two arms.

Pediatric Patients

The safety and effectiveness of EPOGEN® were evaluated in a randomized, double-blind, placebo-controlled, multicenter study in anemic patients ages 5 to 18 receiving chemotherapy for the treatment of various childhood malignancies. Two hundred twenty-two patients were randomized (1:1) to EPOGEN® or placebo. EPOGEN® was administered at 600 Units/kg (maximum 40,000 Units) intravenously once per week for 16 weeks. If hemoglobin had not increased by 1g/dL after the first 4-5 weeks of therapy, EPOGEN® was increased to 900 Units/kg (maximum 60,000 Units). Among the EPOGEN®-treated patients 60% required dose escalation to 900 Units/kg/week.

The effect of EPOGEN® on transfusion requirements is shown in the table below:

Percentage of Patients Transfused:			
On Study[a]		After 28 Days Post-Randomization	
EPOGEN® (n=111)	Placebo (n=111)	EPOGEN® (n= 111)	Placebo (n=111)
65% (72)	77% (86)	51%(57)[b]	69% (77)

[a] Includes all transfusions from day 1 through the end of study
[b] Adjusted 2 sided p <0.05

There was no evidence of an improvement in health-related quality of life, including no evidence of an effect on fatigue, energy or strength, in patients receiving EPOGEN® as compared to those receiving placebo.

Surgery Patients

EPOGEN® has been studied in a placebo-controlled, double-blind trial enrolling 316 patients scheduled for major, elective orthopedic hip or knee surgery who were expected to require ≥ 2 units of blood and who were not able or willing to participate in an autologous blood donation program. Based on previous studies which demonstrated that pretreatment hemoglobin is a predictor of risk of receiving transfusion,[20,28] patients were stratified into one of three groups based on their pretreatment hemoglobin [≤ 10 (n = 2), > 10 to ≤ 13 (n = 96), and > 13 to ≤ 15 g/dL (n = 218)] and then randomly assigned to receive 300 Units/kg EPOGEN®, 100 Units/kg EPOGEN® or placebo by SC injection for 10 days before surgery, on the day of surgery, and for 4 days after surgery.[18] All patients received oral iron and a low-dose post-operative warfarin regimen.[18]

Treatment with EPOGEN® 300 Units/kg significantly (p = 0.024) reduced the risk of allogeneic transfusion in patients with a pretreatment hemoglobin of > 10 to ≤ 13; 5/31 (16%) of EPOGEN® 300 Units/kg, 6/26 (23%) of EPOGEN® 100 Units/kg, and 13/29 (45%) of placebo-treated patients were transfused.[18] There was no significant difference in the number of patients transfused between EPOGEN® (9% 300 Units/kg, 6% 100 Units/kg) and placebo (13%) in the > 13 to ≤ 15 g/dL hemoglobin stratum. There were too few patients in the ≤ 10 g/dL group to determine if EPOGEN® is useful in this hemoglobin strata. In the > 10 to ≤ 13 g/dL pretreatment stratum, the mean number of units transfused per EPOGEN®-treated patient (0.45 units blood for 300 Units/kg, 0.42 units blood for 100 Units/kg) was less than the mean transfused per placebo-treated patient (1.14 units) (overall p = 0.028). In addition,

mean hemoglobin, hematocrit, and reticulocyte counts increased significantly during the presurgery period in patients treated with EPOGEN®.[18]

EPOGEN® was also studied in an open-label, parallel-group trial enrolling 145 subjects with a pretreatment hemoglobin level of ≥ 10 to ≤ 13 g/dL who were scheduled for major orthopedic hip or knee surgery and who were not participating in an autologous program.[19] Subjects were randomly assigned to receive one of two SC dosing regimens of EPOGEN® (600 Units/kg once weekly for 3 weeks prior to surgery and on the day of surgery, or 300 Units/kg once daily for 10 days prior to surgery, on the day of surgery and for 4 days after surgery). All subjects received oral iron and appropriate pharmacologic anticoagulation therapy.

From pretreatment to presurgery, the mean increase in hemoglobin in the 600 Units/kg weekly group (1.44 g/dL) was greater than observed in the 300 Units/kg daily group.[19] The mean increase in absolute reticulocyte count was smaller in the weekly group ($0.11 \times 10^6/mm^3$) compared to the daily group ($0.17 \times 10^6/mm^3$). Mean hemoglobin levels were similar for the two treatment groups throughout the postsurgical period.

The erythropoietic response observed in both treatment groups resulted in similar transfusion rates [11/69 (16%) in the 600 Units/kg weekly group and 14/71 (20%) in the 300 Units/kg daily group].[19] The mean number of units transfused per subject was approximately 0.3 units in both treatment groups.

CONTRAINDICATIONS

EPOGEN® is contraindicated in patients with:

1. Uncontrolled hypertension.
2. Known hypersensitivity to mammalian cell-derived products.
3. Known hypersensitivity to Albumin (Human).

WARNINGS

Pediatrics

Risk in Premature Infants

The multidose preserved formulation contains benzyl alcohol. Benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications in premature infants which are sometimes fatal.

Adults

Increased Mortality, Serious Cardiovascular and Thromboembolic Events

EPOGEN® and other erythropoiesis-stimulating agents (ESAs) increased the risk for death and for serious cardiovascular events in controlled clinical trials when administered to target a hemoglobin of greater than 12 g/dL. There was an increased risk of serious arterial and venous thromboembolic events, including myocardial infarction, stroke, congestive heart failure, and hemodialysis graft occlusion. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may also contribute to these risks.

To reduce cardiovascular risks, use the lowest dose of EPOGEN® that will gradually increase the hemoglobin concentration to a level sufficient to avoid the need for RBC transfusion. The hemoglobin concentration should not exceed 12 g/dL; the rate of hemoglobin increase should not exceed 1 g/dL in any two week period (see DOSAGE AND ADMINISTRATION).

In a randomized prospective trial, 1432 anemic chronic renal failure patients who were not undergoing dialysis were assigned to Epoetin alfa (rHuEPO) treatment targeting a maintenance hemoglobin concentration of 13.5 g/dL or 11.3 g/dL. A major cardiovascular event (death, myocardial infarction, stroke or hospitalization for congestive heart failure) occurred among 125 (18%) of the 715 patients in the higher hemoglobin group compared to 97 (14%) among the 717 patients in the lower hemoglobin group (HR 1.3, 95% CI: 1.0, 1.7, p = 0.03).[43]

Increased risk for serious cardiovascular events was also reported from a randomized, prospective trial of 1265 hemodialysis patients with clinically evident cardiac disease (ischemic heart disease or congestive heart failure). In this trial, patients were assigned to EPOGEN® treatment targeted to a maintenance hematocrit of either 42 ± 3% or 30 ± 3%.[40] Increased mortality was observed in 634 patients randomized to a target hematocrit of 42% [221 deaths (35% mortality)] compared to 631 patients targeted to remain at a hematocrit of 30% [185 deaths (29% mortality)]. The reason for the increased mortality observed in this study is unknown, however, the incidence of non-fatal myocardial infarctions (3.1% vs. 2.3%), vascular access thromboses (39% vs. 29%), and all other thrombotic events (22% vs. 18%) were also higher in the group randomized to achieve a hematocrit of 42%.

An increased incidence of thrombotic events has also been observed in patients with cancer treated with erythropoietic agents.

In a randomized controlled study (referred to as the 'BEST' study) with another ESA in 939 women with metastatic breast cancer receiving chemotherapy, patients received either weekly Epoetin alfa or placebo for up to a year. This study was designed to show that survival was superior when an ESA was administered to prevent anemia (maintain hemoglobin levels between 12 and 14 g/dL or hematocrit between 36% and 42%). The study was terminated prematurely when interim results demonstrated that a higher mortality at 4 months (8.7% vs. 3.4%) and a higher rate of fatal thrombotic events (1.1% vs. 0.2%) in the first 4 months of the study were observed among patients treated with Epoetin alfa. Based on Kaplan-Meier estimates, at the time of study termination, the 12-month survival was lower in the Epoetin alfa group than in the placebo group (70% vs. 76%; HR 1.37, 95% CI: 1.07, 1.75; p = 0.012).[46]

A systematic review of 57 randomized controlled trials (including the BEST and ENHANCE studies) evaluating 9353 patients with cancer compared ESAs plus red blood cell transfusion with red blood cell transfusion alone for prophylaxis or treatment of anemia in cancer patients with or without concurrent antineoplastic therapy. An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 patients) was observed in ESA-treated patients. An overall survival hazard ratio of 1.08, (95% CI: 0.99, 1.18; 42 trials and 8167 patients) was observed in ESA-treated patients.[44]

An increased incidence of deep vein thrombosis (DVT) in patients receiving Epoetin alfa undergoing surgical orthopedic procedures has been observed (see ADVERSE REACTIONS, Surgery Patients: Thrombotic/Vascular Events). In a randomized controlled study (referred to as the 'SPINE' study), 681 adult patients, not receiving prophylactic anticoagulation and undergoing spinal surgery, received either 4 doses of 600 U/kg Epoetin alfa (7, 14, and 21 days before surgery, and the day of surgery) and standard of care (SOC) treatment, or SOC treatment alone. Preliminary analysis showed a higher incidence of DVT, determined by either Color Flow Duplex Imaging or by clinical symptoms, in the Epoetin alfa group [16 patients (4.7%)] compared to the SOC group [7 patients (2.1%)]. In addition, 12 patients in the Epoetin alfa group and 7 patients in the SOC group had other thrombotic vascular events.
Antithrombotic prophylaxis should be strongly considered when ESAs are used for the reduction of allogeneic RBC transfusions in surgical patients (see BOXED WARNINGS and DOSAGE AND ADMINISTRATION).

Increased mortality was also observed in a randomized placebo-controlled study of EPOGEN® in adult patients who were undergoing coronary artery bypass surgery (7 deaths in 126 patients randomized to EPOGEN® versus no deaths among 56 patients receiving placebo). Four of these deaths occurred during the period of study drug administration and all four deaths were associated with thrombotic events.[45] ESAs are not approved for reduction of allogeneic red blood cell transfusions in patients scheduled for cardiac surgery.

Increased Mortality and/or Tumor Progression

Erythropoiesis-stimulating agents, when administered to target a hemoglobin of greater than 12 g/dL, shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy. ESAs also shortened survival in patients with metastatic breast cancer receiving chemotherapy when administered to target a hemoglobin of greater than 12 g/dL.

The ENHANCE study was a randomized controlled study in 351 head and neck cancer patients where Epoetin beta or placebo was administered to achieve target hemoglobin of 14 and 15 g/dL for women and men, respectively. Locoregional progression-free survival was significantly shorter in patients receiving Epoetin beta, HR 1.62 (95% CI: 1.22, 2.14; p = 0.0008) with a median of 406 days Epoetin beta vs. 745 days placebo.[41]

The DAHANCA 10 study, conducted in 522 patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy were randomized to darbepoetin alfa or placebo. An interim analysis in 484 patients demonstrated a 10% increase in locoregional failure rate among darbepoetin alfa-treated patients (p = 0.01). At the time of study termination, there was a trend toward worse survival in the darbepoetin alfa-treated arm (p = 0.08).

The BEST study was previously described (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events). Mortality at 4 months (8.7% vs. 3.4%) was significantly higher in the Epoetin alfa arm. The most common investigator-attributed cause of death within the first 4 months was disease progression; 28 of 41 deaths in the Epoetin alfa arm and 13 of 16 deaths in the placebo arm were attributed to disease progression. Investigator assessed time to tumor progression was not different between the two groups.[46]

In a Phase 3, double-blind, randomized (darbepoetin alfa vs. placebo), 16-week study in 989 anemic patients with active malignant disease neither receiving nor planning to receive chemotherapy or radiation therapy, there was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions. In addition, there were more deaths in the darbepoetin alfa treatment group [26% (136/515)] than the placebo group [20% (94/470)] at 16 weeks (completion of treatment phase). With a median survival follow up of 4.3 months, the absolute number of deaths was greater in the darbepoetin alfa treatment group [49% (250/515)] compared with the placebo group [46% (216/470); HR 1.29, 95% CI: 1.08, 1.55].

In a Phase 3, multicenter, randomized (Epoetin alfa vs. placebo), double-blind study, patients with advanced non-small-cell lung cancer unsuitable for curative therapy were treated with Epoetin alfa targeting hemoglobin levels between 12 and 14 g/dL. Following an interim analysis of 70 of 300 patients planned, a significant difference in median survival in favor of the patients on the placebo arm of the trial was observed (63 vs. 129 days; HR 1.84; p = 0.04).

Pure Red Cell Aplasia
Cases of pure red cell aplasia (PRCA) and of severe anemia, with or without other cytopenias, associated with neutralizing antibodies to erythropoietin have been reported in patients treated with EPOGEN®. This has been reported predominantly in patients with CRF receiving EPOGEN® by subcutaneous administration. Any patient who develops a sudden loss of response to EPOGEN®, accompanied by severe anemia and low reticulocyte count, should be evaluated for the etiology of loss of effect, including the presence of neutralizing antibodies to erythropoietin (see PRECAUTIONS: Lack or Loss of Response). If anti-erythropoietin antibody-associated anemia is suspected, withhold EPOGEN® and other erythropoietic proteins. Contact Amgen (1-800-77AMGEN) to perform assays for binding and neutralizing antibodies. EPOGEN® should be permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other erythropoietic proteins as antibodies may cross-react (see ADVERSE REACTIONS: Immunogenicity).

Albumin (Human)
EPOGEN® contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

Chronic Renal Failure Patients
Hypertension: Patients with uncontrolled hypertension should not be treated with EPOGEN®; blood pressure should be controlled adequately before initiation of therapy. Up to 80% of patients with CRF have a history of hypertension.[29] Although there do not appear to be any direct pressor effects of EPOGEN®, blood pressure may rise during EPOGEN® therapy. During the early phase of treatment when the hematocrit is increasing, approximately 25% of patients on dialysis may require initiation of, or increases in, antihypertensive therapy. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with EPOGEN®.

Special care should be taken to closely monitor and aggressively control blood pressure in patients treated with EPOGEN®. Patients should be advised as to the importance of compliance with antihypertensive therapy and dietary restrictions. If blood pressure is difficult to control by initiation of appropriate measures, the hemoglobin may be reduced by decreasing or withholding the dose of EPOGEN®. A clinically significant decrease in hemoglobin may not be observed for several weeks.

It is recommended that the dose of EPOGEN® be decreased if the hemoglobin increase exceeds 1 g/dL in any 2-week period, because of the possible association of excessive rate of rise of hemoglobin with an exacerbation of hypertension. In CRF patients on hemodialysis with clinically evident ischemic heart disease or congestive heart failure, the hemoglobin should be managed carefully, not to exceed 12 g/dL (see WARNINGS: Mortality, Serious Cardiovascular and Thromboembolic Events and DOSAGE AND ADMINISTRATION: Chronic Renal Failure Patients).

Seizures: Seizures have occurred in patients with CRF participating in EPOGEN® clinical trials.

In adult patients on dialysis, there was a higher incidence of seizures during the first 90 days of therapy (occurring in approximately 2.5% of patients) as compared with later timepoints.

Given the potential for an increased risk of seizures during the first 90 days of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely. Patients should be cautioned to avoid potentially hazardous activities such as driving or operating heavy machinery during this period.

While the relationship between seizures and the rate of rise of hemoglobin is uncertain, it is recommended that the dose of EPOGEN® be decreased if the hemoglobin increase exceeds 1 g/dL in any 2-week period.

Thrombotic Events: During hemodialysis, patients treated with EPOGEN® may require increased anticoagulation with heparin to prevent clotting of the artificial kidney (see ADVERSE REACTIONS for more information about thrombotic events).

Other thrombotic events (eg, myocardial infarction, cerebrovascular accident, transient ischemic attack) have occurred in clinical trials at an annualized rate of less than 0.04 events per patient year of EPOGEN® therapy. These trials were conducted in adult patients with CRF (whether on dialysis or not) in whom the target hematocrit was 32% to 40%. However, the risk of thrombotic events, including vascular access thrombosis, was significantly increased in adult patients with ischemic heart disease or congestive heart failure receiving EPOGEN® therapy with the goal of reaching a normal hematocrit (42%) as compared to a target hematocrit of 30%. Patients with pre-existing cardiovascular disease should be monitored closely.

Zidovudine-treated HIV-infected Patients
In contrast to CRF patients, EPOGEN® therapy has not been linked to exacerbation of hypertension, seizures, and thrombotic events in HIV-infected patients. However, the clinical data do not rule out an increased risk for serious cardiovascular events.

PRECAUTIONS
The parenteral administration of any biologic product should be attended by appropriate precautions in case allergic or other untoward reactions occur (see CONTRAINDICATIONS). In clinical trials, while transient rashes were occasionally observed concurrently with EPOGEN® therapy, no serious allergic or anaphylactic reactions were reported (see ADVERSE REACTIONS for more information regarding allergic reactions).

The safety and efficacy of EPOGEN® therapy have not been established in patients with a known history of a seizure disorder or underlying hematologic disease (eg, sickle cell anemia, myelodysplastic syndromes, or hypercoagulable disorders).

In some female patients, menses have resumed following EPOGEN® therapy; the possibility of pregnancy should be discussed and the need for contraception evaluated.

Hematology
Exacerbation of porphyria has been observed rarely in patients with CRF treated with EPOGEN®. However, EPOGEN® has not caused increased urinary excretion of porphyrin metabolites in normal volunteers, even in the presence of a rapid erythropoietic response. Nevertheless, EPOGEN® should be used with caution in patients with known porphyria.

In preclinical studies in dogs and rats, but not in monkeys, EPOGEN® therapy was associated with subclinical bone marrow fibrosis. Bone marrow fibrosis is a known complication of CRF in humans and may be related to secondary hyperparathyroidism or unknown factors. The incidence of bone marrow fibrosis was not increased in a study of adult patients on dialysis who were treated with EPOGEN® for 12 to 19 months, compared to the incidence of bone marrow fibrosis in a matched group of patients who had not been treated with EPOGEN®.

Hemoglobin in CRF patients should be measured twice a week; zidovudine-treated HIV-infected and cancer patients should have hemoglobin measured once a week until hemoglobin has been stabilized, and measured periodically thereafter.

Lack or Loss of Response
If the patient fails to respond or to maintain a response to doses within the recommended dosing range, the following etiologies should be considered and evaluated:

1. Iron deficiency: Virtually all patients will eventually require supplemental iron therapy (see IRON EVALUATION).
2. Underlying infectious, inflammatory, or malignant processes.
3. Occult blood loss.
4. Underlying hematologic diseases (ie, thalassemia, refractory anemia, or other myelodysplastic disorders).
5. Vitamin deficiencies: Folic acid or vitamin B_{12}.
6. Hemolysis.
7. Aluminum intoxication.
8. Osteitis fibrosa cystica.
9. Pure Red Cell Aplasia (PRCA) or anti-erythropoietin antibody-associated anemia: In the absence of another etiology, the patient should be evaluated for evidence of PRCA and sera should be tested for the presence of antibodies to erythropoietin (see WARNINGS: Pure Red Cell Aplasia).

Iron Evaluation
During EPOGEN® therapy, absolute or functional iron deficiency may develop. Functional iron deficiency, with normal ferritin levels but low transferrin saturation, is presumably due to the inability to mobilize iron stores rapidly enough to support increased erythropoiesis. Transferrin saturation should be at least 20% and ferritin should be at least 100 ng/mL.

Prior to and during EPOGEN® therapy, the patient's iron status, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, should be evaluated. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels which will adequately support erythropoiesis stimulated by EPOGEN®. All surgery patients being treated with EPOGEN® should receive adequate iron supplementation throughout the course of therapy in order to support erythropoiesis and avoid depletion of iron stores.

Drug Interaction
No evidence of interaction of EPOGEN® with other drugs was observed in the course of clinical trials.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Carcinogenic potential of EPOGEN® has not been evaluated. EPOGEN® does not induce bacterial gene mutation (Ames Test), chromosomal aberrations in mammalian cells, micronuclei in mice, or gene mutation at the HGPRT locus. In female rats treated IV with EPOGEN®, there was a trend for slightly increased fetal wastage at doses of 100 and 500 Units/kg.

Pregnancy Category C
EPOGEN® has been shown to have adverse effects in rats when given in doses 5 times the human dose. There are no adequate and well-controlled studies in pregnant women. EPOGEN® should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

In studies in female rats, there were decreases in body weight gain, delays in appearance of abdominal hair, delayed eyelid opening, delayed ossification, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 Units/kg group. In female rats treated IV, there was a trend for slightly increased fetal wastage at doses of 100 and 500 Units/kg. EPOGEN® has not shown any adverse effect at doses as high as 500 Units/kg in pregnant rabbits (from day 6 to 18 of gestation).

Nursing Mothers

Postnatal observations of the live offspring (F1 generation) of female rats treated with EPOGEN® during gestation and lactation revealed no effect of EPOGEN® at doses of up to 500 Units/kg. There were, however, decreases in body weight gain, delays in appearance of abdominal hair, eyelid opening, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 Units/kg group. There were no EPOGEN®-related effects on the F2 generation fetuses.

It is not known whether EPOGEN® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when EPOGEN® is administered to a nursing woman.

Pediatric Use

See WARNINGS: Pediatrics.

Pediatric Patients on Dialysis: EPOGEN® is indicated in infants (1 month to 2 years), children (2 years to 12 years), and adolescents (12 years to 16 years) for the treatment of anemia associated with CRF requiring dialysis. Safety and effectiveness in pediatric patients less than 1 month old have not been established (see CLINICAL EXPERIENCE: CHRONIC RENAL FAILURE, PEDIATRIC PATIENTS ON DIALYSIS). The safety data from these studies show that there is no increased risk to pediatric CRF patients on dialysis when compared to the safety profile of EPOGEN® in adult CRF patients (see ADVERSE REACTIONS and WARNINGS). Published literature[30-33] provides supportive evidence of the safety and effectiveness of EPOGEN® in pediatric CRF patients on dialysis.

Pediatric Patients Not Requiring Dialysis: Published literature[33,34] has reported the use of EPOGEN® in 133 pediatric patients with anemia associated with CRF not requiring dialysis, ages 3 months to 20 years, treated with 50 to 250 Units/kg SC or IV, QW to TIW. Dose-dependent increases in hemoglobin and hematocrit were observed with reductions in transfusion requirements.

Pediatric HIV-infected Patients: Published literature [35,36] has reported the use of EPOGEN® in 20 zidovudine-treated anemic HIV-infected pediatric patients ages 8 months to 17 years, treated with 50 to 400 Units/kg SC or IV, 2 to 3 times per week. Increases in hemoglobin levels and in reticulocyte counts, and decreases in or elimination of blood transfusions were observed.

Pediatric Cancer Patients on Chemotherapy: The safety and effectiveness of EPOGEN® were evaluated in a randomized, double-blind, placebo-controlled, multicenter study (see CLINICAL EXPERIENCE, Weekly (QW) Dosing, Pediatric Patients).

Geriatric Use

Among 1051 patients enrolled in the 5 clinical trials of EPOGEN® for reduction of allogeneic blood transfusions in patients undergoing elective surgery 745 received EPOGEN® and 306 received placebo. Of the 745 patients who received EPOGEN®, 432 (58%) were aged 65 and over, while 175 (23%) were 75 and over. No overall differences in safety or effectiveness were observed between geriatric and younger patients. The dose requirements for EPOGEN® in geriatric and younger patients within the 4 trials using the TIW schedule were similar. Insufficient numbers of patients were enrolled in the study using the weekly dosing regimen to determine whether the dosing requirements differ for this schedule.

Of the 882 patients enrolled in the 3 studies of chronic renal failure patients on dialysis, 757 received EPOGEN® and 125 received placebo. Of the 757 patients who received EPOGEN®, 361 (47%) were aged 65 and over, while 100 (13%) were 75 and over. No differences in safety or effectiveness were observed between geriatric and younger patients. Dose selection and adjustment for an elderly patient should be individualized to achieve and maintain the target hematocrit (See DOSAGE AND ADMINISTRATION).

Insufficient numbers of patients age 65 or older were enrolled in clinical studies of EPOGEN® for the treatment of anemia associated with pre-dialysis chronic renal failure, cancer chemotherapy, and Zidovudine-treatment of HIV infection to determine whether they respond differently from younger subjects.

Information for Patients

Patients should be informed of the increased risks of mortality, serious cardiovascular events, thromboembolic events, and tumor progression when used in off-label dose regimens or populations (see WARNINGS). In those situations in which the physician determines that a patient or their caregiver can safely and effectively administer EPOGEN® at home, instruction as to the proper dosage and administration should be provided. Patients should be referred to the full "Information for Patients" insert and that it is not a disclosure of all possible effects. Patients should be informed of the possible side effects of EPOGEN® and of the signs and symptoms of allergic drug reaction and advised of appropriate actions. If home use is prescribed for a patient, the patient should be thoroughly instructed in the importance of proper disposal and cautioned against the reuse of needles, syringes, or drug product. A puncture-resistant container should be available for the disposal of used syringes and needles, and guidance provided on disposal of the full container.

Chronic Renal Failure Patients

Patients with CRF Not Requiring Dialysis

Blood pressure and hemoglobin should be monitored no less frequently than for patients maintained on dialysis. Renal function and fluid and electrolyte balance should be closely monitored.

Hematology

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of EPOGEN® before adjusting the dose. Because of the time required for erythropoiesis and the red cell half-life, an interval of 2 to 6 weeks may occur between the time of a dose adjustment (initiation, increase, decrease, or discontinuation) and a significant change in hemoglobin.

In order to avoid reaching the suggested target hemoglobin too rapidly, or exceeding the suggested target (hemoglobin level of 12 g/dL), the guidelines for dose and frequency of dose adjustments (see DOSAGE AND ADMINISTRATION) should be followed.

For patients who respond to EPOGEN® with a rapid increase in hemoglobin (eg, more than 1 g/dL in any 2-week period), the dose of EPOGEN® should be reduced because of the possible association of excessive rate of rise of hemoglobin with an exacerbation of hypertension.

The elevated bleeding time characteristic of CRF decreases toward normal after correction of anemia in adult patients treated with EPOGEN®. Reduction of bleeding time also occurs after correction of anemia by transfusion.

Laboratory Monitoring

The hemoglobin should be determined twice a week until it has stabilized in the suggested target range and the maintenance dose has been established. After any dose adjustment, the hemoglobin should also be determined twice weekly for at least 2 to 6 weeks until it has been determined that the hemoglobin has stabilized in response to the dose change. The hemoglobin should then be monitored at regular intervals.

A complete blood count with differential and platelet count should be performed regularly. During clinical trials, modest increases were seen in platelets and white blood cell counts. While these

changes were statistically significant, they were not clinically significant and the values remained within normal ranges.

In patients with CRF, serum chemistry values (including blood urea nitrogen [BUN], uric acid, creatinine, phosphorus, and potassium) should be monitored regularly. During clinical trials in adult patients on dialysis, modest increases were seen in BUN, creatinine, phosphorus, and potassium. In some adult patients with CRF not on dialysis treated with EPOGEN®, modest increases in serum uric acid and phosphorus were observed. While changes were statistically significant, the values remained within the ranges normally seen in patients with CRF.

Diet
The importance of compliance with dietary and dialysis prescriptions should be reinforced. In particular, hyperkalemia is not uncommon in patients with CRF. In US studies in patients on dialysis, hyperkalemia has occurred at an annualized rate of approximately 0.11 episodes per patient-year of EPOGEN® therapy, often in association with poor compliance to medication, diet, and/or dialysis.

Dialysis Management
Therapy with EPOGEN® results in an increase in hematocrit and a decrease in plasma volume which could affect dialysis efficiency. In studies to date, the resulting increase in hematocrit did not appear to adversely affect dialyzer function[9,10] or the efficiency of high flux hemodialysis.[11] During hemodialysis, patients treated with EPOGEN® may require increased anticoagulation with heparin to prevent clotting of the artificial kidney.

Patients who are marginally dialyzed may require adjustments in their dialysis prescription. As with all patients on dialysis, the serum chemistry values (including BUN, creatinine, phosphorus, and potassium) in patients treated with EPOGEN® should be monitored regularly to assure the adequacy of the dialysis prescription.

Renal Function
In adult patients with CRF not on dialysis, renal function and fluid and electrolyte balance should be closely monitored. In patients with CRF not on dialysis, placebo-controlled studies of progression of renal dysfunction over periods of greater than 1 year have not been completed. In shorter term trials in adult patients with CRF not on dialysis, changes in creatinine and creatinine clearance were not significantly different in patients treated with EPOGEN® compared with placebo-treated patients. Analysis of the slope of 1/serum creatinine versus time plots in these patients indicates no significant change in the slope after the initiation of EPOGEN® therapy.

Zidovudine-treated HIV-infected Patients
Hypertension
Exacerbation of hypertension has not been observed in zidovudine-treated HIV-infected patients treated with EPOGEN®. However, EPOGEN® should be withheld in these patients if pre-existing hypertension is uncontrolled, and should not be started until blood pressure is controlled. In double-blind studies, a single seizure has been experienced by a patient treated with EPOGEN®.[25]

Cancer Patients on Chemotherapy
Hypertension
Hypertension, associated with a significant increase in hemoglobin, has been noted rarely in patients treated with EPOGEN®. Nevertheless, blood pressure in patients treated with EPOGEN® should be monitored carefully, particularly in patients with an underlying history of hypertension or cardiovascular disease.

Seizures
In double-blind, placebo-controlled trials, 3.2% (n = 2/63) of patients treated with EPOGEN® TIW and 2.9% (n = 2/68) of placebo-treated patients had seizures. Seizures in 1.6% (n = 1/63) of patients treated with EPOGEN® TIW occurred in the context of a significant increase in blood pressure and hematocrit from baseline values. However, both patients treated with EPOGEN® also had underlying CNS pathology which may have been related to seizure activity.

In a placebo-controlled, double-blind trial utilizing weekly dosing with EPOGEN®, 1.2% (n = 2/168) of safety-evaluable patients treated with EPOGEN® and 1% (n = 1/165) of placebo-treated patients had seizures. Seizures in the patients treated with weekly EPOGEN® occurred in the context of a significant increase in hemoglobin from baseline values however significant increases in blood pressure were not seen. These patients may have had other CNS pathology.

Thrombotic Events
In double-blind, placebo-controlled trials, 3.2% (n = 2/63) of patients treated with EPOGEN® TIW and 11.8% (n = 8/68) of placebo-treated patients had thrombotic events (eg, pulmonary embolism, cerebrovascular accident), (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events).

In a placebo-controlled, double-blind trial utilizing weekly dosing with EPOGEN®, 6.0% (n = 10/168) of safety-evaluable patients treated with EPOGEN® and 3.6% (n = 6/165) (p = 0.444) of placebo-treated patients had clinically significant thrombotic events (deep vein thrombosis requiring anticoagulant therapy, embolic event including pulmonary embolism, myocardial infarction, cerebral ischemia, left ventricular failure and thrombotic microangiopathy). A definitive relationship between the rate of hemoglobin increase and the occurrence of clinically significant thrombotic events could not be evaluated due to the limited schedule of hemoglobin measurements in this study.

The safety and efficacy of EPOGEN® were evaluated in a randomized, double-blind, placebo-controlled, multicenter study that enrolled 222 anemic patients ages 5 to 18 receiving treatment for a variety of childhood malignancies. Due to the study design (small sample size and the heterogeneity of the underlying malignancies and of anti-neoplastic treatments employed), a determination of the effect of EPOGEN® on the incidence of thrombotic events could not be performed. In the EPOGEN® arm, the overall incidence of thrombotic events was 10.8% and the incidence of serious or life-threatening events was 7.2%.

Surgery Patients
Hypertension
Blood pressure may rise in the perioperative period in patients being treated with EPOGEN®. Therefore, blood pressure should be monitored carefully.

ADVERSE REACTIONS

Immunogenicity
As with all therapeutic proteins, there is the potential for immunogenicity. Neutralizing antibodies to erythropoietin, in association with PRCA or severe anemia (with or without other cytopenias), have been reported in patients receiving EPOGEN® (see WARNINGS: Pure Red Cell Aplasia) during post-marketing experience.

There has been no systematic assessment of immune responses, i.e., the incidence of either binding or neutralizing antibodies to EPOGEN®, in controlled clinical trials.

Where reported, the incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies across products within this class (erythropoietic proteins) may be misleading.

Chronic Renal Failure Patients
In double-blind, placebo-controlled studies involving over 300 patients with CRF, the events reported in greater than 5% of patients treated with EPOGEN® during the blinded phase were:

Percent of Patients Reporting Event

Event	Patients Treated With EPOGEN® (n = 200)	Placebo-treated Patients (n = 135)
Hypertension	24%	19%
Headache	16%	12%
Arthralgias	11%	6%
Nausea	11%	9%
Edema	9%	10%
Fatigue	9%	14%
Diarrhea	9%	6%
Vomiting	8%	5%
Chest Pain	7%	9%
Skin Reaction (Administration Site)	7%	12%
Asthenia	7%	12%
Dizziness	7%	13%
Clotted Access	7%	2%

Significant adverse events of concern in patients with CRF treated in double-blind, placebo-controlled trials occurred in the following percent of patients during the blinded phase of the studies:

Seizure	1.1%	1.1%
CVA/TIA	0.4%	0.6%
MI	0.4%	1.1%
Death	0%	1.7%

In the US EPOGEN® studies in adult patients on dialysis (over 567 patients), the incidence (number of events per patient-year) of the most frequently reported adverse events were: hypertension (0.75), headache (0.40), tachycardia (0.31), nausea/vomiting (0.26), clotted vascular access (0.25), shortness of breath (0.14), hyperkalemia (0.11), and diarrhea (0.11). Other reported events occurred at a rate of less than 0.10 events per patient per year.

Events reported to have occurred within several hours of administration of EPOGEN® were rare, mild, and transient, and included injection site stinging in dialysis patients and flu-like symptoms such as arthralgias and myalgias.

In all studies analyzed to date, EPOGEN® administration was generally well-tolerated, irrespective of the route of administration.

Pediatric CRF Patients: In pediatric patients with CRF on dialysis, the pattern of most adverse events was similar to that found in adults. Additional adverse events reported during the double-blind phase in >10% of pediatric patients in either treatment group were: abdominal pain, dialysis access complications including access infections and peritonitis in those receiving peritoneal dialysis, fever, upper respiratory infection, cough, pharyngitis, and constipation. The rates are similar between the treatment groups for each event.

Hypertension: Increases in blood pressure have been reported in clinical trials, often during the first 90 days of therapy. On occasion, hypertensive encephalopathy and seizures have been observed in patients with CRF treated with EPOGEN®. When data from all patients in the US phase 3 multicenter trial were analyzed, there was an apparent trend of more reports of hypertensive adverse events in patients on dialysis with a faster rate of rise of hematocrit (greater than 4 hematocrit points in any 2-week period). However, in a double-blind, placebo-controlled trial, hypertensive adverse events were not reported at an increased rate in the group treated with EPOGEN® (150 Units/kg TIW) relative to the placebo group.

Seizures: There have been 47 seizures in 1010 patients on dialysis treated with EPOGEN® in clinical trials, with an exposure of 986 patient-years for a rate of approximately 0.048 events per patient-year. However, there appeared to be a higher rate of seizures during the first 90 days of therapy (occurring in approximately 2.5% of patients) when compared to subsequent 90-day periods. The baseline incidence of seizures in the untreated dialysis population is difficult to determine; it appears to be in the range of 5% to 10% per patient-year.[37-39]

Thrombotic Events: In clinical trials where the maintenance hematocrit was 35 ± 3% on EPOGEN®, clotting of the vascular access (A-V shunt) has occurred at an annualized rate of about 0.25 events per patient-year, and other thrombotic events (eg, myocardial infarction, cerebral vascular accident, transient ischemic attack, and pulmonary embolism) occurred at a rate of 0.04 events per patient-year. In a separate study of 1111 untreated dialysis patients, clotting of the vascular access occurred at a rate of 0.50 events per patient-year. However, in CRF patients on hemodialysis who also had clinically evident ischemic heart disease or congestive heart failure, the risk of A-V shunt thrombosis was higher (39% vs 29%, $p < 0.001$), and myocardial infarctions, vascular ischemic events, and venous thrombosis were increased, in patients targeted to a hematocrit of 42 ± 3% compared to those maintained at 30 ± 3% (see WARNINGS).

In patients treated with commercial EPOGEN®, there have been rare reports of serious or unusual thromboembolic events including migratory thrombophlebitis, microvascular thrombosis, pulmonary embolus, and thrombosis of the retinal artery, and temporal and renal veins. A causal relationship has not been established.

Allergic Reactions: There have been no reports of serious allergic reactions or anaphylaxis associated with EPOGEN® administration during clinical trials. Skin rashes and urticaria have been observed rarely and when reported have generally been mild and transient in nature.

There have been rare reports of potentially serious allergic reactions including urticaria with associated respiratory symptoms or circumoral edema, or urticaria alone. Most reactions occurred in situations where a causal relationship could not be established. Symptoms recurred with rechallenge in a few instances, suggesting that allergic reactivity may occasionally be associated with EPOGEN® therapy. If an anaphylactoid reaction occurs, EPOGEN® should be immediately discontinued and appropriate therapy initiated.

Zidovudine-treated HIV-infected Patients

In double-blind, placebo-controlled studies of 3 months duration involving approximately 300 zidovudine-treated HIV-infected patients, adverse events with an incidence of ≥ 10% in either patients treated with EPOGEN® or placebo-treated patients were:

Percent of Patients Reporting Event

Event	Patients Treated With EPOGEN® (n = 144)	Placebo-treated Patients (n = 153)
Pyrexia	38%	29%
Fatigue	25%	31%
Headache	19%	14%
Cough	18%	14%
Diarrhea	16%	18%
Rash	16%	8%
Congestion, Respiratory	15%	10%
Nausea	15%	12%
Shortness of Breath	14%	13%
Asthenia	11%	14%
Skin Reaction, Medication Site	10%	7%
Dizziness	9%	10%

In the 297 patients studied, EPOGEN® was not associated with significant increases in opportunistic infections or mortality.[25] In 71 patients from this group treated with EPOGEN® at 150 Units/kg TIW, serum p24 antigen levels did not appear to increase.[27] Preliminary data showed no enhancement of HIV replication in infected cell lines in vitro.[25]

Peripheral white blood cell and platelet counts are unchanged following EPOGEN® therapy.

Allergic Reactions: Two zidovudine-treated HIV-infected patients had urticarial reactions within 48 hours of their first exposure to study medication. One patient was treated with EPOGEN® and one was

treated with placebo (EPOGEN® vehicle alone). Both patients had positive immediate skin tests against their study medication with a negative saline control. The basis for this apparent pre-existing hypersensitivity to components of the EPOGEN® formulation is unknown, but may be related to HIV-induced immunosuppression or prior exposure to blood products.

Seizures: In double-blind and open-label trials of EPOGEN® in zidovudine-treated HIV-infected patients, 10 patients have experienced seizures.[25] In general, these seizures appear to be related to underlying pathology such as meningitis or cerebral neoplasms, not EPOGEN® therapy.

Cancer Patients on Chemotherapy

In double-blind, placebo-controlled studies of up to 3 months duration involving 131 cancer patients, adverse events with an incidence > 10% in either patients treated with EPOGEN® or placebo-treated patients were as indicated below:

Percent of Patients Reporting Event

Event	Patients Treated With EPOGEN® (n = 63)	Placebo-treated Patients (n = 68)
Pyrexia	29%	19%
Diarrhea	21%*	7%
Nausea	17%*	32%
Vomiting	17%	15%
Edema	17%*	1%
Asthenia	13%	16%
Fatigue	13%	15%
Shortness of Breath	13%	9%
Parasthesia	11%	6%
Upper Respiratory Infection	11%	4%
Dizziness	5%	12%
Trunk Pain	3%*	16%

* Statistically significant

Although some statistically significant differences between patients being treated with EPOGEN® and placebo-treated patients were noted, the overall safety profile of EPOGEN® appeared to be consistent with the disease process of advanced cancer. During double-blind and subsequent open-label therapy in which patients (n = 72 for total exposure to EPOGEN®) were treated for up to 32 weeks with doses as high as 927 Units/kg, the adverse experience profile of EPOGEN® was consistent with the progression of advanced cancer.

Three hundred thirty-three (333) cancer patients enrolled in a placebo-controlled double-blind trial utilizing Weekly dosing with EPOGEN® for up to 4 months were evaluable for adverse events. The incidence of adverse events was similar in both the treatment and placebo arms.

Surgery Patients

Adverse events with an incidence of ≥ 10% are shown in the following table:

	Percent of Patients Reporting Event				
Event	**Patients Treated With EPOGEN® 300 U/kg (n = 112)[a]**	**Patients Treated With EPOGEN® 100 U/kg (n = 101) [a]**	**Placebo-treated Patients (n = 103)[a]**	**Patients Treated With EPOGEN® 600 U/kg (n = 73)[b]**	**Patients Treated With EPOGEN® 300 U/kg (n = 72)[b]**
Pyrexia	51%	50%	60%	47%	42%
Nausea	48%	43%	45%	45%	58%
Constipation	43%	42%	43%	51%	53%
Skin Reaction, Medication Site	25%	19%	22%	26%	29%
Vomiting	22%	12%	14%	21%	29%
Skin Pain	18%	18%	17%	5%	4%
Pruritus	16%	16%	14%	14%	22%
Insomnia	13%	16%	13%	21%	18%
Headache	13%	11%	9%	10%	19%
Dizziness	12%	9%	12%	11%	21%
Urinary Tract Infection	12%	3%	11%	11%	8%
Hypertension	10%	11%	10%	5%	10%
Diarrhea	10%	7%	12%	10%	6%
Deep Venous Thrombosis	10%	3%	5%	0%[c]	0%[c]
Dyspepsia	9%	11%	6%	7%	8%
Anxiety	7%	2%	11%	11%	4%
Edema	6%	11%	8%	11%	7%

[a] Study including patients undergoing orthopedic surgery treated with EPOGEN® or placebo for 15 days

[b] Study including patients undergoing orthopedic surgery treated with EPOGEN® 600 Units/kg weekly x 4 or 300 Units/kg daily x 15

[c] Determined by clinical symptoms

Thrombotic/Vascular Events: In three double-blind, placebo-controlled orthopedic surgery studies, the rate of deep venous thrombosis (DVT) was similar among Epoetin alfa and placebo-treated patients in the recommended population of patients with a pretreatment hemoglobin of > 10 g/dL to ≤ 13 g/dL.[18,20,28] However, in 2 of 3 orthopedic surgery studies the overall rate (all pretreatment hemoglobin

groups combined) of DVTs detected by postoperative ultrasonography and/or surveillance venography was higher in the group treated with Epoetin alfa than in the placebo-treated group (11% vs. 6%). This finding was attributable to the difference in DVT rates observed in the subgroup of patients with pretreatment hemoglobin > 13 g/dL.

In the orthopedic surgery study of patients with pretreatment hemoglobin of > 10 g/dL to ≤ 13 g/dL which compared two dosing regimens (600 Units/kg weekly x 4 and 300 Units/kg daily x 15), 4 subjects in the 600 Units/kg weekly EPOGEN® group (5%) and no subjects in the 300 Units/kg daily group had a thrombotic vascular event during the study period.[19]

In a study examining the use of Epoetin alfa in 182 patients scheduled for coronary artery bypass graft surgery, 23% of patients treated with Epoetin alfa and 29% treated with placebo experienced thrombotic/vascular events. There were 4 deaths among the Epoetin alfa-treated patients that were associated with a thrombotic/vascular event (see WARNINGS).

OVERDOSAGE

The expected manifestations of EPOGEN® overdosage include signs and symptoms associated with an excessive and/or rapid increase in hemoglobin concentration, including any of the cardiovascular events described in WARNINGS and listed in ADVERSE REACTIONS. Patients receiving an overdosage of EPOGEN® should be monitored closely for cardiovascular events and hematologic abnormalities. Polycythemia should be managed acutely with phlebotomy, as clinically indicated. Following resolution of the effects due to EPOGEN® overdosage, reintroduction of EPOGEN® therapy should be accompanied by close monitoring for evidence of rapid increases in hemoglobin concentration (>1 gm/dL per 14 days). In patients with an excessive hematopoietic response, reduce the EPOGEN® dose in accordance with the recommendations described in DOSAGE AND ADMINISTRATION.

DOSAGE AND ADMINISTRATION

IMPORTANT: Use the lowest dose of EPOGEN® that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for RBC transfusion (see BOXED WARNINGS and WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events). EPOGEN® dosing regimens are different for each of the indications described in this section of the package insert. EPOGEN® should be administered under the supervision of a healthcare professional. The dosages recommended below are based upon those used in clinical studies supporting marketing approval.

Chronic Renal Failure Patients

The recommended range for the starting dose of EPOGEN® is 50 to 100 Units/kg TIW for adult patients. The recommended starting dose for pediatric CRF patients on dialysis is 50 Units/kg TIW. The dose of EPOGEN® should be reduced as the hemoglobin approaches 12 g/dL or increases by more than 1 g/dL in any 2-week period. The dose should be adjusted for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for red blood cell transfusion and not to exceed 12 g/dL.

EPOGEN® may be given either as an IV or SC injection. ***In patients on hemodialysis, the IV route is recommended*** (see WARNINGS: Pure Red Cell Aplasia) and EPOGEN® usually has been administered as an IV bolus TIW. While the administration of EPOGEN® is independent of the dialysis

procedure, EPOGEN® may be administered into the venous line at the end of the dialysis procedure to obviate the need for additional venous access. In adult patients with CRF not on dialysis, EPOGEN® may be given either as an IV or SC injection.

Patients who have been judged competent by their physicians to self-administer EPOGEN® without medical or other supervision may give themselves either an IV or SC injection. The table below provides general therapeutic guidelines for patients with CRF:

Starting Dose:	
Adults	50 to 100 Units/kg TIW; IV or SC
Pediatric Patients	50 Units/kg TIW; IV or SC
Reduce Dose When:	1. Hgb approaches 12 g/dL or, 2. Hgb increases > 1 g/dL in any 2-week period
Increase Dose If:	Hgb does not increase by 2 g/dL after 8 weeks of therapy, and Hgb remains at a level not sufficient to avoid the need for RBC transfusion
Maintenance Dose:	Individually titrate to achieve and maintain the lowest Hgb level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL

During therapy, hematological parameters should be monitored regularly (see LABORATORY MONITORING). Doses must be individualized to ensure that Hgb is maintained at an appropriate level for each patient.

Pretherapy Iron Evaluation: Prior to and during EPOGEN® therapy, the patient's iron stores, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, should be evaluated. Transferrin saturation should be at least 20%, and ferritin should be at least 100 ng/mL. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels that will adequately support erythropoiesis stimulated by EPOGEN®.

Dose Adjustment: The dose should be adjusted for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL.

Increases in dose should not be made more frequently than once a month. If the hemoglobin is increasing and approaching 12 g/dL, the dose should be reduced by approximately 25%. If the hemoglobin continues to increase, dose should be temporarily withheld until the hemoglobin begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose. If the hemoglobin increases by more than 1 g/dL in a 2-week period, the dose should be decreased by approximately 25%.

If the increase in the hemoglobin is less than 1 g/dL over 4 weeks and iron stores are adequate (see PRECAUTIONS: Laboratory Monitoring), the dose of EPOGEN® may be increased by approximately 25% of the previous dose. Further increases may be made at 4-week intervals until the specified hemoglobin is obtained.

Maintenance Dose: The maintenance dose must be individualized for each patient on dialysis. In the US phase 3 multicenter trial in patients on hemodialysis, the median maintenance dose was 75

Units/kg TIW, with a range from 12.5 to 525 Units/kg TIW. Almost 10% of the patients required a dose of 25 Units/kg, or less, and approximately 10% of the patients required more than 200 Units/kg TIW to maintain their hematocrit in the suggested target range. In pediatric hemodialysis and peritoneal dialysis patients, the median maintenance dose was 167 Units/kg/week (49 to 447 Units/kg per week) and 76 Units/kg per week (24 to 323 Units/kg/week) administered in divided doses (TIW or BIW), respectively to achieve the target range of 30% to 36%.

If the transferrin saturation is greater than 20%, the dose of EPOGEN® may be increased. Such dose increases should not be made more frequently than once a month, unless clinically indicated, as the response time of the hemoglobin to a dose increase can be 2 to 6 weeks. Hemoglobin should be measured twice weekly for 2 to 6 weeks following dose increases. In adult patients with CRF not on dialysis, the maintenance dose must also be individualized. EPOGEN® doses of 75 to 150 Units/kg/week have been shown to maintain hematocrits of 36% to 38% for up to 6 months.

Lack or Loss of Response: If a patient fails to respond or maintain a response, an evaluation for causative factors should be undertaken (see WARNINGS: Pure Red Cell Aplasia, PRECAUTIONS: Lack or Loss of Response, and PRECAUTIONS: Iron Evaluation). If the transferrin saturation is less than 20%, supplemental iron should be administered.

Zidovudine-treated HIV-infected Patients

Prior to beginning EPOGEN®, it is recommended that the endogenous serum erythropoietin level be determined (prior to transfusion). Available evidence suggests that patients receiving zidovudine with endogenous serum erythropoietin levels > 500 mUnits/mL are unlikely to respond to therapy with EPOGEN®.

In zidovudine-treated HIV-infected patients the dosage of EPOGEN® should be titrated for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for blood transfusion and not to exceed 12 g/dL.

Starting Dose: For adult patients with serum erythropoietin levels ≤ 500 mUnits/mL who are receiving a dose of zidovudine ≤ 4200 mg/week, the recommended starting dose of EPOGEN® is 100 Units/kg as an IV or SC injection TIW for 8 weeks. For pediatric patients, see PRECAUTIONS: PEDIATRIC USE.

Increase Dose: During the dose adjustment phase of therapy, the hemoglobin should be monitored weekly. If the response is not satisfactory in terms of reducing transfusion requirements or increasing hemoglobin after 8 weeks of therapy, the dose of EPOGEN® can be increased by 50 to 100 Units/kg TIW. Response should be evaluated every 4 to 8 weeks thereafter and the dose adjusted accordingly by 50 to 100 Units/kg increments TIW. If patients have not responded satisfactorily to an EPOGEN® dose of 300 Units/kg TIW, it is unlikely that they will respond to higher doses of EPOGEN®.

Maintenance Dose: After attainment of the desired response (ie, reduced transfusion requirements or increased hemoglobin), the dose of EPOGEN® should be titrated to maintain the response based on factors such as variations in zidovudine dose and the presence of intercurrent infectious or inflammatory episodes. If the hemoglobin exceeds 12 g/dL, the dose should be discontinued until the hemoglobin drops below 11 g/dL. The dose should be reduced by 25% when treatment is resumed and then titrated to maintain the desired hemoglobin.

Cancer Patients on Chemotherapy

Although no specific serum erythropoietin level has been established which predicts which patients would be unlikely to respond to EPOGEN® therapy, treatment of patients with grossly elevated serum erythropoietin levels (eg, > 200 mUnits/mL) is not recommended. The hemoglobin should be

monitored on a weekly basis in patients receiving EPOGEN® therapy until hemoglobin becomes stable. The dose of EPOGEN® should be titrated for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for blood transfusion and not to exceed 12 g/dL (See recommended Dose Modifications, below).

Recommended Dose: The initial recommended dose of EPOGEN® in adults is 150 Units/kg SC TIW or 40,000 Units SC Weekly. For pediatric patients, weekly dosing is recommended.

Dose Modification

TIW Dosing

Starting Dose:	
Adults	150 Units/kg SC TIW
Reduce Dose by 25% when:	1. Hgb approaches 12 g/dL or, 2. Hgb increases > 1 g/dL in any 2-week period
Withhold Dose if:	Hgb exceeds 12 g/dL, until the hemoglobin falls below 11 g/dL and restart dose at 25% below the previous dose
Increase Dose to 300 Units/kg TIW if:	response is not satisfactory (no reduction in transfusion requirements or rise in hemoglobin) after 8 weeks to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL

Weekly Dosing

Starting Dose:	
Adults	40,000 Units SC
Pediatrics	600 Units/kg IV (maximum 40,000 Units)
Reduce Dose by 25% when:	Hgb approaches 12 g/dL or increases > 1 g/dL in any 2-weeks
Withhold Dose if:	Hgb exceeds 12 g/dL, until the hemoglobin falls below 11 g/dL, and restart dose at 25% below the previous dose
Increase Dose if: For Adults: 60,000 Units SC Weekly For Pediatrics: 900 Units/kg IV (maximum 60,000 Units) if:	response is not satisfactory (no increase in hemoglobin by $\geq$ 1 g/dL after 4 weeks of therapy, in the absence of a RBC transfusion) to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL

Surgery Patients

Prior to initiating treatment with EPOGEN® a hemoglobin should be obtained to establish that it is > 10 to $\leq$ 13 g/dL.[18] The recommended dose of EPOGEN® is 300 Units/kg/day subcutaneously for 10 days before surgery, on the day of surgery, and for 4 days after surgery.

An alternate dose schedule is 600 Units/kg EPOGEN® subcutaneously in once weekly doses (21, 14, and 7 days before surgery) plus a fourth dose on the day of surgery.[19]

All patients should receive adequate iron supplementation. Iron supplementation should be initiated no later than the beginning of treatment with EPOGEN® and should continue throughout the course of therapy. Antithrombotic prophylaxis should be strongly considered (see BOXED WARNINGS).

PREPARATION AND ADMINISTRATION OF EPOGEN®

1. Do not shake. It is not necessary to shake EPOGEN®. Prolonged vigorous shaking may denature any glycoprotein, rendering it biologically inactive.

2. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.

3. Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from the vial containing EPOGEN®, and wipe the septum with a disinfectant. Insert the needle into the vial, and withdraw into the syringe an appropriate volume of solution.

4. **Single-dose:** 1 mL vial contains no preservative. Use one dose per vial; do not re-enter the vial. Discard unused portions.

   Multidose: 1 mL and 2 mL vials contain preservative. Store at 2° to 8° C after initial entry and between doses. Discard 21 days after initial entry.

5. Do not dilute or administer in conjunction with other drug solutions. However, at the time of SC administration, preservative-free EPOGEN® from single-use vials may be admixed in a syringe with bacteriostatic 0.9% sodium chloride injection, USP, with benzyl alcohol 0.9% (bacteriostatic saline) at a 1:1 ratio using aseptic technique. The benzyl alcohol in the bacteriostatic saline acts as a local anesthetic which may ameliorate SC injection site discomfort. Admixing is not necessary when using the multidose vials of EPOGEN® containing benzyl alcohol.

HOW SUPPLIED

EPOGEN®, containing Epoetin alfa, is available in the following packages:

1 mL **Single-dose, Preservative-free** Solution
- 2000 Units/mL (NDC 55513-126-10)
- 3000 Units/mL (NDC 55513-267-10)
- 4000 Units/mL (NDC 55513-148-10)
- 10,000 Units/mL (NDC 55513-144-10)
- 40,000 Units/mL (NDC 55513-823-10)

Supplied in dispensing packs containing 10 single-dose vials.

2 mL **Multidose, Preserved** Solution
- 10,000 Units/mL (NDC 55513-283-10)

1 mL **Multidose, Preserved** Solution
- 20,000 Units/mL (NDC 55513-478-10)

Supplied in dispensing packs containing 10 multidose vials.

STORAGE

Store at 2° to 8° C (36 ° to 46° F). Do not freeze or shake.

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PROCRIT®
EPOETIN ALFA

Full Prescribing Information

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PROCRIT®
(Epoetin alfa)
FOR INJECTION

WARNINGS: Erythropoiesis-Stimulating Agents

Use the lowest dose of PROCRIT® that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion (see DOSAGE AND ADMINISTRATION).

PROCRIT® and other erythropoiesis-stimulating agents (ESAs) increased the risk for death and for serious cardiovascular events when administered to target a hemoglobin of greater than 12 g/dL (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events).

Cancer Patients: Use of ESAs

- **shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a hemoglobin of greater than 12 g/dL;**
- **shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to target a hemoglobin of greater than 12 g/dL;**
- **increased the risk of death when administered to target a hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for this population.**

(See WARNINGS: Increased Mortality and/or Tumor Progression)

Patients receiving ESAs pre-operatively for reduction of allogeneic red blood cell transfusions: A higher incidence of deep venous thrombosis was documented in patients receiving PROCRIT® who were not receiving prophylactic anticoagulation. Antithrombotic prophylaxis should be strongly considered when PROCRIT® is used to reduce allogeneic red blood cell transfusions (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events).

DESCRIPTION

Erythropoietin is a glycoprotein which stimulates red blood cell production. It is produced in the kidney and stimulates the division and differentiation of committed erythroid progenitors in the bone marrow. PROCRIT® (Epoetin alfa), a 165 amino acid glycoprotein manufactured by recombinant DNA technology, has the same biological effects as endogenous erythropoietin.[1] It has a molecular weight of 30,400 daltons and is produced by mammalian cells into which the human erythropoietin gene has been introduced. The product contains the identical amino acid sequence of isolated natural erythropoietin.

PROCRIT® is formulated as a sterile, colorless liquid in an isotonic sodium chloride/sodium citrate buffered solution or a sodium chloride/sodium phosphate buffered solution for intravenous (IV) or subcutaneous (SC) administration.

Single-dose, Preservative-free Vial: Each 1 mL of solution contains 2000, 3000, 4000 or 10,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 5.8 mg sodium citrate, 5.8 mg sodium chloride, and 0.06 mg citric acid in Water for Injection, USP (pH 6.9 ± 0.3). This formulation contains no preservative.

Single-dose, Preservative-free Vial: 1 mL (40,000 Units/mL). Each 1 mL of solution contains 40,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 1.2 mg sodium phosphate monobasic monohydrate, 1.8 mg sodium phosphate dibasic anhydrate, 0.7 mg sodium citrate, 5.8 mg sodium chloride, and 6.8 mcg citric acid in Water for Injection, USP (pH 6.9 ± 0.3). This formulation contains no preservative.

Multidose, Preserved Vial: 2 mL (20,000 Units, 10,000 Units/mL). Each 1 mL of solution contains 10,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 1.3 mg sodium citrate, 8.2 mg sodium chloride, 0.11 mg citric acid, and 1% benzyl alcohol as preservative in Water for Injection, USP (pH 6.1 ± 0.3).

Multidose, Preserved Vial: 1 mL (20,000 Units/mL). Each 1 mL of solution contains 20,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 1.3 mg sodium citrate, 8.2 mg sodium chloride, 0.11 mg citric acid, and 1% benzyl alcohol as preservative in Water for Injection, USP (pH 6.1 ± 0.3).

CLINICAL PHARMACOLOGY

Chronic Renal Failure Patients

Endogenous production of erythropoietin is normally regulated by the level of tissue oxygenation. Hypoxia and anemia generally increase the production of erythropoietin, which in turn stimulates erythropoiesis.[2] In normal subjects, plasma erythropoietin levels range from 0.01 to 0.03 Units/mL and increase up to 100- to 1000-fold during hypoxia or anemia.[2] In contrast, in patients with chronic renal failure (CRF), production of erythropoietin is impaired, and this erythropoietin deficiency is the primary cause of their anemia.[3,4]

Chronic renal failure is the clinical situation in which there is a progressive and usually irreversible decline in kidney function. Such patients may manifest the sequelae of renal dysfunction, including anemia, but do not necessarily require regular dialysis. Patients with end-stage renal disease (ESRD) are those patients with CRF who require regular dialysis or kidney transplantation for survival.

PROCRIT® has been shown to stimulate erythropoiesis in anemic patients with CRF, including both patients on dialysis and those who do not require regular dialysis.[4-13] The first evidence of a response to the three times weekly (TIW) administration of PROCRIT® is an increase in the reticulocyte count within 10 days, followed by increases in the red cell count, hemoglobin, and hematocrit, usually within 2 to 6 weeks.[4,5] Because of the length of time required for erythropoiesis – several days for erythroid progenitors to mature and be released into the circulation – a clinically significant increase in hematocrit is usually not observed in less than 2 weeks and may require up to 6 weeks in some patients. Once the hematocrit reaches the suggested target range (30% to 36%), that level can be sustained by PROCRIT® therapy in the absence of iron deficiency and concurrent illnesses.

The rate of hematocrit increase varies between patients and is dependent upon the dose of PROCRIT®, within a therapeutic range of approximately 50 to 300 Units/kg TIW.[4] A greater biologic response is not observed at doses exceeding 300 Units/kg TIW.[6] Other factors affecting the rate and extent of response include availability of iron stores, the baseline hematocrit, and the presence of concurrent medical problems.

Zidovudine-treated HIV-infected Patients

Responsiveness to PROCRIT® in HIV-infected patients is dependent upon the endogenous serum erythropoietin level prior to treatment. Patients with endogenous serum erythropoietin levels ≤ 500 mUnits/mL, and who are receiving a dose of zidovudine ≤ 4200 mg/week, may respond to PROCRIT® therapy. Patients with endogenous serum erythropoietin levels > 500 mUnits/mL do not appear to respond to PROCRIT® therapy. In a series of four clinical trials involving 255 patients, 60% to 80% of HIV-infected patients treated with zidovudine had endogenous serum erythropoietin levels ≤500 mUnits/mL.

Response to PROCRIT® in zidovudine-treated HIV-infected patients is manifested by reduced transfusion requirements and increased hematocrit.

Cancer Patients on Chemotherapy

A series of clinical trials enrolled 131 anemic cancer patients who received PROCRIT® TIW and who were receiving cyclic cisplatin- or non cisplatin-containing chemotherapy. Endogenous baseline serum erythropoietin levels varied among patients in these trials with approximately 75% (n = 83/110) having endogenous serum erythropoietin levels ≤ 132 mUnits/mL, and approximately 4% (n = 4/110) of patients having endogenous serum erythropoietin levels > 500 mUnits/mL. In general, patients with lower baseline serum erythropoietin levels responded more vigorously to PROCRIT® than patients with higher baseline erythropoietin levels. Although no specific serum erythropoietin level can be stipulated above which patients would be unlikely to respond to PROCRIT® therapy, treatment of patients with grossly elevated serum erythropoietin levels (eg, > 200 mUnits/mL) is not recommended.

Pharmacokinetics

In adult and pediatric patients with CRF, the elimination half-life of plasma erythropoietin after intravenously administered PROCRIT® ranges from 4 to 13 hours.[14-16] The half-life is approximately 20% longer in CRF patients than that in healthy subjects. After SC administration, peak plasma levels are achieved within 5 to 24 hours. The half-life is similar between adult patients with serum creatinine level greater than 3 and not on dialysis and those maintained on dialysis. The pharmacokinetic data indicate no apparent difference in PROCRIT® half-life among adult patients above or below 65 years of age.

The pharmacokinetic profile of PROCRIT® in children and adolescents appears to be similar to that of adults. Limited data are available in neonates.[17] A study of 7 preterm very low birth weight neonates and 10 healthy adults given IV erythropoietin suggested that distribution volume was approximately 1.5 to 2 times higher in the preterm neonates than in the healthy adults, and clearance was approximately 3 times higher in the preterm neonates than in the healthy adults.[42]

The pharmacokinetics of PROCRIT® have not been studied in HIV-infected patients.

A pharmacokinetic study comparing 150 Units/kg SC TIW to 40,000 Units SC weekly dosing regimen was conducted for 4 weeks in healthy subjects (n = 12) and for 6 weeks in anemic cancer patients (n = 32) receiving cyclic chemotherapy. There was no accumulation of serum erythropoietin after the 2 dosing regimens during the study period. The 40,000 Units weekly regimen had a higher C_{max} (3- to 7-fold), longer T_{max} (2- to 3-fold), higher $AUC_{0\text{-}168h}$ (2- to 3-fold) of erythropoietin and lower clearance (50%) than the 150 Units/kg TIW regimen. In anemic cancer patients, the average $t_{1/2}$ was similar (40 hours with range of 16 to 67 hours) after both dosing regimens. After the 150 Units/kg TIW dosing, the values of T_{max} and clearance are similar (13.3 ± 12.4 vs. 14.2 ± 6.7 hours, and 20.2 ± 15.9 vs. 23.6 ± 9.5 mL/h/kg) between Week 1 when patients were receiving chemotherapy (n = 14) and Week 3 when patients were not receiving chemotherapy (n = 4). Differences were observed after the 40,000 Units weekly dosing with longer T_{max} (38 ± 18 hours) and lower clearance (9.2 ± 4.7 mL/h/kg) during Week 1 when patients were receiving chemotherapy (n = 18) compared with those (22 ± 4.5 hours, 13.9 ± 7.6 mL/h/kg) during Week 3 when patients were not receiving chemotherapy (n = 7).

The bioequivalence between the 10,000 Units/mL citrate-buffered Epoetin alfa formulation and the 40,000 Units/mL phosphate-buffered Epoetin alfa formulation has been demonstrated after SC administration of single 750 Units/kg doses to healthy subjects.

INDICATIONS AND USAGE

Treatment of Anemia of Chronic Renal Failure Patients

PROCRIT® is indicated for the treatment of anemia associated with CRF, including patients on dialysis (ESRD) and patients not on dialysis. PROCRIT® is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients.

Non-dialysis patients with symptomatic anemia considered for therapy should have a hemoglobin less than 10 g/dL.

PROCRIT® is not intended for patients who require immediate correction of severe anemia. PROCRIT® may obviate the need for maintenance transfusions but is not a substitute for emergency transfusion.

Prior to initiation of therapy, the patient's iron stores should be evaluated. Transferrin saturation should be at least 20% and ferritin at least 100 ng/mL. Blood pressure should be adequately controlled prior to initiation of PROCRIT® therapy, and must be closely monitored and controlled during therapy.

PROCRIT® should be administered under the guidance of a qualified physician (see DOSAGE AND ADMINISTRATION).

Treatment of Anemia in Zidovudine-treated HIV-infected Patients

PROCRIT® is indicated for the treatment of anemia related to therapy with zidovudine in HIV-infected patients. PROCRIT® is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients. PROCRIT® is not indicated for the treatment of anemia in HIV-infected patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding, which should be managed appropriately.

PROCRIT®, at a dose of 100 Units/kg TIW, is effective in decreasing the transfusion requirement and increasing the red blood cell level of anemic, HIV-infected patients treated with zidovudine, when the endogenous serum erythropoietin level is ≤ 500 mUnits/mL and when patients are receiving a dose of zidovudine ≤ 4200 mg/week.

Treatment of Anemia in Cancer Patients on Chemotherapy

PROCRIT® is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. PROCRIT® is indicated to decrease the need for transfusions in patients who will be receiving concomitant chemotherapy for a minimum of 2 months. PROCRIT® is not indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding, which should be managed appropriately.

Reduction of Allogeneic Blood Transfusion in Surgery Patients

PROCRIT® is indicated for the treatment of anemic patients (hemoglobin > 10 to ≤ 13 g/dL) scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions.[18-20] PROCRIT® is indicated for patients at high risk for perioperative transfusions with significant, anticipated blood loss. PROCRIT® is not indicated for anemic patients who are willing to donate autologous blood (see BOXED WARNINGS and DOSAGE AND ADMINISTRATION).

CLINICAL EXPERIENCE: RESPONSE TO PROCRIT®

Chronic Renal Failure Patients

Response to PROCRIT® was consistent across all studies. In the presence of adequate iron stores (see IRON EVALUATION), the time to reach the target hematocrit is a function of the baseline hematocrit and the rate of hematocrit rise.

The rate of increase in hematocrit is dependent upon the dose of PROCRIT® administered and individual patient variation. In clinical trials at starting doses of 50 to 150 Units/kg TIW, adult patients responded with an average rate of hematocrit rise of:

Starting Dose (TIW IV)	HEMATOCRIT INCREASE	
	POINTS/DAY	POINTS/2 WEEKS
50 Units/kg	0.11	1.5
100 Units/kg	0.18	2.5
150 Units/kg	0.25	3.5

Over this dose range, approximately 95% of all patients responded with a clinically significant increase in hematocrit, and by the end of approximately 2 months of therapy virtually all patients were transfusion-independent. Changes in the quality of life of adult patients treated with PROCRIT® were assessed as part of a phase 3 clinical trial.[5,8] Once the target hematocrit (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 (VO_2 max), energy, and strength with a significant reduction in aching, dizziness, anxiety, shortness of breath, muscle weakness, and leg cramps.[8,21]

Adult Patients on Dialysis: Thirteen clinical studies were conducted, involving IV administration to a total of 1010 anemic patients on dialysis for 986 patient-years of PROCRIT® therapy. In the three largest of these clinical trials, the median maintenance dose necessary to maintain the hematocrit between 30% to 36% was approximately 75 Units/kg TIW. In the US multicenter phase 3 study, approximately 65% of the patients required doses of 100 Units/kg TIW, or less, to maintain their hematocrit at approximately 35%. Almost 10% of patients required a dose of 25 Units/kg, or less, and approximately 10% required a dose of more than 200 Units/kg TIW to maintain their hematocrit at this level.

A multicenter unit dose study was also conducted in 119 patients receiving peritoneal dialysis who self-administered PROCRIT® subcutaneously for approximately 109 patient-years of experience. Patients responded to PROCRIT® administered SC in a manner similar to patients receiving IV administration.[22]

Pediatric Patients on Dialysis: One hundred twenty-eight children from 2 months to 19 years of age with CRF requiring dialysis were enrolled in 4 clinical studies of PROCRIT®. The largest study was a placebo-controlled, randomized trial in 113 children with anemia (hematocrit ≤ 27%) undergoing peritoneal dialysis or hemodialysis. The initial dose of PROCRIT® was 50 Units/kg IV or SC TIW. The dose of study drug was titrated to achieve either a hematocrit of 30% to 36% or an absolute increase in hematocrit of 6 percentage points over baseline.

At the end of the initial 12 weeks, a statistically significant rise in mean hematocrit (9.4% vs 0.9%) was observed only in the PROCRIT® arm. The proportion of children achieving a hematocrit of 30%, or an increase in hematocrit of 6 percentage points over baseline, at any time during the first 12 weeks was higher in the PROCRIT® arm (96% vs 58%). Within 12 weeks of initiating PROCRIT® therapy, 92.3% of the pediatric patients were transfusion-independent as compared to 65.4% who received placebo. Among patients who received 36 weeks of PROCRIT®, hemodialysis patients required a higher median maintenance dose (167 Units/kg/week [n = 28] vs 76 Units/kg/week [n = 36]) and took longer to achieve a hematocrit of 30% to 36% (median time to response 69 days vs 32 days) than patients undergoing peritoneal dialysis.

Patients With CRF Not Requiring Dialysis

Four clinical trials were conducted in patients with CRF not on dialysis involving 181 patients treated with PROCRIT® for approximately 67 patient-years of experience. These patients responded to PROCRIT® therapy in a manner similar to that observed in patients on dialysis. Patients with CRF not on dialysis demonstrated a dose-dependent and sustained increase in hematocrit when PROCRIT® was administered by either an IV or SC route, with similar rates of rise of hematocrit when PROCRIT® was administered by either route. Moreover, PROCRIT® doses of 75 to 150 Units/kg per week have been shown to maintain hematocrits of 36% to 38% for up to 6 months.[23-24]

Zidovudine-treated HIV-infected Patients

PROCRIT® has been studied in four placebo-controlled trials enrolling 297 anemic (hematocrit < 30%) HIV-infected (AIDS) patients receiving concomitant therapy with zidovudine (all patients were treated with Epoetin alfa manufactured by Amgen Inc). In the subgroup of patients (89/125 PROCRIT® and 88/130 placebo) with prestudy endogenous serum erythropoietin levels ≤ 500 mUnits/mL, PROCRIT® reduced the mean cumulative number of units of blood transfused per patient by approximately 40% as compared to the placebo group.[24] Among those patients who required transfusions at baseline, 43% of patients treated with PROCRIT® versus 18% of placebo-treated patients were transfusion-independent during the second and third months of therapy. PROCRIT® therapy also resulted in significant increases in hematocrit in comparison to placebo. When examining the results according to the weekly dose of zidovudine received during month 3 of therapy, there was a statistically significant ($p < 0.003$) reduction in transfusion requirements in patients treated with PROCRIT® (n = 51) compared to placebo treated patients (n = 54) whose mean weekly zidovudine dose was ≤ 4200 mg/week.[25]

Approximately 17% of the patients with endogenous serum erythropoietin levels ≤ 500 mUnits/mL receiving PROCRIT® in doses from 100 to 200 Units/kg TIW achieved a hematocrit of 38% without administration of transfusions or significant reduction in zidovudine dose. In the subgroup of patients whose prestudy endogenous serum erythropoietin levels were > 500 mUnits/mL, PROCRIT® therapy did not reduce transfusion requirements or increase hematocrit, compared to the corresponding responses in placebo-treated patients.

In a 6 month open-label PROCRIT® study, patients responded with decreased transfusion requirements and sustained increases in hematocrit and hemoglobin with doses of PROCRIT® up to 300 Units/kg TIW.[25-27]

Responsiveness to PROCRIT® therapy may be blunted by intercurrent infectious/inflammatory episodes and by an increase in zidovudine dosage. Consequently, the dose of PROCRIT® must be titrated based on these factors to maintain the desired erythropoietic response.

Cancer Patients on Chemotherapy

Adult Patients

Three-Times Weekly (TIW) Dosing

PROCRIT® administered TIW has been studied in a series of six placebo-controlled, double-blind trials that enrolled 131 anemic cancer patients receiving PROCRIT® or matching placebo. Across all studies, 72 patients were treated with concomitant non cisplatin-containing chemotherapy regimens and 59 patients were treated with concomitant cisplatin-containing chemotherapy regimens. Patients were randomized to PROCRIT® 150 Units/kg or placebo subcutaneously TIW for 12 weeks in each study.

The results of the pooled data from these six studies are shown in the table below. Because of the length of time required for erythropoiesis and red cell maturation, the efficacy of PROCRIT® (reduction in

proportion of patients requiring transfusions) is not manifested until 2 to 6 weeks after initiation of PROCRIT®.

Proportion of Patients Transfused During Chemotherapy (Efficacy Population[a])

Chemotherapy Regimen	On Study[b]		During Months 2 and 3[c]	
	PROCRIT®	Placebo	PROCRIT®	Placebo
Regimens without cisplatin	44% (15/34)	44% (16/36)	21% (6/29)	33% (11/33)
Regimens containing cisplatin	50% (14/28)	63% (19/30)	23% (5/22)[d]	56% (14/25)
Combined	47% (29/62)	53% (35/66)	22% (11/51)[d]	43% (25/58)

[a] Limited to patients remaining on study at least 15 days (1 patient excluded from PROCRIT®, 2 patients excluded from placebo).

[b] Includes all transfusions from day 1 through the end of study.

[c] Limited to patients remaining on study beyond week 6 and includes only transfusions during weeks 5-12.

[d] Unadjusted 2-sided $p < 0.05$.

Intensity of chemotherapy in the above trials was not directly assessed, however the degree and timing of neutropenia was comparable across all trials. Available evidence suggests that patients with lymphoid and solid cancers respond similarly to PROCRIT® therapy, and that patients with or without tumor infiltration of the bone marrow respond similarly to PROCRIT® therapy.

Weekly (QW) Dosing

PROCRIT® was also studied in a placebo-controlled, double-blind trial utilizing weekly dosing in a total of 344 anemic cancer patients. In this trial, 61 (35 placebo arm and 26 in the PROCRIT® arm) patients were treated with concomitant cisplatin containing regimens and 283 patients received concomitant chemotherapy regimens that did not contain cisplatinum. Patients were randomized to PROCRIT® 40,000 Units weekly (n = 174) or placebo (n = 170) SC for a planned treatment period of 16 weeks. If hemoglobin had not increased by > 1 g/dL, after 4 weeks of therapy or the patient received RBC transfusion during the first 4 weeks of therapy, study drug was increased to 60,000 Units weekly. Forty-three percent of patients in the Epoetin alfa group required an increase in PROCRIT® dose to 60,000 Units weekly.[25]

Results demonstrated that PROCRIT® therapy reduced the proportion of patients transfused in day 29 through week 16 of the study as compared to placebo. Twenty-five patients (14%) in the PROCRIT® group received transfusions compared to 48 patients (28%) in the placebo group ($p = 0.0010$) between day 29 and week 16 or the last day on study.

Comparable intensity of chemotherapy for patients enrolled in the two study arms was suggested by similarities in mean dose and frequency of administration for the 10 most commonly administered chemotherapy agents, and similarity in the incidence of changes in chemotherapy during the trial in the two arms.

Pediatric Patients

The safety and effectiveness of PROCRIT® were evaluated in a randomized, double-blind, placebo-controlled, multicenter study in anemic patients ages 5 to 18 receiving chemotherapy for the treatment of various childhood malignancies. Two hundred twenty-two patients were randomized (1:1) to PROCRIT® or placebo. PROCRIT® was administered at 600 Units/kg (maximum 40,000 Units) intravenously once per week for 16 weeks. If hemoglobin had not increased by 1g/dL after the first 4-5 weeks of therapy, PROCRIT® was increased to 900 Units/kg (maximum 60,000 Units). Among the PROCRIT®-treated patients 60% required dose escalation to 900 Units/kg/week.

The effect of PROCRIT® on transfusion requirements is shown in the table below:

Percentage of Patients Transfused:			
On Study[a]		After 28 Days Post-Randomization	
PROCRIT® (n=111)	Placebo (n=111)	PROCRIT® (n=111)	Placebo (n=111)
65% (72)	77% (86)	51%(57)[b]	69% (77)

[a] Includes all transfusions from day 1 through the end of study

[b] Adjusted 2 sided $p < 0.05$

There was no evidence of an improvement in health-related quality of life, including no evidence of an effect on fatigue, energy or strength, in patients receiving PROCRIT® as compared to those receiving placebo.

Surgery Patients

PROCRIT® has been studied in a placebo-controlled, double-blind trial enrolling 316 patients scheduled for major, elective orthopedic hip or knee surgery who were expected to require ≥ 2 units of blood and who were not able or willing to participate in an autologous blood donation program. Based on previous studies which demonstrated that pretreatment hemoglobin is a predictor of risk of receiving transfusion,[20,28] patients were stratified into one of three groups based on their pretreatment hemoglobin [≤ 10 (n = 2), > 10 to ≤ 13 (n = 96), and > 13 to ≤ 15 g/dL (n = 218)] and then randomly assigned to receive 300 Units/kg PROCRIT®, 100 Units/kg PROCRIT® or placebo by SC injection for 10 days before surgery, on the day of surgery, and for 4 days after surgery.[18] All patients received oral iron and a low-dose post-operative warfarin regimen.[18]

Treatment with PROCRIT® 300 Units/kg significantly ($p = 0.024$) reduced the risk of allogeneic transfusion in patients with a pretreatment hemoglobin of >10 to ≤13; 5/31 (16%) of PROCRIT® 300 Units/kg, 6/26 (23%) of PROCRIT® 100 Units/kg, and 13/29 (45%) of placebo-treated patients were transfused.[18] There was no significant difference in the number of patients transfused between PROCRIT® (9% 300 Units/kg, 6% 100 Units/kg) and placebo (13%) in the >13 to ≤15 g/dL hemoglobin stratum. There were too few patients in the ≤10 g/dL group to determine if PROCRIT® is useful in this hemoglobin strata. In the > 10 to ≤ 13 g/dL pretreatment stratum, the mean number of units transfused per PROCRIT®-treated patient (0.45 units blood for 300 Units/kg, 0.42 units blood for 100 Units/kg) was less than the mean transfused per placebo-treated patient (1.14 units) (overall $p = 0.028$). In addition, mean hemoglobin, hematocrit, and reticulocyte counts increased significantly during the presurgery period in patients treated with PROCRIT®.[18]

PROCRIT® was also studied in an open-label, parallel-group trial enrolling 145 subjects with a pretreatment hemoglobin level of ≥10 to ≤13 g/dL who were scheduled for major orthopedic hip or knee surgery and who were not participating in an autologous program.[19] Subjects were randomly assigned to receive one of two SC dosing regimens of PROCRIT® (600 Units/kg once weekly for 3 weeks prior to surgery and on the day of surgery, or 300 Units/kg once daily for 10 days prior to surgery, on the day of surgery and for 4 days after surgery). All subjects received oral iron and appropriate pharmacologic anticoagulation therapy.

From pretreatment to presurgery, the mean increase in hemoglobin in the 600 Units/kg weekly group (1.44 g/dL) was greater than observed in the 300 Units/kg daily group.[19] The mean increase in absolute reticulocyte count was smaller in the weekly group ($0.11 \times 10^6/mm^3$) compared to the daily group ($0.17 \times 10^6/mm^3$). Mean hemoglobin levels were similar for the two treatment groups throughout the postsurgical period.

The erythropoietic response observed in both treatment groups resulted in similar transfusion rates [11/69 (16%) in the 600 Units/kg weekly group and 14/71 (20%) in the 300 Units/kg daily group].[19] The mean number of units transfused per subject was approximately 0.3 units in both treatment groups.

CONTRAINDICATIONS

PROCRIT® is contraindicated in patients with:

1. Uncontrolled hypertension.
2. Known hypersensitivity to mammalian cell-derived products.
3. Known hypersensitivity to Albumin (Human).

WARNINGS

Pediatrics

Risk in Premature Infants

The multidose preserved formulation contains benzyl alcohol. Benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications in premature infants which are sometimes fatal.

Adults

Increased Mortality, Serious Cardiovascular and Thromboembolic Events

PROCRIT® and other erythropoiesis-stimulating agents (ESAs) increased the risk for death and for serious cardiovascular events in controlled clinical trials when administered to target a hemoglobin of greater than 12 g/dL. There was an increased risk of serious arterial and venous thromboembolic events, including myocardial infarction, stroke, congestive heart failure, and hemodialysis graft occlusion. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may also contribute to these risks.

To reduce cardiovascular risks, use the lowest dose of PROCRIT® that will gradually increase the hemoglobin concentration to a level sufficient to avoid the need for RBC transfusion. The hemoglobin concentration should not exceed 12 g/dL; the rate of hemoglobin increase should not exceed 1 g/dL in any two week period (see DOSAGE AND ADMINISTRATION).

In a randomized prospective trial, 1432 anemic chronic renal failure patients who were not undergoing dialysis were assigned to Epoetin alfa (rHuEPO) treatment targeting a maintenance hemoglobin concentration of 13.5 g/dL or 11.3 g/dL. A major cardiovascular event (death, myocardial infarction, stroke or hospitalization for congestive heart failure) occurred among 125 (18%) of the 715 patients in the higher hemoglobin group compared to 97 (14%) among the 717 patients in the lower hemoglobin group (HR 1.3, 95% CI: 1.0, 1.7, $p = 0.03$).[43]

Increased risk for serious cardiovascular events was also reported from a randomized, prospective trial of 1265 hemodialysis patients with clinically evident cardiac disease (ischemic heart disease or congestive heart failure). In this trial, patients were assigned to PROCRIT® treatment targeted to a maintenance hematocrit of either 42 ± 3% or 30 ± 3%.[40] Increased mortality was observed in 634 patients randomized to a target hematocrit of 42% [221 deaths (35% mortality)] compared to 631 patients targeted to remain at a hematocrit of 30% [185 deaths (29% mortality)]. The reason for the increased mortality observed in this study is unknown, however, the incidence of non-fatal myocardial infarctions (3.1% vs. 2.3%), vascular access thromboses (39% vs. 29%), and all other thrombotic events (22% vs. 18%) were also higher in the group randomized to achieve a hematocrit of 42%.

An increased incidence of thrombotic events has also been observed in patients with cancer treated with erythropoietic agents.

In a randomized controlled study (referred to as the 'BEST' study) with another ESA in 939 women with metastatic breast cancer receiving chemotherapy, patients received either weekly Epoetin alfa or placebo for up to a year. This study was designed to show that survival was superior when an ESA was administered to prevent anemia (maintain hemoglobin levels between 12 and 14 g/dL or hematocrit between 36% and 42%). The study was terminated prematurely when interim results demonstrated that a higher mortality at 4 months (8.7% vs. 3.4%) and a higher rate of fatal thrombotic events (1.1% vs. 0.2%) in the first 4 months of the study were observed among patients treated with Epoetin alfa. Based on Kaplan-Meier estimates, at the time of study termination, the 12-month survival was lower in the Epoetin alfa group than in the placebo group (70% vs. 76%; HR 1.37, 95% CI: 1.07, 1.75; $p = 0.012$).[46]

A systematic review of 57 randomized controlled trials (including the BEST and ENHANCE studies) evaluating 9353 patients with cancer compared ESAs plus red blood cell transfusion with red blood cell transfusion alone for prophylaxis or treatment of anemia in cancer patients with or without concurrent antineoplastic therapy. An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 patients) was observed in ESA-treated patients. An overall survival hazard ratio of 1.08, (95% CI: 0.99, 1.18; 42 trials and 8167 patients) was observed in ESA-treated patients.[44]

An increased incidence of deep vein thrombosis (DVT) in patients receiving Epoetin alfa undergoing surgical orthopedic procedures has been observed (see ADVERSE REACTIONS, Surgery Patients: Thrombotic/Vascular Events). In a randomized controlled study (referred to as the 'SPINE' study), 681 adult patients, not receiving prophylactic anticoagulation and undergoing spinal surgery, received either 4 doses of 600 U/kg Epoetin alfa (7, 14, and 21 days before surgery, and the day of surgery) and standard of care (SOC) treatment, or SOC treatment alone. Preliminary analysis showed a higher incidence of DVT, determined by either Color Flow Duplex Imaging or by clinical symptoms, in the Epoetin alfa group [16 patients (4.7%)] compared to the SOC group [7 patients (2.1%)]. In addition, 12 patients in the Epoetin alfa group and 7 patients in the SOC group had other thrombotic vascular events. Antithrombotic prophylaxis should be strongly considered when ESAs are used for the reduction of allogeneic RBC transfusions in surgical patients (see BOXED WARNINGS and DOSAGE AND ADMINISTRATION).

Increased mortality was also observed in a randomized placebo-controlled study of PROCRIT® in adult patients who were undergoing coronary artery bypass surgery (7 deaths in 126 patients randomized to PROCRIT® versus no deaths among 56 patients receiving placebo). Four of these deaths occurred during the period of study drug administration and all four deaths were associated with thrombotic events.[45] ESAs are not approved for reduction of allogeneic red blood cell transfusions in patients scheduled for cardiac surgery.

Increased Mortality and/or Tumor Progression

Erythropoiesis-stimulating agents, when administered to target a hemoglobin of greater than 12 g/dL, shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy. ESAs also shortened survival in patients with metastatic breast cancer receiving chemotherapy when administered to target a hemoglobin of greater than 12 g/dL.

The ENHANCE study was a randomized controlled study in 351 head and neck cancer patients where Epoetin beta or placebo was administered to achieve target hemoglobin of 14 and 15 g/dL for women and men, respectively. Locoregional progression-free survival was significantly shorter in patients receiving Epoetin beta, HR 1.62

(95% CI: 1.22, 2.14; p = 0.0008) with a median of 406 days Epoetin beta vs. 745 days placebo.[41]

The DAHANCA 10 study, conducted in 522 patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy were randomized to darbepoetin alfa or placebo. An interim analysis in 484 patients demonstrated a 10% increase in locoregional failure rate among darbepoetin alfa-treated patients (p = 0.01). At the time of study termination, there was a trend toward worse survival in the darbepoetin alfa-treated arm (p = 0.08).

The BEST study was previously described (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events). Mortality at 4 months (8.7% vs. 3.4%) was significantly higher in the Epoetin alfa arm. The most common investigator-attributed cause of death within the first 4 months was disease progression; 28 of 41 deaths in the Epoetin alfa arm and 13 of 16 deaths in the placebo arm were attributed to disease progression. Investigator assessed time to tumor progression was not different between the two groups.[46]

In a Phase 3, double-blind, randomized (darbepoetin alfa vs. placebo), 16-week study in 989 anemic patients with active malignant disease neither receiving nor planning to receive chemotherapy or radiation therapy, there was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions. In addition, there were more deaths in the darbepoetin alfa treatment group [26% (136/515)] than the placebo group [20% (94/470)] at 16 weeks (completion of treatment phase). With a median survival follow up of 4.3 months, the absolute number of deaths was greater in the darbepoetin alfa treatment group [49% (250/515)] compared with the placebo group [46% (216/470); HR 1.29, 95% CI: 1.08, 1.55].

In a Phase 3, multicenter, randomized (Epoetin alfa vs. placebo), double-blind study, patients with advanced non-small-cell lung cancer unsuitable for curative therapy were treated with Epoetin alfa targeting hemoglobin levels between 12 and 14 g/dL. Following an interim analysis of 70 of 300 patients planned, a significant difference in median survival in favor of the patients on the placebo arm of the trial was observed (63 vs. 129 days; HR 1.84; p = 0.04).

Pure Red Cell Aplasia

Cases of pure red cell aplasia (PRCA) and of severe anemia, with or without other cytopenias, associated with neutralizing antibodies to erythropoietin, have been reported in patients treated with PROCRIT®. This has been reported predominantly in patients with CRF receiving PROCRIT® by subcutaneous administration. Any patient who develops a sudden loss of response to PROCRIT®, accompanied by severe anemia and low reticulocyte count, should be evaluated for the etiology of loss of effect, including the presence of neutralizing antibodies to erythropoietin (see PRECAUTIONS: LACK OR LOSS OF RESPONSE). If anti-erythropoietin antibody-associated anemia is suspected, withhold PROCRIT® and other erythropoietic proteins. Contact ORTHO BIOTECH (1 888 2ASK OBI or 1-888-227-5624) to perform assays for binding and neutralizing antibodies. PROCRIT® should be permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other erythropoetic proteins as antibodies may cross-react (see ADVERSE REACTIONS: IMMUNOGENICITY).

Albumin (Human)

PROCRIT® contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

Chronic Renal Failure Patients

Hypertension: Patients with uncontrolled hypertension should not be treated with PROCRIT®; blood pressure should be controlled adequately before initiation of therapy. Up to 80% of patients with CRF have a history of hypertension.[29] Although there do not appear to be any direct pressor effects of PROCRIT®, blood pressure may rise during PROCRIT® therapy. During the early phase of treatment when the hematocrit is increasing, approximately 25% of patients on dialysis may require initiation of, or increases in, antihypertensive therapy. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with PROCRIT®.

Special care should be taken to closely monitor and aggressively control blood pressure in patients treated with PROCRIT®. Patients should be advised as to the importance of compliance with antihypertensive therapy and dietary restrictions. If blood pressure is difficult to control by initiation of appropriate measures, the hemoglobin may be reduced by decreasing or withholding the dose of PROCRIT®. A clinically significant decrease in hemoglobin may not be observed for several weeks.

It is recommended that the dose of PROCRIT® be decreased if the hemoglobin increase exceeds 1 g/dL in any 2-week period, because of the possible association of excessive rate of rise of hemoglobin with an exacerbation of hypertension. In CRF patients on hemodialysis with clinically evident ischemic heart disease or congestive heart failure, the hemoglobin should be managed carefully, not to exceed 12 g/dL (see WARNINGS: Mortality, Serious Cardiovascular and Thromboembolic Events and DOSAGE AND ADMINISTRATION: Chronic Renal Failure Patients).

Seizures: Seizures have occurred in patients with CRF participating in PROCRIT® clinical trials.

In adult patients on dialysis, there was a higher incidence of seizures during the first 90 days of therapy (occurring in approximately 2.5% of patients) as compared with later timepoints.

Given the potential for an increased risk of seizures during the first 90 days of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely. Patients should be cautioned to avoid potentially hazardous activities such as driving or operating heavy machinery during this period.

While the relationship between seizures and the rate of rise of hemoglobin is uncertain, it is recommended that the dose of PROCRIT® be decreased if the hemoglobin increase exceeds 1 g/dL in any 2-week period.

Thrombotic Events: During hemodialysis, patients treated with PROCRIT® may require increased anticoagulation with heparin to prevent clotting of the artificial kidney (see ADVERSE REACTIONS for more information about thrombotic events).

Other thrombotic events (eg, myocardial infarction, cerebrovascular accident, transient ischemic attack) have occurred in clinical trials at an annualized rate of less than 0.04 events per patient year of PROCRIT® therapy. These trials were conducted in adult patients with CRF (whether on dialysis or not) in whom the target hematocrit was 32% to 40%. However, the risk of thrombotic events, including vascular access thrombosis, was significantly increased in adult patients with ischemic heart disease or congestive heart failure receiving PROCRIT® therapy with the goal of reaching a normal hematocrit (42%) as compared to a target hematocrit of 30%. Patients with pre-existing cardiovascular disease should be monitored closely.

Zidovudine-treated HIV-infected Patients

In contrast to CRF patients, PROCRIT® therapy has not been linked to exacerbation of hypertension, seizures, and thrombotic events in HIV-infected patients. However, the clinical data do not rule out an increased risk for serious cardiovascular events.

PRECAUTIONS

The parenteral administration of any biologic product should be attended by appropriate precautions in case allergic or other untoward reactions occur (see CONTRAINDICATIONS). In clinical trials, while transient rashes were occasionally observed concurrently with PROCRIT® therapy, no serious allergic or anaphylactic reactions were reported (see ADVERSE REACTIONS for more information regarding allergic reactions).

The safety and efficacy of PROCRIT® therapy have not been established in patients with a known history of a seizure disorder or underlying hematologic disease (eg, sickle cell anemia, myelodysplastic syndromes, or hypercoagulable disorders).

In some female patients, menses have resumed following PROCRIT® therapy; the possibility of pregnancy should be discussed and the need for contraception evaluated.

Hematology

Exacerbation of porphyria has been observed rarely in patients with CRF treated with PROCRIT®. However, PROCRIT® has not caused increased urinary excretion of porphyrin metabolites in normal volunteers, even in the presence of a rapid erythropoietic response. Nevertheless, PROCRIT® should be used with caution in patients with known porphyria.

In preclinical studies in dogs and rats, but not in monkeys, PROCRIT® therapy was associated with subclinical bone marrow fibrosis. Bone marrow fibrosis is a known complication of CRF in humans and may be related to secondary hyperparathyroidism or unknown factors. The incidence of bone marrow fibrosis was not increased in a study of adult patients on dialysis who were treated with PROCRIT® for 12 to 19 months, compared to the incidence of bone marrow fibrosis in a matched group of patients who had not been treated with PROCRIT®.

Hemoglobin in CRF patients should be measured twice a week; zidovudine-treated HIV-infected and cancer patients should have hemoglobin measured once a week until hemoglobin has been stabilized, and measured periodically thereafter.

Lack or Loss of Response

If the patient fails to respond or to maintain a response to doses within the recommended dosing range, the following etiologies should be considered and evaluated:

1. Iron deficiency: Virtually all patients will eventually require supplemental iron therapy (see IRON EVALUATION).
2. Underlying infectious, inflammatory, or malignant processes.
3. Occult blood loss.
4. Underlying hematologic diseases (ie, thalassemia, refractory anemia, or other myelodysplastic disorders).
5. Vitamin deficiencies: Folic acid or vitamin B12.
6. Hemolysis.
7. Aluminum intoxication.
8. Osteitis fibrosa cystica.
9. Pure Red Cell Aplasia (PRCA) or anti-erythropoietin antibody-associated anemia: In the absence of another etiology, the patient should be evaluated for evidence of PRCA and sera should be tested for the presence of antibodies to erythropoietin (see WARNINGS: PURE RED CELL APLASIA).

Iron Evaluation

During PROCRIT® therapy, absolute or functional iron deficiency may develop. Functional iron deficiency, with normal ferritin levels but low transferrin saturation, is presumably due to the inability to mobilize iron stores rapidly enough to support increased erythropoiesis. Transferrin saturation should be at least 20% and ferritin should be at least 100 ng/mL.

Prior to and during PROCRIT® therapy, the patient's iron status, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, should be evaluated. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels which will adequately support erythropoiesis stimulated by PROCRIT®. All surgery patients being treated with PROCRIT® should receive adequate iron supplementation throughout the course of therapy in order to support erythropoiesis and avoid depletion of iron stores.

Drug Interactions

No evidence of interaction of PROCRIT® with other drugs was observed in the course of clinical trials.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenic potential of PROCRIT® has not been evaluated. PROCRIT® does not induce bacterial gene mutation (Ames Test), chromosomal aberrations in mammalian cells, micronuclei in mice, or gene mutation at the HGPRT locus. In female rats treated IV with PROCRIT®, there was a trend for slightly increased fetal wastage at doses of 100 and 500 Units/kg.

Pregnancy Category C

PROCRIT® has been shown to have adverse effects in rats when given in doses 5 times the human dose. There are no adequate and well-controlled studies in pregnant women. PROCRIT® should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

In studies in female rats, there were decreases in body weight gain, delays in appearance of abdominal hair, delayed eyelid opening, delayed ossification, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 Units/kg group. In female rats treated IV, there was a trend for slightly increased fetal wastage at doses of 100 and 500 Units/kg. PROCRIT® has not shown any adverse effect at doses as high as 500 Units/kg in pregnant rabbits (from day 6 to 18 of gestation).

Nursing Mothers

Postnatal observations of the live offspring (F1 generation) of female rats treated with PROCRIT® during gestation and lactation revealed no effect of PROCRIT® at doses of up to 500 Units/kg. There were, however, decreases in body weight gain, delays in appearance of abdominal hair, eyelid opening, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 Units/kg group. There were no PROCRIT®-related effects on the F2 generation fetuses.

It is not known whether PROCRIT® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PROCRIT® is administered to a nursing woman.

Pediatric Use

See WARNINGS: Pediatrics

Pediatric Patients on Dialysis: PROCRIT® is indicated in infants (1 month to 2 years), children (2 years to 12 years), and adolescents (12 years to 16 years) for the treatment of anemia associated with CRF requiring dialysis. Safety and effectiveness in pediatric patients

less than 1 month old have not been established (see CLINICAL EXPERIENCE: CHRONIC RENAL FAILURE, PEDIATRIC PATIENTS ON DIALYSIS). The safety data from these studies show that there is no increased risk to pediatric CRF patients on dialysis when compared to the safety profile of PROCRIT® in adult CRF patients (see ADVERSE REACTIONS and WARNINGS). Published literature[30-33] provides supportive evidence of the safety and effectiveness of PROCRIT® in pediatric CRF patients on dialysis.

Pediatric Patients Not Requiring Dialysis: Published literature[33,34] has reported the use of PROCRIT® in 133 pediatric patients with anemia associated with CRF not requiring dialysis, ages 3 months to 20 years, treated with 50 to 250 Units/kg SC or IV, QW to TIW. Dose-dependent increases in hemoglobin and hematocrit were observed with reductions in transfusion requirements.

Pediatric HIV-infected Patients: Published literature[35,36] has reported the use of PROCRIT® in 20 zidovudine-treated anemic HIV-infected pediatric patients ages 8 months to 17 years, treated with 50 to 400 Units/kg SC or IV, 2 to 3 times per week. Increases in hemoglobin levels and in reticulocyte counts, and decreases in or elimination of blood transfusions were observed.

Pediatric Cancer Patients on Chemotherapy: The safety and effectiveness of PROCRIT® were evaluated in a randomized, double-blind, placebo-controlled, multicenter study (see CLINICAL EXPERIENCE, WEEKLY (QW) DOSING, PEDIATRIC PATIENTS).

Geriatric Use

Among 1051 patients enrolled in the 5 clinical trials of PROCRIT® for reduction of allogeneic blood transfusions in patients undergoing elective surgery 745 received PROCRIT® and 306 received placebo. Of the 745 patients who received PROCRIT®, 432 (58%) were aged 65 and over, while 175 (23%) were 75 and over. No overall differences in safety or effectiveness were observed between geriatric and younger patients. The dose requirements for PROCRIT® in geriatric and younger patients within the 4 trials using the TIW schedule were similar. Insufficient numbers of patients were enrolled in the study using the weekly dosing regimen to determine whether the dosing requirements differ for this schedule.

Of the 882 patients enrolled in the 3 studies of chronic renal failure patients on dialysis, 757 received PROCRIT® and 125 received placebo. Of the 757 patients who received PROCRIT®, 361 (47%) were aged 65 and over, while 100 (13%) were 75 and over. No differences in safety or effectiveness were observed between geriatric and younger patients. Dose selection and adjustment for an elderly patient should be individualized to achieve and maintain the target hematocrit (see DOSAGE AND ADMINISTRATION).

Insufficient numbers of patients age 65 or older were enrolled in clinical studies of PROCRIT® for the treatment of anemia associated with pre-dialysis chronic renal failure, cancer chemotherapy, and Zidovudine-treatment of HIV infection to determine whether they respond differently from younger subjects.

Information for Patients

Patients should be informed of the increased risks of mortality, serious cardiovascular events, thromboembolic events, and tumor progression when used in off-label dose regimens or populations (see WARNINGS). In those situations in which the physician determines that a patient or their caregiver can safely and effectively administer PROCRIT® at home, instruction as to the proper dosage and administration should be provided. Patients should be referred to the full "Information for Patients" insert and that it is not a disclosure of all possible effects.

Patients should be informed of the possible side effects of PROCRIT® and of the signs and symptoms of allergic drug reaction and advised of appropriate actions. If home use is prescribed for a patient, the patient should be thoroughly instructed in the importance of proper disposal and cautioned against the reuse of needles, syringes, or drug product. A puncture-resistant container should be available for the disposal of used syringes and needles, and guidance provided on disposal of the full container.

Chronic Renal Failure Patients

Patients with CRF Not Requiring Dialysis

Blood pressure and hemoglobin should be monitored no less frequently than for patients maintained on dialysis. Renal function and fluid and electrolyte balance should be closely monitored.

Hematology

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of PROCRIT® before adjusting the dose. Because of the time required for erythropoiesis and the red cell half-life, an interval of 2 to 6 weeks may occur between the time of a dose adjustment (initiation, increase, decrease, or discontinuation) and a significant change in hemoglobin.

In order to avoid reaching the suggested target hemoglobin too rapidly, or exceeding the suggested target (hemoglobin level of 12 g/dL), the guidelines for dose and frequency of dose adjustments (see DOSAGE AND ADMINISTRATION) should be followed.

For patients who respond to PROCRIT® with a rapid increase in hemoglobin (eg, more than 1 g/dL in any 2-week period), the dose of PROCRIT® should be reduced because of the possible association of excessive rate of rise of hemoglobin with an exacerbation of hypertension.

The elevated bleeding time characteristic of CRF decreases toward normal after correction of anemia in adult patients treated with PROCRIT®. Reduction of bleeding time also occurs after correction of anemia by transfusion.

Laboratory Monitoring

The hemoglobin should be determined twice a week until it has stabilized in the suggested target range and the maintenance dose has been established. After any dose adjustment, the hemoglobin should also be determined twice weekly for at least 2 to 6 weeks until it has been determined that the hemoglobin has stabilized in response to the dose change. The hemoglobin should then be monitored at regular intervals.

A complete blood count with differential and platelet count should be performed regularly. During clinical trials, modest increases were seen in platelets and white blood cell counts. While these changes were statistically significant, they were not clinically significant and the values remained within normal ranges.

In patients with CRF, serum chemistry values (including blood urea nitrogen [BUN], uric acid, creatinine, phosphorus, and potassium) should be monitored regularly. During clinical trials in adult patients on dialysis, modest increases were seen in BUN, creatinine, phosphorus, and potassium. In some adult patients with CRF not on dialysis treated with PROCRIT®, modest increases in serum uric acid and phosphorus were observed. While changes were statistically significant, the values remained within the ranges normally seen in patients with CRF.

Diet

The importance of compliance with dietary and dialysis prescriptions should be reinforced. In particular, hyperkalemia is not uncommon in patients with CRF. In US studies in patients on dialysis, hyperkalemia

has occurred at an annualized rate of approximately 0.11 episodes per patient-year of PROCRIT® therapy, often in association with poor compliance to medication, diet, and/or dialysis.

Dialysis Management

Therapy with PROCRIT® results in an increase in hematocrit and a decrease in plasma volume which could affect dialysis efficiency. In studies to date, the resulting increase in hematocrit did not appear to adversely affect dialyzer function[9,10] or the efficiency of high flux hemodialysis.[11] During hemodialysis, patients treated with PROCRIT® may require increased anticoagulation with heparin to prevent clotting of the artificial kidney.

Patients who are marginally dialyzed may require adjustments in their dialysis prescription. As with all patients on dialysis, the serum chemistry values (including BUN, creatinine, phosphorus, and potassium) in patients treated with PROCRIT® should be monitored regularly to assure the adequacy of the dialysis prescription.

Renal Function

In adult patients with CRF not on dialysis, renal function and fluid and electrolyte balance should be closely monitored. In patients with CRF not on dialysis, placebo-controlled studies of progression of renal dysfunction over periods of greater than 1 year have not been completed. In shorter term trials in adult patients with CRF not on dialysis, changes in creatinine and creatinine clearance were not significantly different in patients treated with PROCRIT® compared with placebo-treated patients. Analysis of the slope of 1/serum creatinine versus time plots in these patients indicates no significant change in the slope after the initiation of PROCRIT® therapy.

Zidovudine-treated HIV-infected Patients

Hypertension

Exacerbation of hypertension has not been observed in zidovudine-treated HIV-infected patients treated with PROCRIT®. However, PROCRIT® should be withheld in these patients if pre-existing hypertension is uncontrolled, and should not be started until blood pressure is controlled. In double-blind studies, a single seizure has been experienced by a patient treated with PROCRIT®.[25]

Cancer Patients on Chemotherapy

Hypertension

Hypertension, associated with a significant increase in hemoglobin, has been noted rarely in patients treated with PROCRIT®. Nevertheless, blood pressure in patients treated with PROCRIT® should be monitored carefully, particularly in patients with an underlying history of hypertension or cardiovascular disease.

Seizures

In double-blind, placebo-controlled trials, 3.2% (n = 2/63) of patients treated with PROCRIT® TIW and 2.9% (n = 2/68) of placebo-treated patients had seizures. Seizures in 1.6% (n = 1/63) of patients treated with PROCRIT® TIW occurred in the context of a significant increase in blood pressure and hematocrit from baseline values. However, both patients treated with PROCRIT® also had underlying CNS pathology which may have been related to seizure activity.

In a placebo-controlled, double-blind trial utilizing weekly dosing with PROCRIT®, 1.2% (n = 2/168) of safety-evaluable patients treated with PROCRIT® and 1% (n = 1/165) of placebo-treated patients had seizures. Seizures in the patients treated with weekly PROCRIT® occurred in the context of a significant increase in hemoglobin from baseline values however significant increases in blood pressure were not seen. These patients may have had other CNS pathology.

Thrombotic Events

In double-blind, placebo-controlled trials, 3.2% (n = 2/63) of patients treated with PROCRIT® TIW and 11.8% (n = 8/68) of placebo-treated patients had thrombotic events (eg, pulmonary embolism, cerebrovascular accident) (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events).

In a placebo-controlled, double-blind trial utilizing weekly dosing with PROCRIT®, 6.0% (n = 10/168) of safety-evaluable patients treated with PROCRIT® and 3.6% (n = 6/165) (p = 0.444) of placebo-treated patients had clinically significant thrombotic events (deep vein thrombosis requiring anticoagulant therapy, embolic event including pulmonary embolism, myocardial infarction, cerebral ischemia, left ventricular failure and thrombotic microangiopathy). A definitive relationship between the rate of hemoglobin increase and the occurrence of clinically significant thrombotic events could not be evaluated due to the limited schedule of hemoglobin measurements in this study.

The safety and efficacy of PROCRIT® were evaluated in a randomized, double-blind, placebo-controlled, multicenter study that enrolled 222 anemic patients ages 5 to 18 receiving treatment for a variety of childhood malignancies. Due to the study design (small sample size and the heterogeneity of the underlying malignancies and of anti-neoplastic treatments employed), a determination of the effect of PROCRIT® on the incidence of thrombotic events could not be performed. In the PROCRIT® arm, the overall incidence of thrombotic events was 10.8% and the incidence of serious or life-threatening events was 7.2%.

Surgery Patients

Hypertension

Blood pressure may rise in the perioperative period in patients being treated with PROCRIT®. Therefore, blood pressure should be monitored carefully.

ADVERSE REACTIONS

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. Neutralizing antibodies to erythropoietin, in association with PRCA or severe anemia (with or without other cytopenias), have been reported in patients receiving PROCRIT® (see WARNINGS: PURE RED CELL APLASIA) during post-marketing experience.

There has been no systematic assessment of immune responses, i.e., the incidence of either binding or neutralizing antibodies to PROCRIT®, in controlled clinical trials.

Where reported, the incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies across products within this class (erythropoietic proteins) may be misleading.

Chronic Renal Failure Patients

In double-blind, placebo-controlled studies involving over 300 patients with CRF, the events reported in greater than 5% of patients treated with PROCRIT® during the blinded phase were:

Event	Percent of Patients Reporting Event: Patients Treated With PROCRIT® (n = 200)	Percent of Patients Reporting Event: Placebo-treated Patients (n = 135)
Hypertension	24%	19%
Headache	16%	12%
Arthralgias	11%	6%
Nausea	11%	9%
Edema	9%	10%
Fatigue	9%	14%
Diarrhea	9%	6%
Vomiting	8%	5%
Chest Pain	7%	9%
Skin Reaction (Administration Site)	7%	12%
Asthenia	7%	12%
Dizziness	7%	13%
Clotted Access	7%	2%
Significant adverse events of concern in patients with CRF treated in double-blind, placebo-controlled trials occurred in the following percent of patients during the blinded phase of the studies:		
Seizure	1.1%	1.1%
CVA/TIA	0.4%	0.6%
MI	0.4%	1.1%
Death	0%	1.7%

In the US PROCRIT® studies in adult patients on dialysis (over 567 patients), the incidence (number of events per patient-year) of the most frequently reported adverse events were: hypertension (0.75), headache (0.40), tachycardia (0.31), nausea/vomiting (0.26), clotted vascular access (0.25), shortness of breath (0.14), hyperkalemia (0.11), and diarrhea (0.11). Other reported events occurred at a rate of less than 0.10 events per patient per year.

Events reported to have occurred within several hours of administration of PROCRIT® were rare, mild, and transient, and included injection site stinging in dialysis patients and flu-like symptoms such as arthralgias and myalgias.

In all studies analyzed to date, PROCRIT® administration was generally well-tolerated, irrespective of the route of administration.

Pediatric CRF Patients: In pediatric patients with CRF on dialysis, the pattern of most adverse events was similar to that found in adults. Additional adverse events reported during the double-blind phase in >10% of pediatric patients in either treatment group were: abdominal pain, dialysis access complications including access infections and peritonitis in those receiving peritoneal dialysis, fever, upper respiratory infection, cough, pharyngitis, and constipation. The rates are similar between the treatment groups for each event.

Hypertension: Increases in blood pressure have been reported in clinical trials, often during the first 90 days of therapy. On occasion, hypertensive encephalopathy and seizures have been observed in patients with CRF treated with PROCRIT®. When data from all patients in the US phase 3 multicenter trial were analyzed, there was an apparent trend of more reports of hypertensive adverse events in patients on dialysis with a faster rate of rise of hematocrit (greater than 4 hematocrit points in any 2-week period). However, in a double-blind, placebo-controlled trial, hypertensive adverse events were not reported at an increased rate in the group treated with PROCRIT® (150 Units/kg TIW) relative to the placebo group.

Seizures: There have been 47 seizures in 1010 patients on dialysis treated with PROCRIT® in clinical trials, with an exposure of 986 patient-years for a rate of approximately 0.048 events per patient-year. However, there appeared to be a higher rate of seizures during the first 90 days of therapy (occurring in approximately 2.5% of patients) when compared to subsequent 90-day periods. The baseline incidence of seizures in the untreated dialysis population is difficult to determine; it appears to be in the range of 5% to 10% per patient-year.[37-39]

Thrombotic Events: In clinical trials where the maintenance hematocrit was 35 ± 3% on PROCRIT®, clotting of the vascular access (A-V shunt) has occurred at an annualized rate of about 0.25 events per patient-year, and other thrombotic events (eg, myocardial infarction, cerebral vascular accident, transient ischemic attack, and pulmonary embolism) occurred at a rate of 0.04 events per patient-year. In a separate study of 1111 untreated dialysis patients, clotting of the vascular access occurred at a rate of 0.50 events per patient-year. However, in CRF patients on hemodialysis who also had clinically evident ischemic heart disease or congestive heart failure, the risk of A-V shunt thrombosis was higher (39% vs 29%, $p < 0.001$), and myocardial infarctions, vascular ischemic events, and venous thrombosis were increased, in patients targeted to a hematocrit of 42 ± 3% compared to those maintained at 30 ± 3% (see WARNINGS).

In patients treated with commercial PROCRIT®, there have been rare reports of serious or unusual thromboembolic events including migratory thrombophlebitis, microvascular thrombosis, pulmonary embolus, and thrombosis of the retinal artery, and temporal and renal veins. A causal relationship has not been established.

Allergic Reactions: There have been no reports of serious allergic reactions or anaphylaxis associated with PROCRIT® administration during clinical trials. Skin rashes and urticaria have been observed rarely and when reported have generally been mild and transient in nature.

There have been rare reports of potentially serious allergic reactions including urticaria with associated respiratory symptoms or circumoral edema, or urticaria alone. Most reactions occurred in situations where a causal relationship could not be established. Symptoms recurred with rechallenge in a few instances, suggesting that allergic reactivity may occasionally be associated with PROCRIT® therapy. If an anaphylactoid reaction occurs, PROCRIT® should be immediately discontinued and appropriate therapy initiated.

Zidovudine-treated HIV-infected Patients

In double-blind, placebo-controlled studies of 3 months duration involving approximately 300 zidovudine-treated HIV-infected patients, adverse events with an incidence of ≥10% in either patients treated with PROCRIT® or placebo-treated patients were:

Event	PERCENT OF PATIENTS REPORTING EVENT Patients Treated With PROCRIT® (n = 144)	Placebo-treated Patients (n = 153)
Pyrexia	38%	29%
Fatigue	25%	31%
Headache	19%	14%
Cough	18%	14%
Diarrhea	16%	18%
Rash	16%	8%
Congestion, Respiratory	15%	10%
Nausea	15%	12%
Shortness of Breath	14%	13%
Asthenia	11%	14%
Skin Reaction Medication Site	10%	7%
Dizziness	9%	10%

In the 297 patients studied, PROCRIT® was not associated with significant increases in opportunistic infections or mortality.[25] In 71 patients from this group treated with PROCRIT® at 150 Units/kg TIW, serum p24 antigen levels did not appear to increase.[27] Preliminary data showed no enhancement of HIV replication in infected cell lines in vitro.[25]

Peripheral white blood cell and platelet counts are unchanged following PROCRIT® therapy.

Allergic Reactions: Two zidovudine-treated HIV-infected patients had urticarial reactions within 48 hours of their first exposure to study medication. One patient was treated with PROCRIT® and one was treated with placebo (PROCRIT® vehicle alone). Both patients had positive immediate skin tests against their study medication with a negative saline control. The basis for this apparent pre-existing hypersensitivity to components of the PROCRIT® formulation is unknown, but may be related to HIV-induced immunosuppression or prior exposure to blood products.

Seizures: In double-blind and open-label trials of PROCRIT® in zidovudine-treated HIV-infected patients, 10 patients have experienced seizures.[25] In general, these seizures appear to be related to underlying pathology such as meningitis or cerebral neoplasms, not PROCRIT® therapy.

Cancer Patients on Chemotherapy

In double-blind, placebo-controlled studies of up to 3 months duration involving 131 cancer patients, adverse events with an incidence > 10% in either patients treated with PROCRIT® or placebo-treated patients were as indicated below:

Event	Percent of Patients Reporting Event Patients Treated With PROCRIT® (n = 63)	Placebo-treated Patients (n = 68)
Pyrexia	29%	19%
Diarrhea	21%*	7%
Nausea	17%*	32%
Vomiting	17%	15%
Edema	17%*	1%
Asthenia	13%	16%
Fatigue	13%	15%
Shortness of Breath	13%	9%
Paresthesia	11%	6%
Upper Respiratory Infection	11%	4%
Dizziness	5%	12%
Trunk Pain	3%*	16%

* Statistically significant

Although some statistically significant differences between patients being treated with PROCRIT® and placebo-treated patients were noted, the overall safety profile of PROCRIT® appeared to be consistent with the disease process of advanced cancer. During double-blind and subsequent open-label therapy in which patients (n = 72 for total exposure to PROCRIT®) were treated for up to 32 weeks with doses as high as 927 Units/kg, the adverse experience profile of PROCRIT® was consistent with the progression of advanced cancer.

Three hundred thirty-three (333) cancer patients enrolled in a placebo-controlled, double-blind trial utilizing Weekly dosing with PROCRIT® for up to 4 months were evaluable for adverse events. The incidence of adverse events was similar in both the treatment and placebo arms.

Surgery Patients

Adverse events with an incidence of ≥ 10% are shown in the following table:

Event	Percent of Patients Reporting Event Patients Treated With PROCRIT® 300 U/kg (n = 112)[a]	Patients Treated With PROCRIT® 100 U/kg (n = 101)[a]	Placebo-treated Patients (n = 103)[a]	Patients Treated With PROCRIT® 600 U/kg (n = 73)[b]	Patients Treated With PROCRIT® 300 U/kg (n = 72)[b]
Pyrexia	51%	50%	60%	47%	42%
Nausea	48%	43%	45%	45%	58%
Constipation	43%	42%	43%	51%	53%
Skin Reaction, Medication Site	25%	19%	22%	26%	29%
Vomiting	22%	12%	14%	21%	29%
Skin Pain	18%	18%	17%	5%	4%
Pruritus	16%	16%	14%	14%	22%
Insomnia	13%	16%	13%	21%	18%
Headache	13%	11%	9%	10%	19%
Dizziness	12%	9%	12%	11%	21%
Urinary Tract Infection	12%	3%	11%	11%	8%
Hypertension	10%	11%	10%	5%	10%
Diarrhea	10%	7%	12%	10%	6%
Deep Venous Thrombosis	10%	3%	5%	0%[c]	0%[c]
Dyspepsia	9%	11%	6%	7%	8%
Anxiety	7%	2%	11%	11%	4%
Edema	6%	11%	8%	11%	7%

[a] Study including patients undergoing orthopedic surgery treated with PROCRIT® or placebo for 15 days

[b] Study including patients undergoing orthopedic surgery treated with PROCRIT® 600 Units/kg weekly x 4 or 300 Units/kg daily x 15

[c] Determined by clinical symptoms

Thrombotic/Vascular Events: In three double-blind, placebo-controlled orthopedic surgery studies, the rate of deep venous thrombosis (DVT) was similar among Epoetin alfa and placebo-treated patients in the recommended population of patients with a pretreatment hemoglobin of > 10 g/dL to ≤ 13 g/dL.[18,20,28] However, in 2 of 3 orthopedic surgery studies the overall rate (all pretreatment hemoglobin groups combined) of DVTs detected by postoperative ultrasonography and/or surveillance venography was higher in the group treated with Epoetin alfa than in the placebo-treated group (11% vs 6%). This finding was attributable to the difference in DVT rates observed in the subgroup of patients with pretreatment hemoglobin > 13 g/dL.

In the orthopedic surgery study of patients with pretreatment hemoglobin of > 10 g/dL to ≤ 13 g/dL which compared two dosing regimens (600 Units/kg weekly x 4 and 300 Units/kg daily x 15), 4 subjects in the 600 Units/kg weekly PROCRIT® group (5%) and no

subjects in the 300 Units/kg daily group had a thrombotic vascular event during the study period.[19]

In a study examining the use of Epoetin alfa in 182 patients scheduled for coronary artery bypass graft surgery, 23% of patients treated with Epoetin alfa and 29% treated with placebo experienced thrombotic/vascular events. There were 4 deaths among the Epoetin alfa-treated patients that were associated with a thrombotic/vascular event (see WARNINGS).

OVERDOSAGE

The expected manifestations of PROCRIT® overdosage include signs and symptoms associated with an excessive and/or rapid increase in hemoglobin concentration, including any of the cardiovascular events described in WARNINGS and listed in ADVERSE REACTIONS. Patients receiving an overdosage of PROCRIT® should be monitored closely for cardiovascular events and hematologic abnormalities. Polycythemia should be managed acutely with phlebotomy, as clinically indicated. Following resolution of the effects due to PROCRIT® overdosage, reintroduction of PROCRIT® therapy should be accompanied by close monitoring for evidence of rapid increases in hemoglobin concentration (>1 gm/dL per 14 days). In patients with an excessive hematopoietic response, reduce the PROCRIT® dose in accordance with the recommendations described in DOSAGE AND ADMINISTRATION.

DOSAGE AND ADMINISTRATION

IMPORTANT: Use the lowest dose of PROCRIT® that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for RBC transfusion (see BOXED WARNINGS and WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events). PROCRIT® dosing regimens are different for each of the indications described in this section of the package insert. PROCRIT® should be administered under the supervision of a healthcare professional. The dosages recommended below are based upon those used in clinical studies supporting marketing approval.

Chronic Renal Failure Patients

The recommended range for the starting dose of PROCRIT® is 50 to 100 Units/kg TIW for adult patients. The recommended starting dose for pediatric CRF patients on dialysis is 50 Units/kg TIW. The dose of PROCRIT® should be reduced as the hemoglobin approaches 12 g/dL or increases by more than 1 g/dL in any 2-week period. The dose should be adjusted for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for red blood cell transfusion and not to exceed 12 g/dL.

PROCRIT® may be given either as an IV or SC injection. **In patients on hemodialysis, the IV route is recommended** (see WARNINGS: PURE RED CELL APLASIA) and PROCRIT® usually has been administered as an IV bolus TIW. While the administration of PROCRIT® is independent of the dialysis procedure, PROCRIT® may be administered into the venous line at the end of the dialysis procedure to obviate the need for additional venous access. In adult patients with CRF not on dialysis, PROCRIT® may be given either as an IV or SC injection.

Patients who have been judged competent by their physicians to self-administer PROCRIT® without medical or other supervision may give themselves either an IV or SC injection. The table below provides general therapeutic guidelines for patients with CRF:

Starting Dose:	
Adults	50 to 100 Units/kg TIW; IV or SC
Pediatric Patients	50 Units/kg TIW; IV or SC
Reduce Dose When:	1. Hgb approaches 12 g/dL or, 2. Hgb increases >1 g/dL in any 2-week period
Increase Dose If:	Hgb does not increase by 2 g/dL after 8 weeks of therapy, and Hgb remains at a level not sufficient to avoid the need for RBC transfusion
Maintenance Dose:	Individually titrate to achieve and maintain the lowest Hgb level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL

During therapy, hematological parameters should be monitored regularly (see LABORATORY MONITORING). Doses must be individualized to ensure that Hgb is maintained at an appropriate level for each patient.

Pretherapy Iron Evaluation: Prior to and during PROCRIT® therapy, the patient's iron stores, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, should be evaluated. Transferrin saturation should be at least 20%, and ferritin should be at least 100 ng/mL. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels that will adequately support erythropoiesis stimulated by PROCRIT®.

Dose Adjustment: The dose should be adjusted for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL.

Increases in dose should not be made more frequently than once a month. If the hemoglobin is increasing and approaching 12 g/dL, the dose should be reduced by approximately 25%. If the hemoglobin continues to increase, dose should be temporarily withheld until the hemoglobin begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose. If the hemoglobin increases by more than 1 g/dL in a 2-week period, the dose should be decreased by approximately 25%.

If the increase in the hemoglobin is less than 1 g/dL over 4 weeks and iron stores are adequate (see PRECAUTIONS: Laboratory Monitoring), the dose of PROCRIT® may be increased by approximately 25% of the previous dose. Further increases may be made at 4-week intervals until the specified hemoglobin is obtained.

Maintenance Dose: The maintenance dose must be individualized for each patient on dialysis. In the US phase 3 multicenter trial in patients on hemodialysis, the median maintenance dose was 75 Units/kg TIW, with a range from 12.5 to 525 Units/kg TIW. Almost 10% of the patients required a dose of 25 Units/kg, or less, and approximately 10% of the patients required more than 200 Units/kg TIW to maintain their hematocrit in the suggested target range. In pediatric hemodialysis and peritoneal dialysis patients, the median maintenance dose was 167 Units/kg/week (49 to 447 Units/kg per week) and 76 Units/kg per week (24 to 323 Units/kg/week) administered in divided doses (TIW or BIW), respectively to achieve the target range of 30% to 36%.

If the transferrin saturation is greater than 20%, the dose of PROCRIT® may be increased. Such dose increases should not be made more frequently than once a month, unless clinically indicated, as the response time of the hemoglobin to a dose increase can be 2 to 6 weeks. Hemoglobin should be measured twice weekly for 2 to 6 weeks following dose increases. In adult patients with CRF not on dialysis, the maintenance dose must also be individualized. PROCRIT® doses of 75 to 150 Units/kg/week have been shown to maintain hematocrits of 36% to 38% for up to 6 months.

Lack or Loss of Response: If a patient fails to respond or maintain a response, an evaluation for causative factors should be undertaken (see WARNINGS: PURE RED CELL APLASIA, PRECAUTIONS: LACK OR LOSS OF RESPONSE, and PRECAUTIONS: IRON EVALUATION). If the transferrin saturation is less than 20%, supplemental iron should be administered.

Zidovudine-treated HIV-infected Patients

Prior to beginning PROCRIT®, it is recommended that the endogenous serum erythropoietin level be determined (prior to transfusion). Available evidence suggests that patients receiving zidovudine with endogenous serum erythropoietin levels > 500 mUnits/mL are unlikely to respond to therapy with PROCRIT®.

In zidovudine-treated HIV-infected patients the dosage of PROCRIT® should be titrated for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for blood transfusion and not to exceed 12 g/dL.

Starting Dose: For adult patients with serum erythropoietin levels ≤ 500 mUnits/mL who are receiving a dose of zidovudine ≤ 4200 mg/week, the recommended starting dose of PROCRIT® is 100 Units/kg as an IV or SC injection TIW for 8 weeks. For pediatric patients, see PRECAUTIONS: PEDIATRIC USE.

Increase Dose: During the dose adjustment phase of therapy, the hemoglobin should be monitored weekly. If the response is not satisfactory in terms of reducing transfusion requirements or increasing hemoglobin after 8 weeks of therapy, the dose of PROCRIT® can be increased by 50 to 100 Units/kg TIW. Response should be evaluated every 4 to 8 weeks thereafter and the dose adjusted accordingly by 50 to 100 Units/kg increments TIW. If patients have not responded satisfactorily to a PROCRIT® dose of 300 Units/kg TIW, it is unlikely that they will respond to higher doses of PROCRIT®.

Maintenance Dose: After attainment of the desired response (ie, reduced transfusion requirements or increased hemoglobin), the dose of PROCRIT® should be titrated to maintain the response based on factors such as variations in zidovudine dose and the presence of intercurrent infectious or inflammatory episodes. If the hemoglobin exceeds 12 g/dL, the dose should be discontinued until the hemoglobin drops below 11 g/dL. The dose should be reduced by 25% when treatment is resumed and then titrated to maintain the desired hemoglobin.

Cancer Patients on Chemotherapy

Although no specific serum erythropoietin level has been established which predicts which patients would be unlikely to respond to PROCRIT® therapy, treatment of patients with grossly elevated serum erythropoietin levels (eg, > 200 mUnits/mL) is not recommended. The hemoglobin should be monitored on a weekly basis in patients receiving PROCRIT® therapy until hemoglobin becomes stable. The dose of PROCRIT® should be titrated for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for blood transfusion and not to exceed 12 g/dL (see recommended Dose Modifications, below).

Recommended Dose: The initial recommended dose of PROCRIT® in adults is 150 Units/kg SC TIW or 40,000 Units SC Weekly. For pediatric patients, weekly dosing is recommended.

Dose Modification

TIW Dosing

Starting Dose:	
Adults	150 Units/kg SC TIW
Reduce Dose by 25% when:	1. Hgb approaches 12 g/dL or, 2. Hgb increases > 1 g/dL in any 2-week period
Withhold Dose if:	Hgb exceeds 12 g/dL, until the hemoglobin falls below 11 g/dL, and restart dose at 25% below the previous dose
Increase Dose to 300 Units/kg TIW if:	response is not satisfactory (no reduction in transfusion requirements or rise in hemoglobin) after 8 weeks to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL

Weekly Dosing

Starting Dose:	
Adults	40,000 Units SC
Pediatrics	600 Units/kg IV (maximum 40,000 Units)
Reduce Dose by 25% when:	Hgb approaches 12 g/dL or increases > 1 g/dL in any 2 weeks
Withhold Dose if:	Hgb exceeds 12 g/dL, until the hemoglobin falls below 11 g/dL, and restart dose at 25% below the previous dose
Increase Dose if: For Adults: 60,000 Units SC Weekly For Pediatrics: 900 Units/kg IV (maximum 60,000 Units)	response is not satisfactory (no increase in hemoglobin by ≥ 1g/dL after 4 weeks of therapy, in the absence of a RBC transfusion) to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL

Surgery Patients

Prior to initiating treatment with PROCRIT® a hemoglobin should be obtained to establish that it is > 10 to ≤ 13 g/dL.[18] The recommended dose of PROCRIT® is 300 Units/kg/day subcutaneously for 10 days before surgery, on the day of surgery, and for 4 days after surgery.

An alternate dose schedule is 600 Units/kg PROCRIT® subcutaneously in once weekly doses (21, 14, and 7 days before surgery) plus a fourth dose on the day of surgery.[19]

All patients should receive adequate iron supplementation. Iron supplementation should be initiated no later than the beginning of treatment with PROCRIT® and should continue throughout the course of therapy. Antithrombotic prophylaxis should be strongly considered (see BOXED WARNINGS).

PREPARATION AND ADMINISTRATION OF PROCRIT®

1. Do not shake. It is not necessary to shake PROCRIT®. Prolonged vigorous shaking may denature any glycoprotein, rendering it biologically inactive.
2. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.
3. Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from the vial containing PROCRIT®, and wipe the septum with a disinfectant. Insert the needle into the vial, and withdraw into the syringe an appropriate volume of solution.
4. **Single-dose:** 1 mL vial contains no preservative. Use one dose per vial; do not re-enter the vial. Discard unused portions.

   Multidose: 1 mL and 2 mL vials contain preservative. Store at 2° to 8°C after initial entry and between doses. Discard 21 days after initial entry.
5. Do not dilute or administer in conjunction with other drug solutions. However, at the time of SC administration, preservative-free PROCRIT® from single-use vials may be admixed in a syringe with bacteriostatic 0.9% sodium chloride injection, USP, with benzyl

alcohol 0.9% (bacteriostatic saline) at a 1:1 ratio using aseptic technique. The benzyl alcohol in the bacteriostatic saline acts as a local anesthetic which may ameliorate SC injection site discomfort. Admixing is not necessary when using the multidose vials of PROCRIT® containing benzyl alcohol.

HOW SUPPLIED

PROCRIT®, containing Epoetin alfa, is available in vials containing color coded labels and caps.

1 mL **Single-Dose, Preservative-free** Solution

Each dosage form is supplied in the following packages:

Cartons containing six (6) **single-dose** vials:
2000 Units/mL (NDC 59676-302-01) (Purple)
3000 Units/mL (NDC 59676-303-01) (Magenta)
4000 Units/mL (NDC 59676-304-01) (Green)
10,000 Units/mL (NDC 59676-310-01) (Red)

Cartons containing four (4) **single-dose** vials:
40,000 Units/mL (NDC 59676-340-01) (Orange)

Trays containing twenty-five (25) **single-dose** vials:
2000 Units/mL (NDC 59676-302-02) (Purple)
3000 Units/mL (NDC 59676-303-02) (Magenta)
4000 Units/mL (NDC 59676-304-02) (Green)
10,000 Units/mL (NDC 59676-310-02) (Red)

2 mL **Multidose, Preserved** Solution

Cartons containing four (4) **multidose** vials:
10,000 Units/mL (NDC 59676-312-04) (Blue)

Cartons containing six (6) **multidose** vials:
10,000 Units/mL (NDC 59676-312-01) (Blue)

1 mL **Multidose, Preserved** Solution

Cartons containing four (4) **multidose** vials:
20,000 Units/mL (NDC 59676-320-04) (Lime)

Cartons containing six (6) **multidose** vials:
20,000 Units/mL (NDC 59676-320-01) (Lime)

STORAGE

Store at 2° to 8° C (36° to 46° F). Do not freeze or shake.

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PROCRIT®
(Epoetin alfa)

INFORMATION FOR PATIENTS

This patient package insert contains information and directions for patients (and their caregivers) whose doctor has determined that they may receive injections of PROCRIT® at home. Please read it carefully. This patient package insert does not include all information about PROCRIT® and does not replace talking with your doctor. You should discuss any questions about treatment with PROCRIT® with your doctor. Only your doctor can prescribe PROCRIT® and determine if it is right for you.

What important information should I know about PROCRIT®?

PROCRIT® works by stimulating your bone marrow to make more red blood cells. You will be asked to have blood tests that will measure the number of red blood cells to see if PROCRIT® is working. Your doctor may refer to the results of your blood tests as hemoglobin and/or hematocrit. It is important to keep all appointments for blood tests to allow your doctor to adjust the dosage of PROCRIT® as needed.

If your hemoglobin is kept too high (over 12 g/dL):

- You increase the chance of heart attack, stroke, heart failure, blood clots and death
- Your tumor may grow faster (if you are a patient with cancer)

If you are a patient with cancer, who has completed all of your planned chemotherapy treatment, PROCRIT® treatment may increase your chance of death regardless of hemoglobin level.

If you undergo surgery while taking PROCRIT®, PROCRIT® treatment increases your chance of a blood clot. Therefore, your physician may prescribe a blood thinner to prevent blood clots.

You should talk to your doctor if you have any questions or concerns about this **important safety information**.

Please also read **'What are the possible or reasonably likely side effects of PROCRIT®?'** below.

What is PROCRIT®?

PROCRIT® is a man-made form of the protein human erythropoietin (ee-rith-row-po-eh-tin). PROCRIT® works by stimulating your bone marrow to make red blood cells. After two to six weeks of treatment, your red blood cell counts may increase and if so, you may be able to avoid the need for red blood cell transfusion. Your doctor will prescribe the lowest dose of PROCRIT® needed to avoid red blood cell transfusions because of the concerns discussed in **'What important information should I know about PROCRIT®?'**

PROCRIT® is used to treat anemia (a lower than normal number of red blood cells).

PROCRIT® may be used to treat your anemia if it is caused by:

- chronic kidney failure (you may or may not be on dialysis)
- chemotherapy used to treat cancer
- certain scheduled surgeries (in order to reduce the need for blood transfusions or if you are at risk for significant blood loss)
- HIV and take a medicine called Zidovudine (AZT).

While you are being treated with PROCRIT®, you will be having blood tests (called hemoglobin and/or hematocrit) to check the number of red blood cells your body is producing. The amount of time it takes to reach the red blood cell level that is right for you, and the dose of PROCRIT® needed to make the red blood cell level rise, is different for each person. You may need PROCRIT® dose adjustments before you reach your correct dose of PROCRIT® and the correct dose may change over time.

Who <u>should not take</u> PROCRIT®?

You should not take PROCRIT® if you have:

- High blood pressure that is not controlled (uncontrolled hypertension).
- Allergies to PROCRIT® or other erythropoietins.
- Previous allergic reactions to any of the ingredients in PROCRIT®. See the list of ingredients in PROCRIT® at the end of the leaflet.

Talk to your doctor if you are not sure if you have these conditions or if you have any questions about this information.

What should I tell my doctor before taking PROCRIT®?

Tell your doctor about all your health conditions and all the medicines you take including prescription and over-the-counter medicines, vitamins, supplements, and herbals. Be sure to tell your doctor if you have:

- Heart disease
- High blood pressure
- Any history of seizures or strokes
- Blood disorders (such as sickle cell anemia, clotting disorders)

In addition, you should tell your doctor if you are:

- Pregnant or nursing
- Planning to become pregnant

PROCRIT® has not been studied in pregnant women and its effects on developing babies are not known. It is also not known if PROCRIT® can get into human breast milk.

Talk to your doctor if you are not sure if you have these conditions or if you have any questions about this information.

Your doctor may monitor your blood pressure and the amount of iron in your blood before you start PROCRIT® and while you are taking PROCRIT®. You or your caregiver may also be asked to monitor your blood pressure every day and to report any changes. When the number of red blood cells increases, your blood pressure may also increase, so your doctor may prescribe new or more blood pressure medicine. You

may be asked to have certain blood tests, such as hemoglobin, hematocrit or blood iron levels. Also, your doctor may prescribe iron for you to take. Be sure to follow your doctor's orders.

What are the possible or reasonable likely side effects of PROCRIT®?

Your blood pressure may increase when the number of red blood cells rises, so your doctor or caregiver may monitor your blood pressure more frequently. Some people have also had infections, low blood pressure, fevers, headaches, muscle aches or soreness, nausea, diarrhea, leg swelling, cough, or chest pain. If you experience any of these symptoms, you should call your doctor.

If you are on hemodialysis, there is a risk of blood clots forming at your vascular access. Call your doctor or dialysis center if you think your access is blocked.

Some patients may have an increased risk of blood clots forming in blood vessels, especially in the leg veins (venous thrombosis). In some patients, pieces of blood clot may travel to the lungs and block the blood circulation in the lungs (pulmonary embolus). **Call your doctor if you experience chest pain, shortness of breath, or pain in the legs with or without swelling.**

It is possible that your body may make antibodies against PROCRIT®. Antibodies to PROCRIT® can block or reduce your body's ability to make red blood cells. If you experience unusual tiredness and lack of energy, ***call your doctor.***

Some people experience redness, swelling, pain or itching at the site of injection. This reaction may be an allergy to the ingredients in PROCRIT®, or it may be a local irritation. If you notice any signs of redness, swelling, or itching at the site of injection, talk to your doctor.

Serious allergic reactions can also happen. These reactions can cause a rash over the whole body, shortness of breath, wheezing, a drop in blood pressure, swelling around the mouth or eyes, fast pulse, or sweating. If at any time a serious allergic reaction occurs, **stop using PROCRIT® and call your doctor or emergency medical personnel immediately (for example, call 911).**

The most common side effects you may have when taking PROCRIT® are:

- Increased blood pressure
- Headache
- Body aches
- Diarrhea
- Nausea
- Vomiting
- Swelling in your legs and arms
- Shortness of breath
- Fever

Some side effects are more common depending on the reasons for which you are taking PROCRIT®. Talk to your doctor for more information about side effects. Make sure to report any side effects to your doctor.

PROCRIT® has other side effects that are not listed here. For a complete list, talk to your doctor.

Call your doctor right away if:

- You take more than the amount prescribed
- You are currently taking PROCRIT® and experience any of these symptoms which may be a sign of a serious problem.
  - Unusual tiredness and lack of energy
  - Redness, swelling, pain or itching at the site of injection and spreading rash over the whole body, shortness of breath, wheezing, a drop in blood pressure, swelling around the mouth and/or eyes, fast pulse, or sweating
  - Convulsion, confusion, dizziness, loss of consciousness

- Increased blood pressure, chest pain, irregular heartbeats
- Stroke, chest pain, shortness of breath, or pain and/or swelling in the legs
- Blood clots in your hemodialysis vascular access port

How should I take PROCRIT®?

In those situations where your doctor has determined that you, as a home dialysis patient, and/or your caregiver can administer PROCRIT® at home, ***always follow the instructions of your doctor concerning the dose, how to administer and how often to administer PROCRIT®.*** Ask your doctor what to do if you miss a dose of PROCRIT®.

Always keep a spare syringe and needle on hand.

When you receive your PROCRIT® from the dialysis center, doctor's office or pharmacy, always check to see that:

1. The name PROCRIT® appears on the carton and vial label.
2. You will be able to use PROCRIT® before the expiration date stamped on the package.

The PROCRIT® solution in the vial should always be clear and colorless. Do not use PROCRIT® if the contents of the vial appear discolored or cloudy, or if the vial appears to contain lumps, flakes, or particles. In addition, if the vial has been shaken vigorously, the solution may appear to be frothy and should not be used. Care should be taken not to shake the PROCRIT® vial before use.

Always use the correct syringe.

Your doctor has instructed you on how to give yourself the correct dosage of PROCRIT®. This dosage will usually be measured in Units per milliliter or cc's. It is important to use a syringe that is marked in tenths of milliliters (for example, 0.2 mL or cc). Using the wrong syringe can lead to a mistake in your dose, and you may receive too much or too little PROCRIT®. Too little PROCRIT® may not be effective in increasing the number of red blood cells. Too much PROCRIT® may lead to serious problems because too many red blood cells are being produced (a hemoglobin or hematocrit that is too high).

Only use disposable syringes and needles. Use the syringe once and dispose of it as instructed by your doctor.

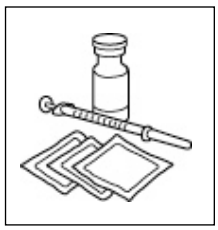
Unless you have been prescribed Multidose PROCRIT® (1 mL or 2 mL vials with a big "M" on the label, each containing a total of 20,000 Units of PROCRIT®), vials of PROCRIT® are for single use. Single use means the vial cannot be used more than once, and any unused portion of the vial should be discarded as directed by your doctor.

However, Multidose PROCRIT® can be used to inject multiple doses as prescribed by your doctor, and may be stored between doses in the refrigerator (but not the freezer) for up to 21 days. Follow your doctor's or dialysis center's instructions on what to do with the used vials.

IMPORTANT: TO HELP AVOID CONTAMINATION AND POSSIBLE INFECTION, FOLLOW THESE INSTRUCTIONS EXACTLY.

Preparing the dose:

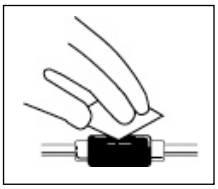
1. Remove the vial of PROCRIT® from the refrigerator and allow it to reach room temperature. Do not leave the vial in direct sunlight. Each PROCRIT® vial is designed to be used only once, unless you are using a Multidose vial. Do not shake PROCRIT®. Assemble the other supplies you will need for your injection (vial; syringe; alcohol antiseptic wipes and a container for disposing the needle).

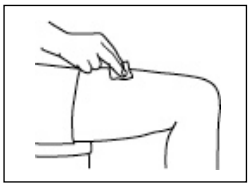


2. Check the date on the PROCRIT® vial to be sure that the drug has not expired.

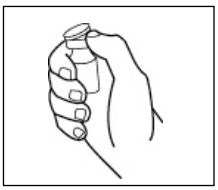
3. Wash your hands thoroughly with soap and water before preparing the medication.

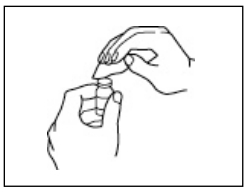
4. Wipe off the venous port of the hemodialysis tubing with an antiseptic swab or cleanse the skin with an antiseptic swab where the injection is to be made. Be careful not to touch the area that has been wiped with the antiseptic.



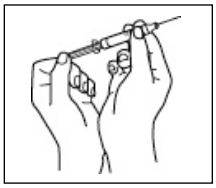


5. Flip off the protective cap but do not remove the gray rubber stopper. Wipe the top of the gray rubber stopper with an antiseptic swab.

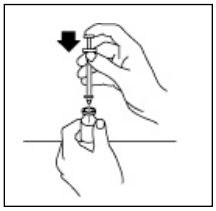




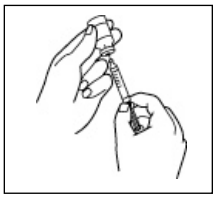
6. Using a syringe and needle that has been ordered by your doctor, carefully remove the needle cover. Then, draw air into the syringe by pulling back on the plunger. The amount of air should be equal to your PROCRIT® dose/volume.



7. With the vial on a flat work surface, put the needle through the gray rubber stopper of the PROCRIT® vial.
8. Push the plunger in to discharge air into the vial. The air injected into the vial will allow PROCRIT® to be easily withdrawn into the syringe.



9. Turn the vial and syringe upside down in one hand. Be sure the tip of the needle is in the PROCRIT® solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw the correct dose of PROCRIT® into the syringe.

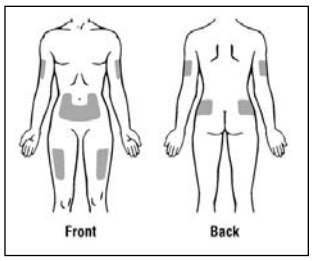


10. Check for air bubbles. A small amount of air is harmless, but too large an air bubble will reduce the PROCRIT® dose. To remove air bubbles, gently tap the syringe with your fingers to move the air bubbles to the top of the syringe, then use the plunger to push the solution and the air back into the vial. Keeping the tip of the needle in the PROCRIT® solution, refill the syringe with your correct dose of PROCRIT®.
11. Double-check that you have the correct dose in the syringe. Remove the needle from the vial. Do not lay the syringe down or allow the needle to touch anything.

Injecting the dose:

PROCRIT® can be injected into your body using two different ways as described below. Make sure you discuss with your doctor and

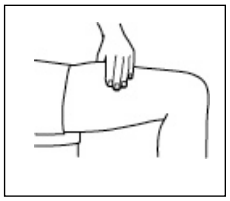
understand which way is best for you. In patients on hemodialysis, the IV route is recommended.

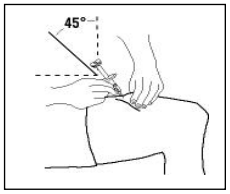


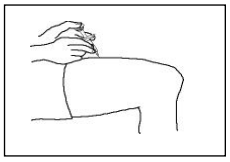
1. SUBCUTANEOUS Route: PROCRIT® can be injected directly into a layer of fat under your skin. This is called a subcutaneous injection. When receiving subcutaneous injections, always change the site for each injection as directed by your doctor. You may wish to record and track the site where you have injected. Do not inject PROCRIT® into an area that is tender, red, bruised, hard, or has scars or stretch marks. Recommended sites for injection are presented in the figure above, including the outer area of the upper arm, the abdomen (except for the two-inch area around the navel), the front of the middle thighs, and the outer area of the buttocks.
2. INTRAVENOUS Route: PROCRIT® can be injected in your vein through a special access port put in by your doctor. This type of PROCRIT® injection is called an intravenous injection. This route is usually for hemodialysis patients. If you have a dialysis vascular access, to make sure it is working, continue to check your access as your doctor or nurse has shown you. Be sure to let your healthcare provider know right away if you are having any problems, or if you have any questions.

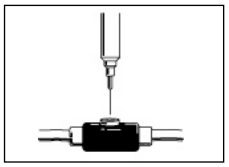
Using the subcutaneous route:

1. With one hand, hold the area surrounding the cleaned skin either by spreading it or by pinching up a large area. Do not touch the cleansed area.
2. Double-check that the correct amount of PROCRIT® is in the syringe.
3. Hold the syringe with the other hand, as you would a pencil, insert the needle into the skin at a 45-degree angle. Let go of the skin and pull the plunger back slightly. If blood comes into the syringe, do not inject PROCRIT®, as the needle has entered a blood vessel; withdraw the syringe, clean a new area, follow steps 1 and 2 and inject at a different site. If blood does not enter the syringe, inject the PROCRIT® by pushing the plunger all the way down.
4. Pull the needle straight out of the skin and immediately press the antiseptic swab over the injection site for several seconds.









Using the intravenous injection route (hemodialysis patients):

1. Insert the needle of the syringe into the clean venous port and inject the PROCRIT®.

How should I dispose of syringes and needles?

Remove the syringe and dispose of the whole unit WITHOUT RECAPPING THE NEEDLE. Use the disposable syringe only once.

Dispose of syringes and needles as directed by your doctor, by following these simple steps:

- Place all used needles and syringes in a labeled hard-plastic container with a screw-on-cap, or a labeled metal container with a plastic lid, such as a coffee can properly labeled as to content. If a metal container is used, cut a small hole in the plastic lid and tape the lid to the metal container. If a hard-plastic container is used, always screw the cap on tightly after each use. When the container is full, tape around the cap or lid, and ***dispose of according to your doctor's instructions.***
- Do not use glass or clear plastic containers, or any container that will be recycled or returned to a store.
- ALWAYS store the container out of the reach of children.
- Please check with your doctor, nurse, or pharmacist for other suggestions. There may be special state and local laws that they will discuss with you. DO NOT THROW THE CONTAINER IN YOUR HOUSEHOLD TRASH.

How should I store PROCRIT®?

PROCRIT® should be stored in the refrigerator, but NEVER in the freezer. Do not use a vial of PROCRIT® that has been frozen. Do not leave the vial in direct sunlight. If you have any questions about PROCRIT® that has been exposed to temperature extremes, be sure to check with your doctor. When traveling, transport PROCRIT® in its original carton in an insulated container with a coolant such as blue ice. To avoid freezing, make sure the PROCRIT® vial does not touch the coolant. Once you arrive, your PROCRIT® should be placed in a refrigerator as soon as possible.

General information about PROCRIT®

Doctors can prescribe medicines for conditions that are not in this leaflet. Use PROCRIT® only for what your doctor prescribed. Do not give it to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet gives the most important patient information about PROCRIT®. For more information talk to your doctor or healthcare provider. You can also visit www.procrit.com or call 1 888 2ASK OBI or 1-888-227-5624.

Active Ingredients: Epoetin alfa

Inactive Ingredients: All formulations include Albumin (Human), sodium citrate, sodium chloride, and citric acid in water for injection. In addition, certain formulations may contain: benzyl alcohol, sodium phosphate monobasic monohydrate or sodium phosphate dibasic anhydrate.

Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

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ORTHO BIOTECH

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Aranesp®
(darbepoetin alfa)
For Injection

WARNINGS: Erythropoiesis-Stimulating Agents

Use the lowest dose of Aranesp® that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion (see DOSAGE AND ADMINISTRATION).

Aranesp® and other erythropoiesis-stimulating agents (ESAs) increased the risk for death and for serious cardiovascular events when administered to target a hemoglobin of greater than 12 g/dL (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events).

Cancer Patients: Use of ESAs

- **shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a hemoglobin of greater than 12 g/dL;**
- **shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to target a hemoglobin of greater than 12 g/dL;**
- **increased the risk of death when administered to target a hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for this population.**

(See WARNINGS: Increased Mortality and/or Tumor Progression)

Patients receiving ESAs pre-operatively for reduction of allogeneic red blood cell transfusions: A higher incidence of deep venous thrombosis was documented in patients receiving Epoetin alfa who were not receiving prophylactic anticoagulation. Aranesp® is not approved for this indication (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events).

DESCRIPTION

Aranesp® is an erythropoiesis stimulating protein, closely related to erythropoietin, that is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Aranesp® is a 165-amino acid protein that differs from recombinant human erythropoietin in containing 5 N-linked oligosaccharide chains, whereas recombinant human erythropoietin contains 3 chains.[1] The two additional N-glycosylation sites result from amino acid substitutions in the erythropoietin peptide backbone. The additional carbohydrate chains increase the approximate molecular weight of the glycoprotein from 30,000 to 37,000 daltons. Aranesp® is formulated as a sterile, colorless, preservative-free protein solution for intravenous (IV) or subcutaneous (SC) administration.

Single-dose vials are available containing 25, 40, 60, 100, 150, 200, 300, or 500 mcg of Aranesp®.

Single-dose prefilled syringes and prefilled SureClick™ autoinjectors are available containing 25, 40, 60, 100, 150, 200, 300, or 500 mcg of Aranesp®. Each prefilled syringe is equipped with a needle guard that covers the needle during disposal.

Single-dose vials, prefilled syringes and autoinjectors are available in two formulations that contain excipients as follows:

> **Polysorbate solution** Each 1 mL contains 0.05 mg polysorbate 80, and is formulated at pH 6.2 ± 0.2 with 2.12 mg sodium phosphate monobasic monohydrate, 0.66 mg sodium phosphate dibasic anhydrous, and 8.18 mg sodium chloride in Water for Injection, USP (to 1 mL).
>
> **Albumin solution** Each 1 mL contains 2.5 mg albumin (human), and is formulated at pH 6.0 ± 0.3 with 2.23 mg sodium phosphate monobasic monohydrate, 0.53 mg sodium phosphate dibasic anhydrous, and 8.18 mg sodium chloride in Water for Injection, USP (to 1 mL).

CLINICAL PHARMACOLOGY

Mechanism of Action

Aranesp® stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. A primary growth factor for erythroid development, erythropoietin is produced in the kidney and released into the bloodstream in response to hypoxia. In responding to hypoxia, erythropoietin interacts with progenitor stem cells to increase red blood cell (RBC) production. Production of endogenous erythropoietin is impaired in patients with chronic renal failure (CRF), and erythropoietin deficiency is the primary cause of their anemia. Increased hemoglobin levels are not generally observed until 2 to 6 weeks after initiating treatment with Aranesp® (see **DOSAGE AND ADMINISTRATION**). In patients with cancer receiving concomitant chemotherapy, the etiology of anemia is multifactorial.

Pharmacokinetics

Adult Patients

The pharmacokinetics of Aranesp® were studied in patients with CRF and cancer patients receiving chemotherapy.

Following intravenous (IV) administration in CRF patients, Aranesp® serum concentration-time profiles were biphasic, with a distribution half-life of approximately 1.4 hours and a mean terminal half-life of 21 hours. The terminal half-life of Aranesp® was approximately 3-fold longer than that of Epoetin alfa when administered intravenously.

Following subcutaneous (SC) administration, absorption is slow and rate limiting. The observed half-life in CRF patients, which reflected the rate of absorption, was 49 hours (range: 27 to 89 hours). Peak concentrations occurred at 34 hours (range: 24 to 72 hours). The bioavailability of Aranesp® as measured in CRF patients after SC administration was 37% (range: 30% to 50%).

Following the first SC dose of 6.75 mcg/kg (equivalent to 500 mcg for a 74-kg patient) in patients with cancer, the mean terminal half-life was 74 hours (range: 24 to 144 hours). Peak concentrations were observed at 90 hours (range: 71 to 123 hours) after a dose of 2.25 mcg/kg, and 71 hours (range: 28 to 120 hours) after a dose of 6.75 mcg/kg. When administered on a once-every-3-week (Q3W) schedule, 48-hour post-dose Aranesp® levels after the fourth dose were similar to those after the first dose.

Over the dose range of 0.45 to 4.5 mcg/kg Aranesp® administered IV or SC on a once-weekly (QW) schedule and 4.5 to 15 mcg/kg administered SC on a Q3W schedule, systemic exposure was approximately proportional to dose. No evidence of accumulation was observed beyond an expected < 2-fold increase in blood levels when compared to the initial dose.

Pediatric Patients

Aranesp® pharmacokinetics were studied in 12 pediatric CRF patients (age 3-16 years) receiving or not receiving dialysis. Following a single IV or SC Aranesp® dose, Cmax and half-life were similar to those obtained in adult CRF patients. Following a single SC dose, the average bioavailability was 54% (range: 32% to 70%), which was higher than that obtained in adult CRF patients.

CLINICAL STUDIES

Throughout this section of the package insert, the Aranesp® study numbers associated with the nephrology and cancer clinical programs are designated with the letters "N" and "C", respectively.

Chronic Renal Failure Patients

The safety and effectiveness of Aranesp® have been assessed in a number of multicenter studies. Two studies evaluated the safety and efficacy of Aranesp® for the correction of anemia in adult patients with CRF, and three studies (2 in adults and 1 in pediatric patients) assessed the ability of Aranesp® to maintain hemoglobin concentrations in patients with CRF who had been receiving other recombinant erythropoietins.

De Novo Use of Aranesp®

In two open-label studies, Aranesp® or Epoetin alfa was administered for the correction of anemia in CRF patients who had not been receiving prior treatment with exogenous erythropoietin. Study N1 evaluated CRF patients receiving dialysis; Study N2 evaluated patients not requiring dialysis (predialysis patients). In both studies, the starting dose of Aranesp® was 0.45 mcg/kg administered once weekly. The starting dose of Epoetin alfa was 50 U/kg 3 times weekly in Study N1 and 50 U/kg twice weekly in Study N2. When necessary, dosage adjustments were instituted to maintain hemoglobin in the study target range of 11 to 13 g/dL. (Note: The recommended hemoglobin target is lower than the target range of these studies. See **DOSAGE AND ADMINISTRATION: General** for recommended clinical hemoglobin target.) The primary efficacy endpoint was the proportion of patients who experienced at least a 1.0 g/dL increase in hemoglobin concentration to a level of at least 11.0 g/dL by 20 weeks (Study N1) or 24 weeks (Study N2). The studies were designed to assess the safety and effectiveness of Aranesp® but not to support conclusions regarding comparisons between the two products.

In Study N1, the hemoglobin target was achieved by 72% (95% CI: 62%, 81%) of the 90 patients treated with Aranesp® and 84% (95% CI: 66%, 95%) of the 31 patients treated with Epoetin alfa. The mean increase in hemoglobin over the initial 4 weeks of Aranesp® treatment was 1.10 g/dL (95% CI: 0.82 g/dL, 1.37 g/dL).

In Study N2, the primary efficacy endpoint was achieved by 93% (95% CI: 87%, 97%) of the 129 patients treated with Aranesp® and 92% (95% CI: 78%, 98%) of the 37 patients treated with Epoetin alfa. The mean increase in hemoglobin from baseline through the initial 4 weeks of Aranesp® treatment was 1.38 g/dL (95% CI: 1.21 g/dL, 1.55 g/dL).

Conversion From Other Recombinant Erythropoietins

Two adult studies (N3 and N4) and one pediatric study (N5) were conducted in patients with CRF who had been receiving other recombinant erythropoietins. The studies compared the abilities of Aranesp® and other erythropoietins to maintain hemoglobin concentrations within a study target range of 9 to 13 g/dL in adults and 10 to 12.5 g/dL in pediatric patients. (Note: The recommended hemoglobin target is lower than the target range of these studies. See **DOSAGE AND ADMINISTRATION: General** for recommended clinical hemoglobin target.) CRF patients who had been receiving stable doses of other recombinant erythropoietins were randomized to Aranesp®, or to continue with their prior erythropoietin at the previous dose and schedule. For patients randomized to Aranesp®, the initial weekly dose was determined on the basis of the previous total weekly dose of recombinant erythropoietin.

Adult Patients

Study N3 was a double-blind study conducted in North America, in which 169 hemodialysis patients were randomized to treatment with Aranesp® and 338 patients continued on Epoetin alfa. Study N4 was an open-label study conducted in Europe and Australia in which 347 patients were randomized to treatment with Aranesp® and 175 patients were randomized to continue on Epoetin alfa or Epoetin beta. Of the 347 patients randomized to Aranesp®, 92% were receiving hemodialysis and 8% were receiving peritoneal dialysis.

In Study N3, a median weekly dose of 0.53 mcg/kg Aranesp® (25th, 75th percentiles: 0.30, 0.93 mcg/kg) was required to maintain hemoglobin in the study target range. In Study N4, a median weekly dose of 0.41 mcg/kg Aranesp® (25th, 75th percentiles: 0.26, 0.65 mcg/kg) was required to maintain hemoglobin in the study target range.

Pediatric Patients

Study N5 was an open-label, randomized study, conducted in the United States in pediatric patients from 1 to 18 years of age with CRF receiving or not receiving dialysis. Patients that were stable on Epoetin alfa were randomized to receive either darbepoetin alfa (n = 82) administered once weekly (SC or IV) or to continue receiving Epoetin alfa (n = 42) at the current dose, schedule, and route of administration. A median weekly dose of 0.41 mcg/kg Aranesp® (25th, 75th percentiles: 0.25, 0.82 mcg/kg) was required to maintain hemoglobin in the study target range.

Cancer Patients Receiving Chemotherapy

Once-Weekly (QW) Dosing

The safety and effectiveness of Aranesp® in reducing the requirement for RBC transfusions in patients undergoing chemotherapy was assessed in a randomized, placebo-controlled, double-blind, multinational study (C1). This study was conducted in anemic (Hgb ≤ 11 g/dL) patients with advanced, small cell or non-small cell lung cancer, who received a platinum-containing chemotherapy regimen. Patients were randomized to receive Aranesp® 2.25 mcg/kg (n = 156) or placebo (n = 158) administered as a single weekly SC injection for up to 12 weeks. The dose was escalated to 4.5 mcg/kg/week at week 6, in subjects with an inadequate response to treatment, defined as less than 1 g/dL hemoglobin increase. There were 67 patients in the Aranesp® arm who had their dose increased from 2.25 to 4.5 mcg/kg/week, at any time during the treatment period.

Efficacy was determined by a reduction in the proportion of patients who were transfused over the 12-week treatment period. A significantly lower proportion of patients in the Aranesp® arm, 26% (95% CI: 20%, 33%) required transfusion compared to 60% (95% CI: 52%, 68%) in the placebo arm (Kaplan-Meier estimate of proportion; $p < 0.001$ by Cochran–Mantel-Haenszel test). Of the 67 patients who received a dose increase, 28% had a 2 g/dL increase in hemoglobin over baseline, generally occurring between weeks 8 to 13. Of the 89 patients who did not receive a dose increase, 69% had a 2 g/dL increase in hemoglobin over baseline, generally occurring between weeks 6 to 13. On-study deaths occurred in 14% (22/156) of patients treated with Aranesp® and 12% (19/158) of the placebo-treated patients.

Once-Every-3-Week (Q3W) Dosing

The safety and effectiveness of Q3W Aranesp® therapy in reducing the requirement for red blood cell (RBC) transfusions in patients undergoing chemotherapy was assessed in a randomized, double-blind, multinational study (C2). This study was conducted in anemic (Hgb < 11 g/dL) patients with non-myeloid malignancies receiving multicycle chemotherapy. Patients were randomized to receive Aranesp® at 500 mcg Q3W (n = 353) or 2.25 mcg/kg (n = 352) administered weekly as a SC injection for up to 15 weeks. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 mcg in the Q3W group and 1.35 mcg/kg in the QW group) if hemoglobin increased by more than 1 g/dL in a 14-day period. Study drug was withheld if hemoglobin exceeded 13 g/dL. In the Q3W group, 254 patients (72%) required dose reductions (median time to first reduction at 6 weeks). In the QW group, 263 patients (75%) required dose reductions (median time to first reduction at 5 weeks).

Efficacy was determined by a comparison of the Kaplan-Meier estimates of the proportion of patients who received at least one RBC transfusion between day 29 and the end of treatment. Three hundred thirty-five patients in the Q3W group and 337 patients in the QW group remained on study through or beyond day 29 and were evaluated for efficacy. Twenty-seven percent (95% CI: 22%, 32%) of patients in the Q3W group and 34% (95% CI: 29%, 39%) in the weekly group required a RBC transfusion. The observed difference in the transfusion rates (Q3W-QW) was -6.7% (95% CI: -13.8%, 0.4%).

INDICATIONS AND USAGE

Aranesp® is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis, and for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.

CONTRAINDICATIONS

Aranesp® is contraindicated in patients with:

- uncontrolled hypertension
- known hypersensitivity to the active substance or any of the excipients

WARNINGS

Increased Mortality, Serious Cardiovascular and Thromboembolic Events

Aranesp® and other erythropoiesis-stimulating agents (ESAs) increased the risk for death and for serious cardiovascular events in controlled clinical trials when administered to target a hemoglobin of greater than 12 g/dL. There was an increased risk of serious arterial and venous thromboembolic events, including myocardial infarction, stroke, congestive heart failure, and hemodialysis graft occlusion. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may also contribute to these risks.

To reduce cardiovascular risks, use the lowest dose of Aranesp® that will gradually increase the hemoglobin concentration to a level sufficient to avoid the need for RBC transfusion. The hemoglobin concentration should not exceed 12 g/dL; the rate of hemoglobin increase should not exceed 1 g/dL in any 2-week period (see **DOSAGE AND ADMINISTRATION**).

In a randomized prospective trial, 1432 anemic chronic renal failure patients who were not undergoing dialysis were assigned to Epoetin alfa (rHuEPO) treatment targeting a maintenance hemoglobin concentration of 13.5 g/dL or 11.3 g/dL. A major cardiovascular event (death, myocardial infarction, stroke, or hospitalization for congestive heart failure) occurred among 125 (18%) of the 715 patients in the higher hemoglobin group compared to 97 (14%) among the 717 patients in the lower hemoglobin group [Hazard Ratio (HR) 1.3, 95% CI: 1.0, 1.7, p = 0.03].[2]

Increased risk for serious cardiovascular events was also reported from a randomized, prospective trial of 1265 hemodialysis patients with clinically evident cardiac disease (ischemic heart disease or congestive heart failure). In this trial, patients were assigned to Epoetin alfa treatment targeted to a maintenance hemoglobin of either 14 ± 1 g/dL or 10 ± 1 g/dL.[3] Higher mortality (35% vs. 29%) was observed in the 634 patients randomized to a target hemoglobin of 14 g/dL than in the 631 patients assigned a target hemoglobin of 10 g/dL. The reason for the increased mortality observed in this study is unknown; however, the incidence of nonfatal myocardial infarction, vascular access thrombosis, and other thrombotic events was also higher in the group randomized to a target hemoglobin of 14 g/dL.

An increased incidence of thrombotic events has also been observed in patients with cancer treated with erythropoietic agents. In patients with cancer who received Aranesp®, pulmonary emboli, thrombophlebitis, and thrombosis occurred more frequently than in placebo controls (see **ADVERSE REACTIONS: *Cancer Patients Receiving Chemotherapy*, Table 4**).

In a randomized controlled study (referred to as the 'BEST' study) with another ESA in 939 women with metastatic breast cancer receiving chemotherapy, patients received either weekly Epoetin alfa or placebo for up to a year. This study was designed to show that survival was superior when an ESA was administered to prevent anemia (maintain hemoglobin levels between 12 and 14 g/dL or hematocrit between 36% and 42%). The trial was terminated prematurely when interim results demonstrated that a higher mortality at 4 months (8.7% vs. 3.4%) and a higher rate of fatal thrombotic events (1.1% vs. 0.2%) in the first 4 months of the study were observed among patients treated with Epoetin alfa. Based on Kaplan-Meier estimates, at the time of study termination, the 12-month survival was lower in the Epoetin alfa group than in the placebo group (70% vs. 76%; HR 1.37, 95% CI: 1.07, 1.75, p = 0.012).[4]

A systematic review of 57 randomized controlled trials (including the BEST and ENHANCE studies) evaluating 9353 patients with cancer compared ESAs plus RBC transfusion with RBC transfusion alone for prophylaxis or treatment of anemia in cancer patients with or without concurrent antineoplastic therapy. An increased relative risk (RR) of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06; 35 trials and 6769 patients) was observed in ESA-treated patients. An overall survival hazard ratio of 1.08 (95% CI: 0.99, 1.18; 42 trials and 8167 patients) was observed in ESA-treated patients.[5]

An increased incidence of deep vein thrombosis (DVT) in patients receiving Epoetin alfa undergoing surgical orthopedic procedures has been observed. In a randomized controlled study (referred to as the 'SPINE' study), 681 adult patients, not receiving prophylactic anticoagulation and undergoing spinal surgery, received Epoetin alfa and standard of care (SOC) treatment, or SOC treatment alone. Preliminary analysis showed a higher incidence of DVT, determined by either Color Flow Duplex Imaging or by clinical symptoms, in the Epoetin alfa group [16 patients (4.7%)] compared to the SOC group [7 patients (2.1%)]. In addition, 12 patients in the Epoetin alfa group and 7 patients in the SOC group had other thrombotic vascular events.

Increased mortality was observed in a randomized placebo-controlled study of Epoetin alfa in adult patients who were undergoing coronary artery bypass surgery (7 deaths in 126 patients randomized to Epoetin alfa versus no deaths among 56 patients receiving placebo). Four of these deaths occurred during the period of study drug administration and all four deaths were associated with thrombotic events.

Aranesp® is not approved for reduction in allogeneic RBC transfusions in patients scheduled for surgical procedures (see **BOXED WARNINGS**).

Increased Mortality and/or Tumor Progression

Erythropoiesis-stimulating agents, when administered to target a hemoglobin of greater than 12 g/dL, shortened the time to tumor progression in patients with advanced head and neck cancer receiving

radiation therapy. ESAs also shortened survival in patients with metastatic breast cancer receiving chemotherapy when administered to target a hemoglobin of greater than 12 g/dL.

The ENHANCE study was a randomized controlled study in 351 head and neck cancer patients where Epoetin beta or placebo was administered to achieve target hemoglobins of 14 and 15 g/dL for women and men, respectively. Locoregional progression-free survival was significantly shorter in patients receiving Epoetin beta (HR 1.62, 95% CI: 1.22, 2.14, p = 0.0008) with a median of 406 days Epoetin beta vs. 745 days placebo.

The DAHANCA 10 study, conducted in 522 patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy were randomized to Aranesp® or placebo. An interim analysis in 484 patients demonstrated a 10% increase in locoregional failure rate among Aranesp®-treated patients (p = 0.01). At the time of study termination, there was a trend toward worse survival in the Aranesp®-treated group (p = 0.08).

The BEST study was previously described (see **WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events**). Mortality at 4 months (8.7% vs. 3.4%) was significantly higher in the Epoetin alfa arm. The most common investigator-attributed cause of death within the first 4 months was disease progression; 28 of 41 deaths in the Epoetin alfa arm and 13 of 16 deaths in the placebo arm were attributed to progressive disease. Investigator-assessed time to tumor progression was not different between the two groups.[4]

In a Phase 3, double-blind, randomized (Aranesp® vs. placebo), 16-week study in 989 anemic patients with active malignant disease neither receiving nor planning to receive chemotherapy or radiation therapy, there was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions. In addition, there were more deaths in the Aranesp® treatment group [26% (136/515)] than the placebo group [20% (94/470)] at 16 weeks (completion of treatment phase). With a median survival follow-up of 4.3 months, the absolute number of deaths was greater in the Aranesp® treatment group [49% (250/515)] compared with the placebo group [46% (216/470); HR 1.29, 95% CI: 1.08, 1.55].

In a Phase 3, multicenter, randomized (Epoetin alfa vs. placebo), double-blind study, patients with advanced non-small cell lung cancer unsuitable for curative therapy were treated with Epoetin alfa targeting hemoglobin levels between 12 and 14 g/dL. Following an interim analysis of 70 of 300 patients planned, a significant difference in median survival in favor of patients in the placebo group was observed (63 vs. 129 days; HR 1.84, p = 0.04).

Hypertension

Patients with uncontrolled hypertension should not be treated with Aranesp®; blood pressure should be controlled adequately before initiation of therapy. Blood pressure may rise during treatment of anemia with Aranesp® or Epoetin alfa. In Aranesp® clinical trials, approximately 40% of patients with CRF required initiation or intensification of antihypertensive therapy during the early phase of treatment when the hemoglobin was increasing. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with Aranesp® or Epoetin alfa.

Special care should be taken to closely monitor and control blood pressure in patients treated with Aranesp®. During Aranesp® therapy, patients should be advised of the importance of compliance with antihypertensive therapy and dietary restrictions. If blood pressure is difficult to control by pharmacologic or dietary measures, the dose of Aranesp® should be reduced or withheld (see **DOSAGE AND ADMINISTRATION**). A clinically significant decrease in hemoglobin may not be observed for several weeks.

Seizures

Seizures have occurred in patients with CRF participating in clinical trials of Aranesp® and Epoetin alfa. During the first several months of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely. While the relationship between seizures and the rate of rise of

hemoglobin is uncertain, it is recommended that the dose of Aranesp® be decreased if the hemoglobin increase exceeds 1 g/dL in any 2-week period.

Pure Red Cell Aplasia

Cases of pure red cell aplasia (PRCA) and of severe anemia, with or without other cytopenias, associated with neutralizing antibodies to erythropoietin have been reported in patients treated with Aranesp®. This has been reported predominantly in patients with CRF receiving Aranesp® by subcutaneous administration. Any patient who develops a sudden loss of response to Aranesp®, accompanied by severe anemia and low reticulocyte count, should be evaluated for the etiology of loss of effect, including the presence of neutralizing antibodies to erythropoietin (see **PRECAUTIONS: Lack or Loss of Response to Aranesp®**). If anti-erythropoietin antibody-associated anemia is suspected, withhold Aranesp® and other erythropoietic proteins. Contact Amgen (1-800-77AMGEN) to perform assays for binding and neutralizing antibodies. Aranesp® should be permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other erythropoietic proteins as antibodies may cross-react (see **ADVERSE REACTIONS: Immunogenicity**).

Albumin (Human)

Aranesp® is supplied in two formulations with different excipients, one containing polysorbate 80 and another containing albumin (human), a derivative of human blood (see **DESCRIPTION**). Based on effective donor screening and product manufacturing processes, Aranesp® formulated with albumin carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS

General

The safety and efficacy of Aranesp® therapy have not been established in patients with underlying hematologic diseases (e.g., hemolytic anemia, sickle cell anemia, thalassemia, porphyria).

The needle cover of the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Lack or Loss of Response to Aranesp®

A lack of response or failure to maintain a hemoglobin response with Aranesp® doses within the recommended dosing range should prompt a search for causative factors. Deficiencies of folic acid, iron, or vitamin B_{12} should be excluded or corrected. Depending on the clinical setting, intercurrent infections, inflammatory or malignant processes, osteofibrosis cystica, occult blood loss, hemolysis, severe aluminum toxicity, and bone marrow fibrosis may compromise an erythropoietic response. In the absence of another etiology, the patient should be evaluated for evidence of PRCA and sera should be tested for the presence of antibodies to erythropoietin (see **WARNINGS: Pure Red Cell Aplasia**).

Hematology

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of Aranesp® before adjusting the dose. Because of the time required for erythropoiesis and the RBC half-life, an interval of 2 to 6 weeks may occur between the time of a dose adjustment (initiation, increase, decrease, or discontinuation) and a significant change in hemoglobin.

In order to prevent the hemoglobin from exceeding the recommended target (12 g/dL) or rising too rapidly (greater than 1 g/dL in 2 weeks), the guidelines for dose and frequency of dose adjustments should be followed (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

Allergic Reactions

There have been rare reports of potentially serious allergic reactions, including skin rash and urticaria, associated with Aranesp®. Symptoms have recurred with rechallenge, suggesting a causal relationship exists in some instances. If a serious allergic or anaphylactic reaction occurs, Aranesp® should be immediately and permanently discontinued and appropriate therapy should be administered.

Patients with CRF Not Requiring Dialysis

Patients with CRF not yet requiring dialysis may require lower maintenance doses of Aranesp® than patients receiving dialysis. Though predialysis patients generally receive less frequent monitoring of blood pressure and laboratory parameters than dialysis patients, predialysis patients may be more responsive to the effects of Aranesp®, and require judicious monitoring of blood pressure and hemoglobin. Renal function and fluid and electrolyte balance should also be closely monitored.

Dialysis Management

Therapy with Aranesp® results in an increase in RBCs and a decrease in plasma volume, which could reduce dialysis efficiency; patients who are marginally dialyzed may require adjustments in their dialysis prescription.

Laboratory Tests

After initiation of Aranesp® therapy, the hemoglobin should be determined weekly until it has stabilized and the maintenance dose has been established (see **DOSAGE AND ADMINISTRATION**). After a dose adjustment, the hemoglobin should be determined weekly for at least 4 weeks, until it has been determined that the hemoglobin has stabilized in response to the dose change. The hemoglobin should then be monitored at regular intervals.

In order to ensure effective erythropoiesis, iron status should be evaluated for all patients before and during treatment, as the majority of patients will eventually require supplemental iron therapy. Supplemental iron therapy is recommended for all patients whose serum ferritin is below 100 mcg/L or whose serum transferrin saturation is below 20%.

Information for Patients

Patients should be informed of the increased risks of mortality, serious cardiovascular events, thromboembolic events, and tumor progression when used in off-label dose regimens or populations (see **WARNINGS**). Patients should be informed of the possible side effects of Aranesp® and be instructed to report them to the prescribing physician. Patients should be informed of the signs and symptoms of allergic drug reactions and be advised of appropriate actions. Patients should be counseled on the importance of compliance with their Aranesp® treatment, dietary and dialysis prescriptions, and the importance of judicious monitoring of blood pressure and hemoglobin concentration should be stressed.

It is recommended that Aranesp® should be administered by a healthcare professional. In those rare cases where it is determined that a patient can safely and effectively administer Aranesp® at home, appropriate instruction on the proper use of Aranesp® should be provided for patients and their caregivers, including careful review of the accompanying “Information for Patients” insert. Patients and caregivers should also be cautioned against the reuse of needles, syringes, prefilled SureClick™ autoinjectors, or drug product, and be thoroughly instructed in their proper disposal. A puncture-resistant container for the disposal of used syringes, autoinjectors, and needles should be made available to the patient. Patients should be informed that the needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex), which should not be handled by persons sensitive to latex.

Drug Interactions

No formal drug interaction studies of Aranesp® have been performed.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenicity: The carcinogenic potential of Aranesp® has not been evaluated in long-term animal studies. Aranesp® did not alter the proliferative response of non-hematological cells in vitro or in vivo. In toxicity studies of approximately 6 months duration in rats and dogs, no tumorigenic or unexpected mitogenic responses were observed in any tissue type. Using a panel of human tissues, the in vitro tissue binding profile of Aranesp® was identical to Epoetin alfa. Neither molecule bound to human tissues other than those expressing the erythropoietin receptor.

Mutagenicity: Aranesp® was negative in the in vitro bacterial and CHO cell assays to detect mutagenicity and in the in vivo mouse micronucleus assay to detect clastogenicity.

Impairment of Fertility: When administered intravenously to male and female rats prior to and during mating, reproductive performance, fertility, and sperm assessment parameters were not affected at any doses evaluated (up to 10 mcg/kg/dose, administered 3 times weekly). An increase in post implantation fetal loss was seen at doses equal to or greater than 0.5 mcg/kg/dose, administered 3 times weekly.

Pregnancy Category C

When Aranesp® was administered intravenously to rats and rabbits during gestation, no evidence of a direct embryotoxic, fetotoxic, or teratogenic outcome was observed at doses up to 20 mcg/kg/day. The only adverse effect observed was a slight reduction in fetal weight, which occurred at doses causing exaggerated pharmacological effects in the dams (1 mcg/kg/day and higher). No deleterious effects on uterine implantation were seen in either species. No significant placental transfer of Aranesp® was observed in rats. An increase in post implantation fetal loss was observed in studies assessing fertility (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility: Impairment of Fertility**).

Intravenous injection of Aranesp® to female rats every other day from day 6 of gestation through day 23 of lactation at doses of 2.5 mcg/kg/dose and higher resulted in offspring (F1 generation) with decreased body weights, which correlated with a low incidence of deaths, as well as delayed eye opening and delayed preputial separation. No adverse effects were seen in the F2 offspring.

There are no adequate and well-controlled studies in pregnant women. Aranesp® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether Aranesp® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Aranesp® is administered to a nursing woman.

Pediatric Use

Pediatric CRF Patients

A study of the conversion from Epoetin alfa to Aranesp® among pediatric CRF patients over 1 year of age showed similar safety and efficacy to the findings from adult conversion studies (see **CLINICAL PHARMACOLOGY** and **CLINICAL STUDIES**). Safety and efficacy in the initial treatment of anemic pediatric CRF patients or in the conversion from another erythropoietin to Aranesp® in pediatric CRF patients less than 1 year of age have not been established.

Pediatric Cancer Patients

The safety and efficacy of Aranesp® in pediatric cancer patients have not been established.

Geriatric Use

Of the 1598 CRF patients in clinical studies of Aranesp®, 42% were age 65 and over, while 15% were age 75 and over. Of the 873 cancer patients in clinical studies receiving Aranesp® and concomitant

chemotherapy, 45% were age 65 and over, while 14% were age 75 and over. No overall differences in safety or efficacy were observed between older and younger patients.

ADVERSE REACTIONS

General

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of Aranesp® cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Neutralizing antibodies to erythropoietin, in association with PRCA or severe anemia (with or without other cytopenias), have been reported in patients receiving Aranesp® (see **WARNINGS: Pure Red Cell Aplasia**) during post-marketing experience.

In clinical studies, the percentage of patients with antibodies to Aranesp® was examined using the BIAcore assay. Sera from 1501 CRF patients and 1159 cancer patients were tested. At baseline, prior to Aranesp® treatment, binding antibodies were detected in 59 (4%) of CRF patients and 36 (3%) of cancer patients. While receiving Aranesp® therapy (range 22-177 weeks), a follow-up sample was taken. One additional CRF patient and eight additional cancer patients developed antibodies capable of binding Aranesp®. None of the patients had antibodies capable of neutralizing the activity of Aranesp® or endogenous erythropoietin at baseline or at end of study. No clinical sequelae consistent with PRCA were associated with the presence of these antibodies.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies across products within this class (erythropoietic proteins) may be misleading.

Chronic Renal Failure Patients

Adult Patients

In all studies, the most frequently reported serious adverse reactions with Aranesp® were vascular access thrombosis, congestive heart failure, sepsis, and cardiac arrhythmia. The most commonly reported adverse reactions were infection, hypertension, hypotension, myalgia, headache, and diarrhea (see **WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events** and **Hypertension**). The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Aranesp®, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were hypotension, hypertension, fever, myalgia, nausea, and chest pain.

The data described below reflect exposure to Aranesp® in 1598 CRF patients, including 675 exposed for at least 6 months, of whom 185 were exposed for greater than 1 year. Aranesp® was evaluated in active-controlled (n = 823) and uncontrolled studies (n = 775).

The rates of adverse events and association with Aranesp® are best assessed in the results from studies in which Aranesp® was used to stimulate erythropoiesis in patients anemic at study baseline (n = 348), and, in particular, the subset of these patients in randomized controlled trials (n = 276). Because there were no substantive differences in the rates of adverse reactions between these subpopulations, or between these subpopulations and the entire population of patients treated with Aranesp®, data from all 1598 patients were pooled.

The population encompassed an age range from 18 to 91 years. Fifty-seven percent of the patients were male. The percentages of Caucasian, Black, Asian, and Hispanic patients were 83%, 11%, 3%, and 1%,

respectively. The median weekly dose of Aranesp® was 0.45 mcg/kg (25th, 75th percentiles: 0.29, 0.66 mcg/kg).

Some of the adverse events reported are typically associated with CRF, or recognized complications of dialysis, and may not necessarily be attributable to Aranesp® therapy. No important differences in adverse event rates between treatment groups were observed in controlled studies in which patients received Aranesp® or other recombinant erythropoietins.

The data in Table 1 reflect those adverse events occurring in at least 5% of patients treated with Aranesp®.

Table 1. Adverse Events Occurring in ≥ 5% of CRF Patients

Event	Patients Treated with Aranesp® (n = 1598)
APPLICATION SITE	
Injection Site Pain	7%
BODY AS A WHOLE	
Peripheral Edema	11%
Fatigue	9%
Fever	9%
Death	7%
Chest Pain, Unspecified	6%
Fluid Overload	6%
Access Infection	6%
Influenza-like Symptoms	6%
Access Hemorrhage	6%
Asthenia	5%
CARDIOVASCULAR	
Hypertension	23%
Hypotension	22%
Cardiac Arrhythmias/Cardiac Arrest	10%
Angina Pectoris/Cardiac Chest Pain	8%
Thrombosis Vascular Access	8%
Congestive Heart Failure	6%
CNS/PNS	
Headache	16%
Dizziness	8%
GASTROINTESTINAL	
Diarrhea	16%
Vomiting	15%
Nausea	14%
Abdominal Pain	12%
Constipation	5%
MUSCULO-SKELETAL	
Myalgia	21%
Arthralgia	11%
Limb Pain	10%
Back Pain	8%

(Continued)

Table 1. Adverse Events Occurring in ≥ 5% of CRF Patients (Continued)

Event	Patients Treated with Aranesp® (n = 1598)
RESISTANCE MECHANISM	
Infection[a]	27%
RESPIRATORY	
Upper Respiratory Infection	14%
Dyspnea	12%
Cough	10%
Bronchitis	6%
SKIN AND APPENDAGES	
Pruritus	8%

[a] Infection includes sepsis, bacteremia, pneumonia, peritonitis, and abscess.

The incidence rates for other clinically significant events are shown in Table 2.

Table 2. Percent Incidence of Other Clinically Significant Events in CRF Patients

Event	Patients Treated with Aranesp® (n = 1598)
Acute Myocardial Infarction	2%
Seizure	1%
Stroke	1%
Transient Ischemic Attack	1%

Pediatric Patients

In Study N5, Aranesp® was administered to 81 pediatric CRF patients who had stable hemoglobin concentrations while previously receiving Epoetin alfa (see **CLINICAL STUDIES**). In this study, the most frequently reported serious adverse reactions with Aranesp® were fever and dialysis access infection. The most commonly reported adverse reactions were fever, headache, upper respiratory infection, hypertension, hypotension, injection site pain, and cough. Aranesp® administration was discontinued because of injection site pain in two patients and moderate hypertension in a third patient.

Studies have not evaluated the effects of Aranesp® when administered to pediatric patients as the initial treatment for the anemia associated with CRF.

Thrombotic Events

Vascular access thrombosis in hemodialysis patients occurred in clinical trials at an annualized rate of 0.22 events per patient year of Aranesp® therapy. Rates of thrombotic events (e.g., vascular access thrombosis, venous thrombosis, and pulmonary emboli) with Aranesp® therapy were similar to those observed with other recombinant erythropoietins in these trials; the median duration of exposure was 12 weeks.

Cancer Patients Receiving Chemotherapy

The incidence data described below reflect the exposure to Aranesp® in 873 cancer patients including patients exposed to Aranesp® QW (547, 63%), Q2W (128, 16%), and Q3W (198, 23%). Aranesp® was

evaluated in seven studies that were active-controlled and/or placebo-controlled studies of up to 6 months duration. The Aranesp®-treated patient demographics were as follows: median age of 63 years (range of 20 to 91 years); 40% male; 88% Caucasian, 5% Hispanic, 4% Black, and 3% Asian. Over 90% of patients had locally advanced or metastatic cancer, with the remainder having early stage disease. Patients with solid tumors (e.g., lung, breast, colon, ovarian cancers) and lymphoproliferative malignancies (e.g., lymphoma, multiple myeloma) were enrolled in the clinical studies. All of the 873 Aranesp®-treated subjects also received concomitant cyclic chemotherapy.

The most frequently reported serious adverse events included death (10%), fever (4%), pneumonia (3%), dehydration (3%), vomiting (2%), and dyspnea (2%). The most commonly reported adverse events were fatigue, edema, nausea, vomiting, diarrhea, fever, and dyspnea (see **Table 3**). Except for those events listed in Tables 3 and 4, the incidence of adverse events in clinical studies occurred at a similar rate compared with patients who received placebo and were generally consistent with the underlying disease and its treatment with chemotherapy. The most frequently reported reasons for discontinuation of Aranesp® were progressive disease, death, discontinuation of the chemotherapy, asthenia, dyspnea, pneumonia, and gastrointestinal hemorrhage. No important differences in adverse event rates between treatment groups were observed in controlled studies in which patients received Aranesp® or other recombinant erythropoietins.

Table 3. Adverse Events Occurring in ≥ 5% of Patients Receiving Chemotherapy

Event	Aranesp® (n = 873)	Placebo (n = 221)
BODY AS A WHOLE		
Fatigue	33%	30%
Edema	21%	10%
Fever	19%	16%
CNS/PNS		
Dizziness	14%	8%
Headache	12%	9%
GASTROINTESTINAL		
Diarrhea	22%	12%
Constipation	18%	17%
METABOLIC/NUTRITION		
Dehydration	5%	3%
MUSCULO-SKELETAL		
Arthralgia	13%	6%
Myalgia	8%	5%
SKIN AND APPENDAGES		
Rash	7%	3%

Table 4. Incidence of Other Clinically Significant Adverse Events in Patients Receiving Chemotherapy

Event	All Aranesp® (n = 873)	Placebo (n = 221)
Hypertension	3.7%	3.2%
Seizures/Convulsions[a]	0.6%	0.5%
Thrombotic Events	6.2%	4.1%
Pulmonary Embolism	1.3%	0.0%
Thrombosis[b]	5.6%	4.1%

[a] Seizures/Convulsions include the preferred terms: Convulsions, Convulsions Grand Mal, and Convulsions Local.

[b] Thrombosis includes: Thrombophlebitis, Thrombophlebitis Deep, Thrombosis Venous, Thrombosis Venous Deep, Thromboembolism, and Thrombosis.

In a randomized controlled trial of Aranesp® 500 mcg Q3W (n = 353) and Aranesp® 2.25 mcg/kg QW (n = 352), the incidences of all adverse events and of serious adverse events were similar between the two groups.

Thrombotic and Cardiovascular Events

Overall, the incidence of thrombotic events was 6.2% for Aranesp® and 4.1% for placebo. However, the following events were reported more frequently in Aranesp®-treated patients than in placebo controls: pulmonary embolism, thromboembolism, thrombosis, and thrombophlebitis (deep and/or superficial). In addition, edema of any type was more frequently reported in Aranesp®-treated patients (21%) than in patients who received placebo (10%).

OVERDOSAGE

The expected manifestations of Aranesp® overdosage include signs and symptoms associated with an excessive and/or rapid increase in hemoglobin concentration, including any of the cardiovascular events described in **WARNINGS** and listed in **ADVERSE REACTIONS**. Patients receiving an overdosage of Aranesp® should be monitored closely for cardiovascular events and hematologic abnormalities. Polycythemia should be managed acutely with phlebotomy, as clinically indicated. Following resolution of the effects due to Aranesp® overdosage, reintroduction of Aranesp® therapy should be accompanied by close monitoring for evidence of rapid increases in hemoglobin concentration (> 1 g/dL in any 2-week period). In patients with an excessive hematopoietic response, reduce the Aranesp® dose in accordance with the recommendations described in **DOSAGE AND ADMINISTRATION**.

DOSAGE AND ADMINISTRATION

General

IMPORTANT: Use the lowest dose of Aranesp® that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for RBC transfusion (see BOXED WARNINGS and WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events). Aranesp® dosing regimens are different for each of the indications described in this section of the package insert. Aranesp® should be administered under the supervision of a healthcare professional. The dosages recommended below are based upon those used in clinical studies supporting marketing approval.

Aranesp® is supplied in vials or in prefilled syringes with UltraSafe® Needle Guards*. Following administration of Aranesp® from the prefilled syringe, the UltraSafe® Needle Guard should be activated to prevent accidental needle sticks.

Aranesp® is also supplied in prefilled SureClick™ autoinjectors containing the same dosage strengths as the prefilled syringes. Because the autoinjectors are designed to deliver the full content, autoinjectors should only be used for patients who need the full dose. If the required dose is not available in an autoinjector, prefilled syringes, or vials should be used to administer the required dose. Autoinjectors are for subcutaneous administration only.

Chronic Renal Failure Patients

Aranesp® is administered either IV or SC as a single weekly injection. ***In patients on hemodialysis, the IV route is recommended*.** The dose should be started and slowly adjusted as described below based on hemoglobin levels. If a patient fails to respond or maintain a response, this should be evaluated (see **WARNINGS: Pure Red Cell Aplasia, PRECAUTIONS: Lack or Loss of Response to Aranesp®** and **PRECAUTIONS: Laboratory Tests**). When Aranesp® therapy is initiated or adjusted, the hemoglobin should be followed weekly until stabilized and monitored at least monthly thereafter.

For patients who respond to Aranesp® with a rapid increase in hemoglobin (e.g., more than 1 g/dL in any 2-week period), the dose of Aranesp® should be reduced.

The dose should be adjusted for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL.

Starting Dose

Correction of Anemia

The recommended starting dose of Aranesp® for the correction of anemia in adult CRF patients is 0.45 mcg/kg body weight, administered as a single IV or SC injection once weekly. Because of individual variability, doses should be titrated to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL (see **DOSAGE AND ADMINISTRATION**).

The use of Aranesp® in pediatric CRF patients as the initial treatment to correct anemia has not been studied.

Maintenance Dose

Aranesp® dosage should be adjusted to maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL. Doses must be individualized to ensure that hemoglobin is maintained at an appropriate level for each patient (see **Dose Adjustment**). For many patients, the appropriate maintenance dose will be lower than the starting dose. Predialysis patients, in particular, may require lower maintenance doses. Some patients have been treated successfully with a SC dose of Aranesp® administered once every 2 weeks.

Dose Adjustment

The dose should be adjusted for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL.

Increases in dose should not be made more frequently than once a month. If the hemoglobin is increasing and approaching 12 g/dL, the dose should be reduced by approximately 25%. If the hemoglobin continues to increase, doses should be temporarily withheld until the hemoglobin begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose. If the hemoglobin increases by more than 1 g/dL in a 2-week period, the dose should be decreased by approximately 25%.

If the increase in hemoglobin is less than 1 g/dL over 4 weeks and iron stores are adequate (see **PRECAUTIONS: Laboratory Tests**), the dose of Aranesp® may be increased by approximately 25% of the previous dose. Further increases may be made at 4-week intervals until the specified hemoglobin is obtained.

Conversion From Epoetin alfa to Aranesp®

The starting weekly dose of Aranesp® for adults and pediatric patients should be estimated on the basis of the weekly Epoetin alfa dose at the time of substitution (see **Table 5**). For pediatric patients receiving a weekly Epoetin alfa dose of < 1500 units/week, the available data are insufficient to determine an Aranesp® conversion dose. Because of individual variability, doses should be titrated to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL. Due to the longer serum half-life, Aranesp® should be administered less frequently than Epoetin alfa. Aranesp® should be administered once a week if a patient was receiving Epoetin alfa 2 to 3 times weekly. Aranesp® should be administered once every 2 weeks if a patient was receiving Epoetin alfa once per week. The route of administration (IV or SC) should be maintained.

Table 5. Estimated Aranesp® Starting Doses (mcg/week) for Patients Based on Previous Epoetin alfa Dose (Units/week)

Previous Weekly Epoetin alfa Dose (Units/week)	Weekly Aranesp® Dose (mcg/week)	
	Adult	Pediatric
< 1,500	6.25	See text*
1,500 to 2,499	6.25	6.25
2,500 to 4,999	12.5	10
5,000 to 10,999	25	20
11,000 to 17,999	40	40
18,000 to 33,999	60	60
34,000 to 89,999	100	100
≥ 90,000	200	200

*For pediatric patients receiving a weekly Epoetin alfa dose of < 1,500 units/week, the available data are insufficient to determine an Aranesp® conversion dose.

Cancer Patients Receiving Chemotherapy

For pediatric patients, see **PRECAUTIONS: Pediatric Use**.

The recommended starting dose for Aranesp® administered weekly is 2.25 mcg/kg as a SC injection.

The recommended starting dose for Aranesp® administered once-every-3-weeks (Q3W) is 500 mcg as a SC injection.

For both dosing schedules, the dose should be adjusted for each patient to maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL. If the rate of hemoglobin increase is more than 1 g/dL per 2-week period or when the hemoglobin exceeds 11 g/dL, the dose should be reduced by 40% of the previous dose. If the hemoglobin exceeds 12 g/dL, Aranesp® should be temporarily withheld until the hemoglobin falls to 11 g/dL. At this point, therapy should be reinitiated at a dose 40% below the previous dose.

For patients receiving weekly administration, if there is less than a 1 g/dL increase in hemoglobin after 6 weeks of therapy, the dose of Aranesp® should be increased up to 4.5 mcg/kg.

Preparation and Administration of Aranesp®

Do not shake Aranesp® or leave vials, syringes, or prefilled SureClick™ autoinjectors exposed to bright light. After removing the vials, prefilled syringes, or autoinjectors from the cartons, keep them covered to protect from room light until administration. Vigorous shaking or exposure to light may denature Aranesp®, causing it to become biologically inactive. Always store vials, prefilled syringes, or autoinjectors of Aranesp® in their carton until use.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials, prefilled syringes, or autoinjectors exhibiting particulate matter or discoloration.

Do not dilute Aranesp®.

Do not administer Aranesp® in conjunction with other drug solutions.

Aranesp® contains no preservatives. Discard any unused portion. **Do not pool unused portions from the vials or prefilled syringes. Do not use the vial, prefilled syringe, or autoinjector more than one time.**

Following administration of Aranesp® from the prefilled syringe, activate the UltraSafe® Needle Guard. Place your hands behind the needle, grasp the guard with one hand, and slide the guard forward until the needle is completely covered and the guard clicks into place. NOTE: If an audible click is not heard, the needle guard may not be completely activated.

The prefilled SureClick™ autoinjector is designed to deliver the full dose. The completion of the injection is signaled by an audible click. Removal of the autoinjector from the injection site automatically extends a needle cover.

The autoinjectors, the syringes used with vials, and the entire prefilled syringe with activated needle guard should be disposed of in a puncture-proof container.

See the accompanying “Information for Patients” leaflet for complete instructions on the preparation and administration of Aranesp® for patients, including injection site selection.

HOW SUPPLIED

Aranesp® is available in single-dose vials in two solutions, an albumin solution and a polysorbate solution. The words “Albumin Free” appear on the polysorbate container labels and the package main panels as well as other panels as space permits. Aranesp® single-dose prefilled syringes and prefilled SureClick™ autoinjectors are available in albumin and polysorbate solutions. Both prefilled syringes and autoinjectors are supplied with a 27-gauge, ½-inch needle.

Each prefilled syringe is equipped with an UltraSafe® Needle Guard that is manually activated to cover the needle during disposal. The needle cover of the prefilled syringe contains dry natural rubber (a derivative of latex). The autoinjector has a needle cover that automatically extends as the autoinjector is removed from the injection site after completion of the injection.

Aranesp® is available in the following packages:

Single-dose Vial, Polysorbate Solution

1 Vial/Pack, 4 Packs/Case	**4 Vials/Pack, 4 Packs/Case**	**4 Vials/Pack, 10 Packs/Case**
200 mcg/1 mL (NDC 55513-006-01)	200 mcg/1 mL (NDC 55513-006-04)	25 mcg/1 mL (NDC 55513-002-04)
300 mcg/1 mL (NDC 55513-110-01)	300 mcg/1 mL (NDC 55513-110-04)	40 mcg/1 mL (NDC 55513-003-04)
500 mcg/1 mL (NDC 55513-008-01)		60 mcg/1 mL (NDC 55513-004-04)
		100 mcg/1 mL (NDC 55513-005-04)
		150 mcg/0.75 mL (NDC 55513-053-04)

Single-dose Vial, Albumin Solution

1 Vial/Pack, 4 Packs/Case	**4 Vials/Pack, 4 Packs/Case**	**4 Vials/Pack, 10 Packs/Case**
200 mcg/1 mL (NDC 55513-014-01)	200 mcg/1 mL (NDC 55513-014-04)	25 mcg/1 mL (NDC 55513-010-04)
300 mcg/1 mL (NDC 55513-015-01)	300 mcg/1 mL (NDC 55513-015-04)	40 mcg/1 mL (NDC 55513-011-04)
500 mcg/1 mL (NDC 55513-016-01)		60 mcg/1 mL (NDC 55513-012-04)
		100 mcg/1 mL (NDC 55513-013-04)
		150 mcg/0.75 mL (NDC 55513-054-04)

Single-dose Prefilled Syringe (SingleJect®) with a 27-gauge, ½-inch needle with an UltraSafe® Needle Guard, Polysorbate Solution

1 Syringe/Pack, 4 Packs/Case	**4 Syringes/Pack, 4 Packs/Case**	**4 Syringes/Pack, 10 Packs/Case**
200 mcg/0.4 mL (NDC 55513-028-01)	200 mcg/0.4 mL (NDC 55513-028-04)	25 mcg/0.42 mL (NDC 55513-057-04)
300 mcg/0.6 mL (NDC 55513-111-01)	300 mcg/0.6 mL (NDC 55513-111-04)	40 mcg/0.4 mL (NDC 55513-021-04)
500 mcg/1 mL (NDC 55513-032-01)		60 mcg/0.3 mL (NDC 55513-023-04)
		100 mcg/0.5 mL (NDC 55513-025-04)
		150 mcg/0.3 mL (NDC 55513-027-04)

Single-dose Prefilled Syringe (SingleJect®) with a 27-gauge, ½-inch needle with an UltraSafe® Needle Guard, Albumin Solution

1 Syringe/Pack, 4 Packs/Case	**4 Syringes/Pack, 4 Packs/Case**	**4 Syringes/Pack, 10 Packs/Case**
200 mcg/0.4 mL (NDC 55513-044-01)	200 mcg/0.4 mL (NDC 55513-044-04)	25 mcg/0.42 mL (NDC 55513-058-04)
300 mcg/0.6 mL (NDC 55513-046-01)	300 mcg/0.6 mL (NDC 55513-046-04)	40 mcg/0.4 mL (NDC 55513-037-04)
500 mcg/1 mL (NDC 55513-048-01)		60 mcg/0.3 mL (NDC 55513-039-04)
		100 mcg/0.5 mL (NDC 55513-041-04)
		150 mcg/0.3 mL (NDC 55513-043-04)

Single-dose prefilled SureClick™ Autoinjector with a 27-gauge, ½-inch needle, Polysorbate Solution

1 Autoinjector/Pack

25 mcg/0.42 mL
(NDC 55513-090-01)

40 mcg/0.4 mL
(NDC 55513-091-01)

60 mcg/0.3 mL

(NDC 55513-092-01)

100 mcg/0.5 mL
(NDC 55513-093-01)

150 mcg/0.3 mL
(NDC 55513-094-01)

200 mcg/0.4 mL
(NDC 55513-095-01)

300 mcg/0.6 mL
(NDC 55513-096-01)

500 mcg/1 mL
(NDC 55513-097-01)

Single-dose prefilled SureClick™ Autoinjector with a 27-gauge, ½-inch needle, Albumin Solution

1 Autoinjector/Pack

25 mcg/0.42 mL
(NDC 55513-080-01)

40 mcg/0.4 mL
(NDC 55513-081-01)

60 mcg/0.3 mL
(NDC 55513-082-01)

100 mcg/0.5 mL
(NDC 55513-083-01)

150 mcg/0.3 mL
(NDC 55513-084-01)

200 mcg/0.4 mL
(NDC 55513-085-01)

300 mcg/0.6 mL
(NDC 55513-086-01)

500 mcg/1 mL
(NDC 55513-087-01)

Storage

Store at 2° to 8°C (36° to 46°F). Do not freeze or shake. Protect from light.

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Rx only

This product, or its use, may be covered by one or more US Patents, including US Patent No. 5,618,698, in addition to others including patents pending.

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