## Table of Contents

## List of Tables



## List of Figures

## INTRODUCTION

The approval of the first recombinant erythropoiesis-stimulating agent (ESA), Epoetin alfa, in 1989 represented an important scientific breakthrough in medicine and revolutionized the care of patients with anemia of chronic renal failure (CRF). Amgen Inc. (Amgen), the United States (US) license holder of Epoetin alfa and darbepoetin alfa, developed erythropoiesis-stimulating agents (ESAs) as supportive therapies to stimulate red blood cell (RBC) production in order to elevate and maintain hemoglobin concentrations in patients with CRF and anemia in order to avoid RBC transfusions and improve patient reported outcomes (PRO). The ability to produce erythropoietin (the hormone produced by the kidneys to stimulate RBC formation) is impaired in chronic kidney disease (CKD) patients and this impairment is the primary cause of anemia in this disease. In the US, Epoetin alfa is marketed under the trade names EPOGEN® by Amgen for the treatment of anemia in dialysis, and PROCRIT® by Centocor Ortho Biotech Inc. for the treatment of anemia in CKD not on dialysis (NOD). Darbepoetin alfa is marketed under the trade name Aranesp® by Amgen for both CKD-NOD and dialysis. Amgen will focus its comments on the use of EPOGEN® in dialysis and Aranesp® in CKD-NOD, while Centocor Ortho Biotech Inc. will provide comments on PROCRIT®. In this document, the term chronic renal failure (CRF) will be used when referring to the US Food and Drug Administration (FDA)-approved label; otherwise the more commonly employed term, CKD, will be used. Additionally, the term ESA will be used when referring to this class of drugs.

ESAs are used to elevate or maintain RBC levels (as manifested by the hemoglobin or hematocrit determinations) and to decrease the need for RBC transfusions. EPOGEN® and Aranesp® are approved for the treatment of anemia associated with CRF, which includes patients receiving and not receiving dialysis. Amgen has prepared this document in response to the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) meeting scheduled by the Centers for Medicare and Medicaid Services (CMS) to review the available evidence on the use of erythropoiesis-stimulating agents (ESAs) to manage anemia in patients who have chronic kidney disease. Since the regulatory approval of ESAs for the treatment of anemia in CKD, safety concerns have been raised based on the results of randomized controlled trials (RCTs) designed to evaluate the potential for cardiovascular (CV) and survival benefit when normalizing hemoglobin with ESAs. These trials treated patients to higher hemoglobin targets—

above the current labeled range (hemoglobin 10-12 g/dL); the hemoglobin targets evaluated in these studies do not reflect how ESAs are used in clinical practice.

There are significant differences in the characteristics of dialysis and CKD-NOD patients, including demographic characteristics, the extent of morbidity and mortality, and the intensity of clinical management required for their treatment[1, 2]. Most notable among these differences is that dialysis patients have significantly more co-morbid conditions, such as: diabetes, hypertension, heart failure, infectious complications, and a more profound erythropoietin deficiency. These patients are subject to continuous blood loss from the dialysis procedure, which results in more profound anemia that is nearly universal in the absence of treatment. Dialysis patients depend on regular dialysis treatments to sustain life; typically, death ensues within two weeks when dialysis treatment is withdrawn[3].

**In dialysis patients**, ESAs are an important therapy in the management of anemia and have a positive benefit to risk profile when used according to the FDA-approved label to reduce the need for RBC transfusions. ESAs are effective at increasing hemoglobin levels in order to reduce the need for transfusions and to improve physical function and exercise tolerance in dialysis patients. Transfusion avoidance protects against cumulative hazards, especially allo-sensitization, which is the generation of antibodies to foreign antigens that may impair or preclude eligibility for renal transplant, and increase the likelihood of transplant rejection. Even the recent technique of removing white cells from blood prior to transfusion (leuko-reduction) does not decrease the hazard of allo-sensitization[4]. Clinical trials and observational data have demonstrated that the risk of transfusion increases substantially when hemoglobin levels fall below 10 g/dL; this supports 10 g/dL as the appropriate lower limit for clinical benefit and aligns with the labeled range. With increasing hemoglobin, the transfusion benefit continuously improves through the labeled hemoglobin range of 12 g/dL. Because of the intrinsic hemoglobin variability seen in dialysis patients, a 2 g/dL range is appropriate, thus supporting the upper hemoglobin level of 12 g/dL, aligning with the label. The hemoglobin target range accommodates hemoglobin variability and allows physicians to treat individual patients to attain the hemoglobin level necessary to avoid transfusion. Additionally, near-complete surveillance of the dialysis population has not provided evidence of an increased rate of death when patients are treated to the FDA-approved ESA labeled hemoglobin range. The evidence supports that the labeled hemoglobin range of 10 to 12 g/dL is necessary and prudent to maximize the benefit of transfusion

avoidance in a way that recognizes and minimizes the risk of cardiovascular (CV) events that have been observed in trials of high hemoglobin targets (≥ 13 g/dL). This range allows physicians to manage anemia in dialysis patients effectively.

**In CKD-NOD patients,** while the prevalence of anemia is lower, anemia can be severe in some patients and transfusions are more common than has been appreciated. Among those with severe anemia, the administration of ESAs is appropriate to avoid the risks of transfusion, and, in particular, the risk of allo-sensitization, which can reduce both transplant eligibility and graft survival. ESA therapy should be initiated when hemoglobin levels decline below 10 g/dL and patients are iron replete. The demonstrated benefit of transfusion reduction with ESA use is observed when hemoglobin levels are treated to above 10 g/dL. ESA therapy should be individualized to achieve and maintain hemoglobin between 10 and 12 g/dL. As with dialysis patients, CKD-NOD patients demonstrate intrinsic hemoglobin variability and the practical limitations of managing hemoglobin require the use of a hemoglobin range in order to administer ESAs to maximize the clinical benefit for each patient. A hemoglobin level of 12 g/dL as the upper end of the hemoglobin range will allow physicians the necessary discretion to manage individual patients so as to reduce transfusions. Avoiding a hemoglobin target > 12 g/dL provides a safety margin against the higher hemoglobin target in the Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT) (≥ 13.0 g/dL) and the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) (~13.5 g/dL) where risks have been identified. The evidence supports that ESAs are an important therapy for anemic CKD-NOD patients in whom transfusion avoidance is a meaningful clinical goal and that ESAs have a positive benefit to risk profile when used according to the FDA-approved labeling in these patients. Nonetheless, in response to the results of the TREAT trial, Amgen is working with global regulatory authorities on potential changes to labeling to provide more detailed guidance to physicians on optimizing dosing to achieve hemoglobin levels within the target range. In addition, safety warnings have been strengthened; further labeling changes are likely.

In this evidence review and accompanying supporting documents, the use of ESAs in CKD patients on dialysis and CKD-NOD patients are presented separately. There is a technical summary at the end of the review which includes a) relevant citations including those reporting the results of the registrational trials, and b) evidence tables summarizing the published literature on transfusion patterns, costs of transfusions, hemoglobin variability, hospitalization, health resource utilization and patient reported

outcomes in CKD patients. These evidence tables include the most commonly cited references; a systematic review was not conducted.

## 1. CKD PATIENTS ON DIALYSIS

In 2007 in the US, there were over 527,000 patients with end-stage renal disease (ESRD) who required either dialysis or a kidney transplant for survival[2]. Typically, patients receive dialysis treatments three times per week. During each dialysis session, their blood is circulated through a dialyzer that removes solutes (such as urea and accumulated fluids that are normally removed by the kidney) and restores electrolyte balance. Dialysis treatment, while life sustaining, compounds the anemia[5] caused by deceased erythropoietin levels[6, 7]. Blood is lost during each dialysis procedure[5], from frequent blood sampling to monitor laboratory parameters, and from increased bleeding tendency attributable to anticoagulation (heparin) therapy administered during the dialysis. There is also an increased risk of gastrointestinal bleeding and re-bleeding after therapy in dialysis patients[8, 9]. Blood loss is estimated to be between 2.5 and 5.1 L (5-10 Units) of blood annually[5], up to double the normal circulating blood volume. Thus, there are many factors contributing to the anemia in dialysis patients, and, in the absence of ESA therapy, anemia is often times very severe.

### 1.1 Treatment of Anemia in Dialysis Patients Prior to ESAs

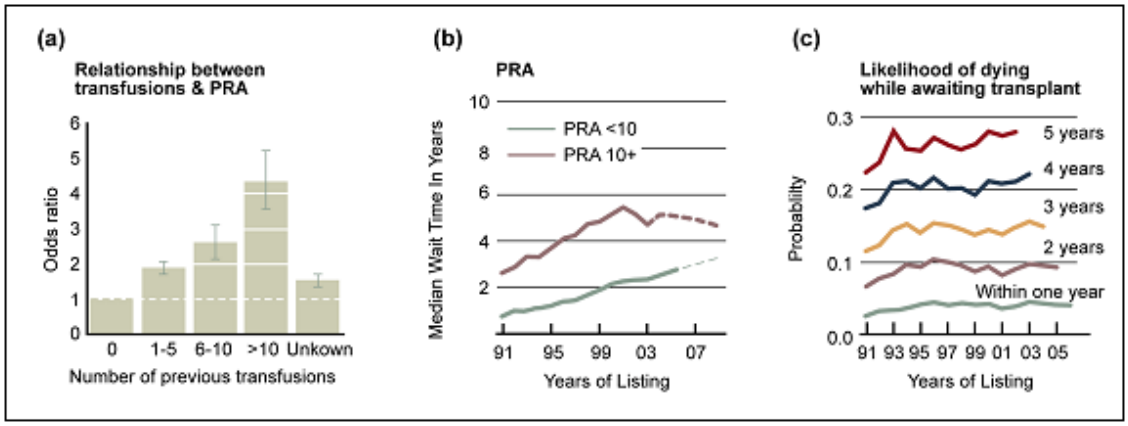
Prior to the development of ESAs, the treatment options for anemia were limited to RBC transfusions, and to a smaller extent, androgen and iron therapy[10]. Androgens and iron therapy had only modest efficacy and substantial side effects, leaving RBC transfusions as the mainstay of anemia therapy in the pre-ESA era. Data from the pre-ESA era indicate that patients had a mean hemoglobin of approximately 7 g/dL[11].

### 1.2 Adverse Sequelae of RBC Transfusion Therapy

RBC transfusions are by their nature only transiently effective in a population that is chronically unable to produce sufficient RBCs[12]. They carry a range of hazards including transmission of blood borne viral diseases, transfusion reactions, acute volume and potassium overload, and more chronically, iron overload[10, 13-16]. In the pre-ESA era, 55-60% of dialysis patients received transfusions to avoid severe anemia[11] (Amgen, data on file).

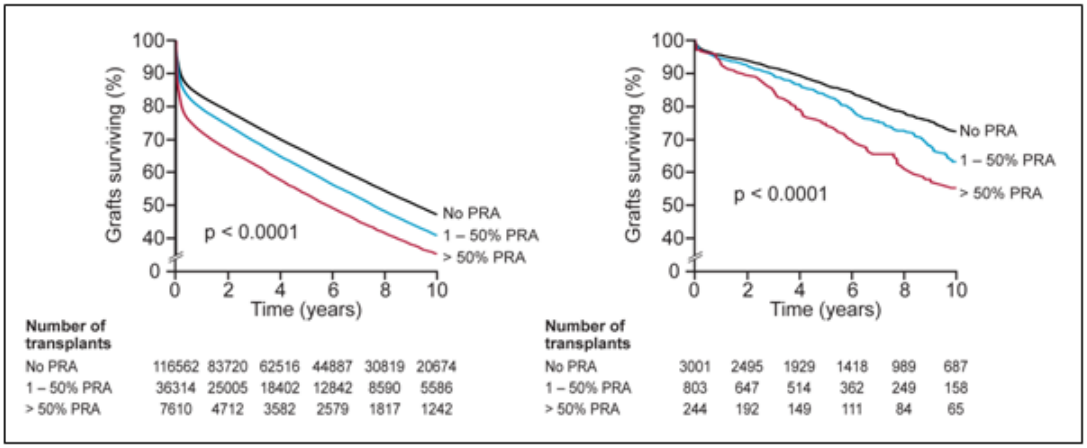
Perhaps the RBC transfusion risk that has the greatest impact on the lives of dialysis patients is the potential for allo-sensitization to foreign antigens[2, 17, 18], as development of such antibodies can *delay* or *preclude* kidney transplantation and impair the function of kidney transplants that do occur[2, 19] (Figure 1a-1c).

**Figure 1. (a) Relationship between the number of transfusions and the risk of allo-sensitization (measured as panel reactive antibody [PRA] > 50%; PRA measures anti-human antibodies in the blood)[18], (b) The median time spent on the transplant wait list by the level of allo-sensitization (measured as PRA < 10% versus > 10%) and (c) The likelihood of dying while waiting for transplant[2].**



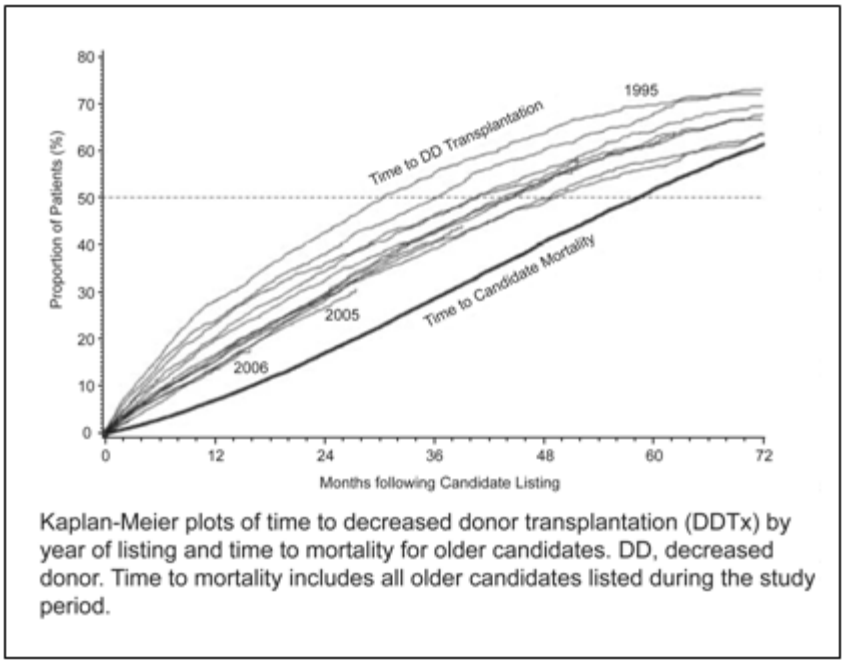

Early research suggested that a single transfusion event could result in sensitization in ~33% of patients[4]. More recent evidence using enhanced methods for detecting allo-sensitization (methods that are now being adopted by the United Network of Organ Sharing [UNOS]) suggest that as many as 75% of patients are sensitized after a single transfusion (D Tynan, personal communication; Amgen, data on file). Sensitization by transfusion is avoidable in these patients; the other two mechanisms that can cause sensitization, pregnancy and previous transplant[17] are not readily mitigated. The risk of transfusion and allo-sensitization may be reduced but not eliminated by leuko-reduction[4]. Allo-sensitization may result in a decline in graft survival[17] among cadaveric transplanted patients who are sensitized (Figure 2a) and also among HLA-identical sibling donors (Figure 2b)[20]. This last finding is notable because these transplants are expected to have lower immunological barriers to transplantation and greatest overall success.

**Figure 2. (a) Long-term (10-year) graft survival of cadaver kidney transplants according to pre-transplant allo-sensitization (measured as PRA), and (b) 10-year follow-up of kidney grafts from HLA-identical sibling donors[20].**




Kidney transplant is the preferred ESRD treatment modality because successfully transplanted patients have superior survival and quality of life and significantly reduced health resource utilization and cost[2]. Receiving a transfusion can limit a dialysis patient's likelihood of receiving a transplant by prolonging their wait for a matching kidney. Patients who wait longer for a transplant are more likely to die rather than receive a kidney[19]. The effect of prolonged waiting time on the risk of death is most pronounced among patients 60 years and older. Recent estimates suggest that nearly 50% will die within 5 years if they have not received a transplant[21] (Figure 3).

**Figure 3. Time to transplantation and death among patients 60 years of age and older on the transplant wait-list[21].**



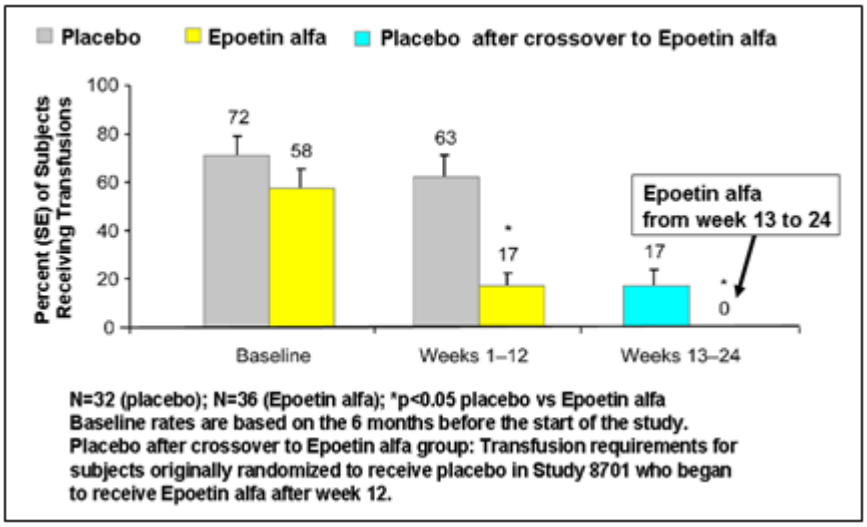

Kaplan-Meier plots of time to decreased donor transplantation (DDTx) by year of listing and time to mortality for older candidates. DD, decreased donor. Time to mortality includes all older candidates listed during the study period.

In the pre-ESA era, while necessary for management of anemia, the risks related to transfusion limited their use, and as a result, hemoglobin levels were maintained at a level of approximately 7 g/dL[11]. Since patients were maintained at these low hemoglobin levels, they experienced persistent, severe fatigue and had restrictions on physical functioning—all of which contributed to a poor quality of life.

### 1.3 Development of ESAs and their Impact on Dialysis Patients

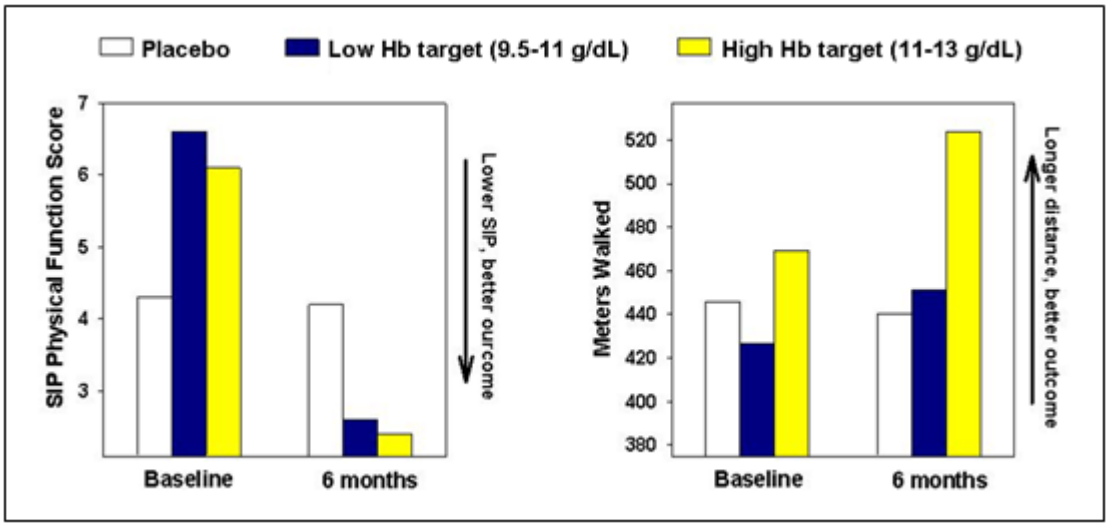
The primary registration trials (five studies) used for the approval of Epoetin alfa demonstrated correction of anemia and virtual elimination of transfusions (>90% reduction) in patients treated with ESAs to a mean hemoglobin of 11.7 g/dL (within the target range of 10.7 to 12.7 g/dL). In placebo treated patients, hemoglobin levels remained low (< 7 g/dL) and these patients continued to receive multiple transfusions, while the Epoetin alfa treated group became nearly transfusion independent (Amgen Clinical Study Report, data on file) (Figure 4).

**Figure 4. Percent of patients receiving a transfusion at baseline and in weeks 1-12 and 13-24 for patients randomized to Epoetin alfa and placebo treatment (Amgen, data on file).**




The original registration studies also evaluated the impact of raising hemoglobin levels with ESA therapy on physical functioning and quality of life. Exercise tolerance (meters walked) and physical function improved compared to placebo in patients receiving Epoetin alfa with both achieved hemoglobin levels of 10.2 g/dL as well as 11.7 g/dL at 6 months[22]. These improvements were statistically significantly different compared to placebo, as well as clinically meaningful (Figure 5). Exercise tolerance and physical function were significantly improved with ESA treatment, rising by approximately 30% after 6 months of treatment as defined by the meters walked[11, 22].

**Figure 5. Improvements in exercise tolerance and physical function observed when hemoglobin levels were increased to a mean of 10.2 g/dL and 11.8 g/dL with EPOGEN® compared to placebo-treated patients (Amgen, data on file; EPOGEN® Prescribing information [PI])**




## 1.4 Current ESA Approved Indications

EPOGEN® and Aranesp® are approved for the treatment of anemia associated with CRF, which includes patients receiving and not receiving dialysis. ESAs are used to elevate or maintain RBC levels (as manifested by the hemoglobin or hematocrit determinations) and to decrease the need for transfusions in these patients. The EPOGEN® label also includes a quality of life benefit (improved exercise tolerance and physical functioning) as demonstrated in the Canadian Erythropoietin Study Group[22] (Amgen, data on file). The benefit on patient reported outcomes, including improvement in energy, physical function and exercise tolerance (as measured by $VO_2$ max), resulting from treatment with ESAs to hemoglobin levels greater than 10 g/dL, has been shown consistently in subsequent open-label and observational studies and summarized in a recent meta-analysis[23] (Figure 6).

**Figure 6. Forest plot of pre-versus post-ESA comparison studies of $VO_2$ [23]**

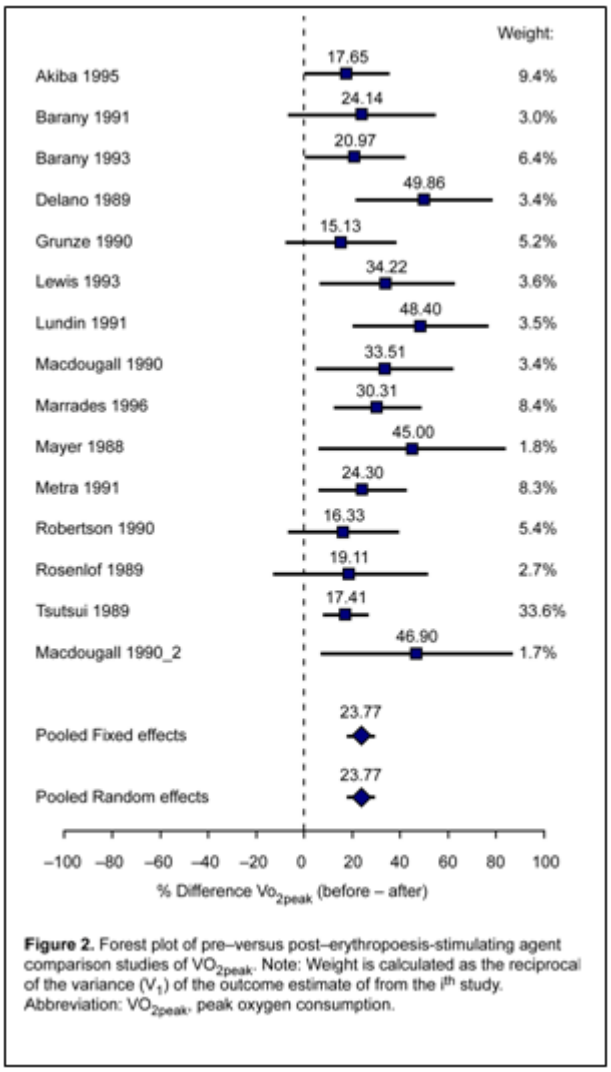


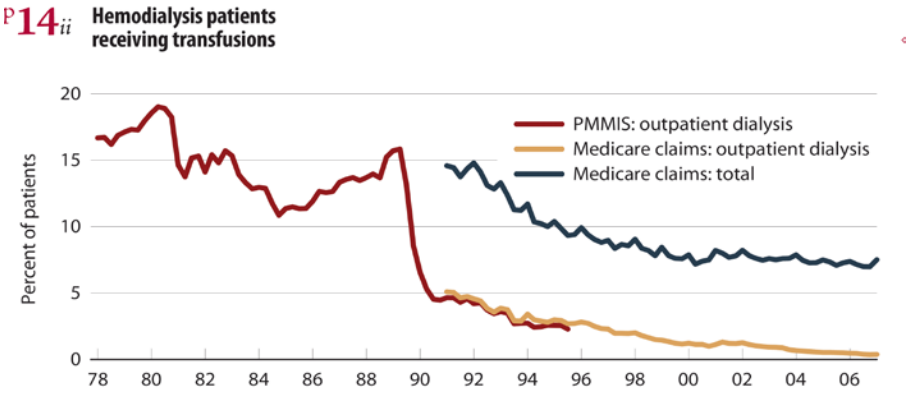

**Figure 2.** Forest plot of pre–versus post–erythropoesis-stimulating agent comparison studies of $VO_{2peak}$. Note: Weight is calculated as the reciprocal of the variance ($V_i$) of the outcome estimate of from the $i^{th}$ study. Abbreviation: $VO_{2peak}$, peak oxygen consumption.

## 1.5 Characteristics of the US Dialysis Population

In the US, extensive data on the health care provided to the majority of dialysis patients (Medicare primary insurer) is captured by the US Renal Data System (USRDS). Consequently, dialysis patients are subject to near complete surveillance; patient care information including medications, biochemical parameters and morbidity and mortality outcomes are systematically collected. This pharmacovigilance system is unique among disease states. Since USRDS has been in continuous operation for over 20 years, the evaluation of trends in treatments and outcomes in the dialysis population is possible.

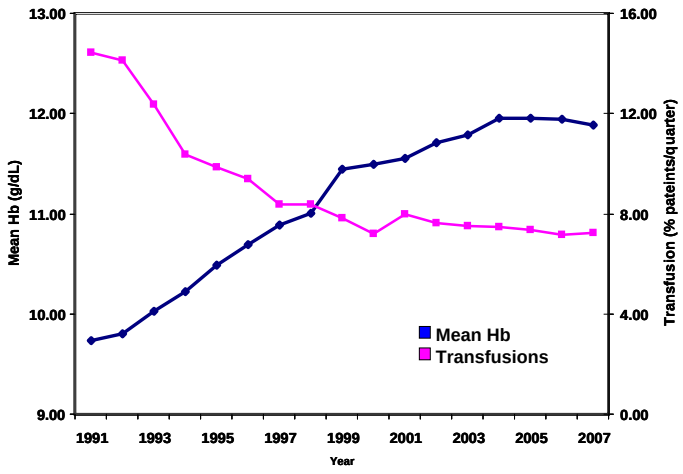
In the pre-ESA era, a substantial fraction of transfusions were administered for chronic anemia in the outpatient dialysis unit. Almost immediately following the introduction of EPOGEN® into clinical practice (June 1989), the transfusion rate among US hemodialysis patients fell sharply (Figure 7).

**Figure 7. Transfusion rate in US dialysis patients over time expressed as percent of patients receiving transfusions in each quarter-year period[2]. Note: PMMIS and Medicare claims represent all outpatient transfusion events occurring in the dialysis unit.**




By 1992 almost 90% of US dialysis patients received ESA therapy and this treatment prevalence continues today[24]. In 1994, the EPOGEN® label was changed to expand the 10 to 11 g/dL hemoglobin range to 10 to 12 g/dL, a change that was supported by clinical practice guidelines. Between 1992, when the mean population hemoglobin was ~9.8 g/dL, and 2000, when, with increased treatment intensity, the mean population hemoglobin had risen to ~11.2 g/dL, the total transfusion rate (inpatient plus outpatient) was again halved[25] (Figure 8).

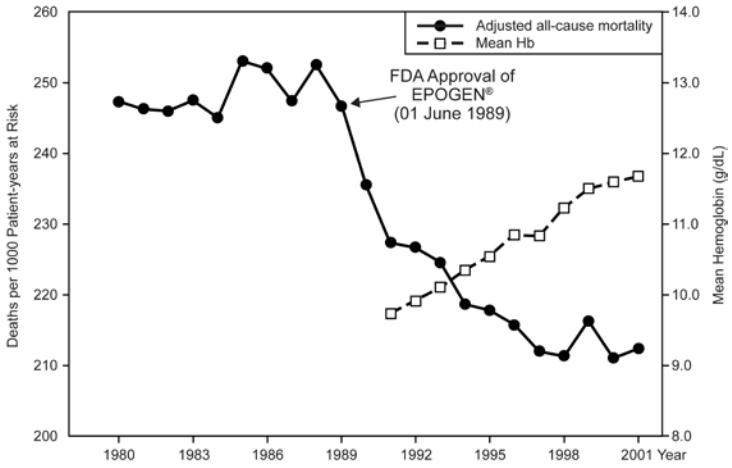
**Figure 8. Hemoglobin levels and transfusion rates between 1991 and 2007[2]**




These data provided important surveillance information on clinical practice and population level blood supply utilization supporting the label range (10-12 g/dL) as an effective strategy for reducing RBC transfusions in outpatient dialysis facilities. The decline in transfusions was primarily in the outpatient setting; the majority of remaining transfusions occur in the inpatient setting (75%)[26].

As part of the routine surveillance of US dialysis patients by USRDS, important clinical outcomes such as mortality are evaluated annually. These data indicate that since the introduction of EPOGEN® into clinical practice and its wide spread adoption as the primary treatment for anemia over the past 20 years, the overall mortality rate in the dialysis population has not increased (Figure 9).

**Figure 9. Mortality rate and hemoglobin levels preceding and following the introduction of EPOGEN®[27 28]**




Thus, there is evidence of an important and tangible clinical benefit of transfusion avoidance, and no evidence of an overt safety signal when patients are treated according to the FDA-approved label in general clinical practice.

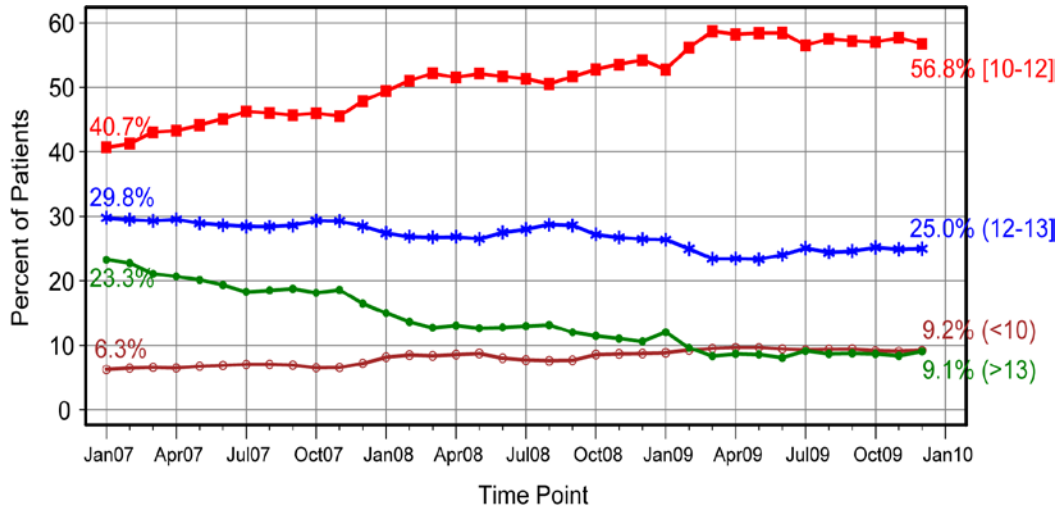
### 1.6 Overview of ESA use in General Dialysis Clinical Practice

The goals of the use of medicines in clinical practice are to maximize benefit and minimize risk consistent with FDA-approved labeling. Reimbursement policies have been designed, in many respects, to enable physicians to treat individual patients consistent with the approved label. For ESAs, the current policy allows physicians to individualize treatment to achieve and maintain hemoglobin levels between 10 and 12 g/dL so as to reduce the need of RBC transfusions and avoid sustained high hemoglobin levels. Research over the past 10 years has described the considerable variation in hemoglobin levels in dialysis patients[29-31] and has highlighted the difficulty of maintaining patients within a narrow hemoglobin range. The current CMS payment policy is clinically-based and takes into account the transient fluctuations in hemoglobin levels that commonly occur in the dialysis patient population.

Reimbursement policies for ESAs have been dynamic over the last two decades, reflecting changes in label and practice guidelines for the treatment of anemia in CKD

and the appropriate administration of ESAs with regard to the safety and efficacy profile. Changes made to the EMP effective January 1, 2008 have had the desired effect in decreasing the occurrence of excessive hemoglobin levels in dialysis patients; the mean population hemoglobin has also decreased. Recently published data indicate that mean hemoglobin levels in the dialysis patient population has decreased from 12.08 g/dL (SD 1.48) in June 2006 to 11.71 g/dL (SD 1.35) in November 2008[32]. Additional surveillance data on ~87% of dialysis centers in the US indicates that as of December 2009, the mean hemoglobin continues to decline and is approximately 11.54 g/dL (Amgen data on file). Analysis of surveillance data also indicates that the majority of physicians (98%) are acting to appropriately reduce ESA doses when hemoglobin levels exceed the FDA-approved target range[33]. Examining specific hemoglobin categories, the percentage of patients with a monthly hemoglobin value greater than 12 g/dL has declined (from 53.1 to 34.1%) and the proportion within the labeled range has increased from 40.7 to 56.8%. (Amgen data on file) (Figure 10). Amgen routinely shares this surveillance data with CMS on an ongoing basis.

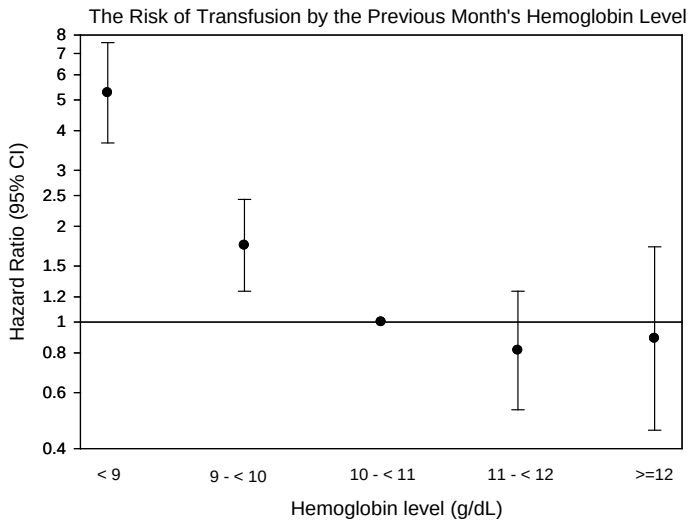
**Figure 10. Percentage of hemoglobin measurements in specific ranges for the dialysis patient population (Amgen data on file; this data is shared with CMS on an ongoing basis)**




## 1.7 10 g/dL as the Lower Threshold for ESA Treatment in Dialysis Patients

As demonstrated in both clinical trials in dialysis patients and in observational data, the risk of transfusion rises significantly as the outpatient hemoglobin in the preceding month falls below 10 g/dL and this risk increases when hemoglobin levels drop further (Amgen, data on file) (Figure 11).

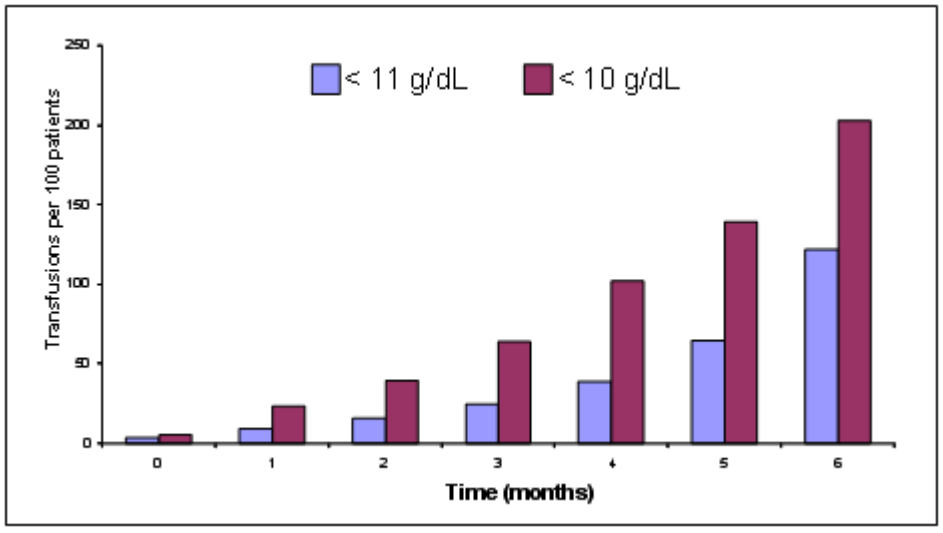
**Figure 11. Transfusion risk by the previous month's hemoglobin level in the lower arm of the Normal Hematocrit Cardiac Trial (NHCT) (Amgen, data on file)**




Data Source: NHCT study, data on file

An analysis of nearly 160,000 US hemodialysis patients in Medicare data further indicate that the risk of transfusion increases substantially the longer hemoglobin levels remain below 10 g/dL[34] (Figure 12).

**Figure 12. Transfusion rates by the number of months with an outpatient hemoglobin below 10 g/dL, and separately below 11 g/dL, in approximately 160,000 US hemodialysis patients in 2004[34].**




The majority of the evidence from RCTs, as well as observational data, have strongly supported that maintaining hemoglobin levels above 10 g/dL is essential for avoiding transfusion, fatigue and decline in physical function. The importance of maintaining hemoglobin levels above 10 g/dL is recognized by the nephrology community as well as

CMS, and is currently incorporated as a quality metric by which dialysis units are evaluated[35]. However, because hemoglobin levels are known to vary within individuals over time (intra-patient variability)[29, 31], and because of the delayed response between ESA dosing and hemoglobin changes[36], it is extremely difficult to maintain hemoglobin levels within a narrow range in many, if not most, patients [29].

In the early registration trials, variation in hemoglobin levels was observed in both placebo-treated and ESA-treated patients (the mean intra-patient standard deviation [SD] in hemoglobin levels was 0.6 g/dL)[37]; this degree of variability continues to be observed in more recent clinical trials. In current clinical practice, the population mean intra-patient hemoglobin SD is near 0.9 g/dL and accounts for ~80% of the total variability (1.4 g/dL) that is observed in cross-sectional evaluations of hemoglobin in the entire US dialysis population[34].

Both the original registration trials and the current FDA-approved ESA labels refer to a 2 g/dL hemoglobin range. The need for this range is based on the following: (i) the recognized need to maintain hemoglobin levels above 10 g/dL to avoid transfusion; (ii) the inherent variability in patient hemoglobin levels over time; and (iii) the continued reduction in transfusions that is observed up to a hemoglobin level of 12 g/dL. Using this range, physicians are effectively managing hemoglobin levels according to patient needs in order to avoid unnecessary RBC transfusions.

The influence of hemoglobin variability on the management of anemia in dialysis patients is well recognized by CMS and has been incorporated into their National Claims Monitoring Policy for ESAs in hemodialysis patients (EMP). The EMP recognizes that in administering ESAs to achieve and maintain the 10-12 g/dl hemoglobin range, their reimbursement policy should account for this inherent variability[38].

### 1.8 Attempts to Improve CV Outcomes in Dialysis Patients by Targeting Hemoglobin Levels Outside the FDA-Approved Range (13 g/dL or higher)

A number of observational studies had evaluated the association between anemia and increased risk of CV outcomes in CKD patients[39-41]. Using the available surveillance data in USRDS, studies have consistently shown that hemoglobin levels below 10 g/dL are associated with increased rates of hospitalization and death and greater healthcare resource utilization[42, 43], and patients who are able to achieve higher hemoglobin levels (10-12 g/dL) had lower hospitalization and mortality rates. To date, no study has evaluated CV morbidity and mortality, or healthcare resource utilization benefits when

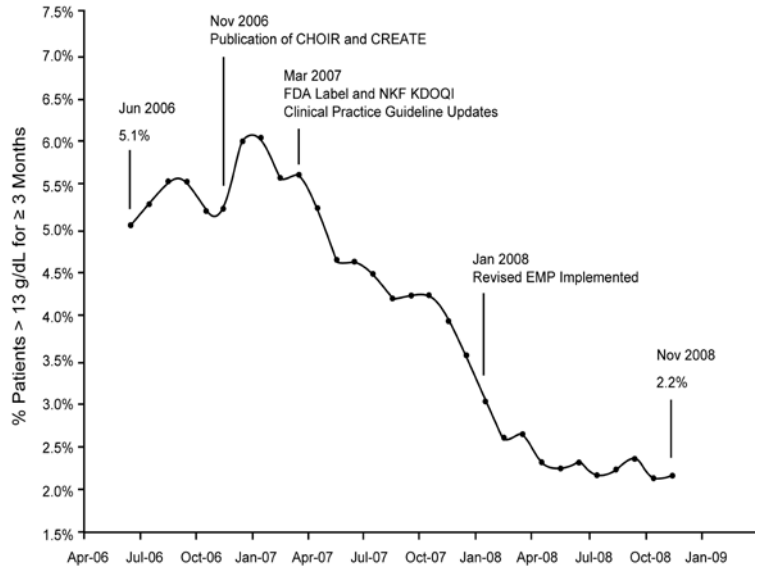
treating with ESAs to within the labeled range. However, studies were undertaken to test the hypothesis that normalization or near normalization of hemoglobin levels (hemoglobin of 13.5 and 14 g/dL) in CKD would result in decreased CV morbidity and mortality; the results of these RCTs did not confirm this hypothesis and hazard, instead of benefit, was demonstrated.

The first and only randomized controlled CV outcome trial to address this issue in dialysis patients, the Normal Hematocrit Cardiac Trial (NHCT), was conducted in subjects with pre-existing CV disease or heart failure and anemia[44]. The second trial was in CKD-NOD patients, the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR)[45]. NHCT was stopped for futility and CHOIR was stopped for hazard before the planned study completion. Although CHOIR was conducted in CKD-NOD patients, it is described here as part of a full discussion of safety with respect to ESA use. Both studies evaluated higher-than-approved hemoglobin targets: (i) NHCT compared the impact of a hemoglobin target of 14.0 g/dL to a target of 10.0 g/dL on the time to mortality or nonfatal myocardial infarction and found an excess of events in the high target arm (hazard ratio [HR] = 1.3, 95% confidence interval [CI]: 0.9-1.8); (ii) CHOIR compared the impact of a hemoglobin target of 13.5 g/dL to a target of 11.3 g/dL on the composite endpoint of death, myocardial infarction, hospitalization for congestive heart failure (without renal replacement therapy) and stroke, and found an excess of events in the high target arm (HR = 1.34, 95%CI: 1.03 – 1.74).

Based on the results of the NHCT trial, the United States PI[46] for ESAs was revised in 1996 to highlight the observed risks and to caution against normalization of hemoglobin levels in CKD. Following the publication of the CHOIR results in 2006, the US prescribing information (USPI) for ESAs were updated in 2007 to include the risks reported in the study and a Boxed Warning.

It is important to note that the mean achieved hemoglobin level in general clinical practice (11.7 g/dL in 2008)[32] is much lower than the mean achieved hemoglobin level of patients in the high target arm of NHCT (13.5 g/dL). Moreover, the proportion of dialysis patients with a hemoglobin level persistently above 13 g/dL for three consecutive months decreased to only 2.2% n 2008[32] (Figure 13).

**Figure 13. Percentage of patients with hemoglobin > 13 g/dL for ≥ 3 months[32]**




## 1.9 Association of Higher Achieved Hemoglobin and Clinical Outcome

Patients with lower hemoglobin levels have worse clinical outcomes and quality of life[23, 43], and this may be due in part to the extent of their comorbidity and other clinical factors that may cause low hemoglobin. Safety information from RCTs (CHOIR and NHCT) consistently demonstrates higher hazard associated with randomization to higher hemoglobin targets. At the same time, analyses of these same trials[28, 44] as well as surveillance data, suggest that patients who are able to achieve higher hemoglobin levels experience better clinical outcomes. This paradox of different clinical outcomes between targeting, as opposed to being able to achieve higher hemoglobin levels, points out the confounding effect of patients' health status on the clinical outcomes related to anemia management.

## 1.10 Association of ESA Dose and Adverse Events: Contribution of Confounding Factors in Dialysis Patients

The totality of the evidence informing the benefit and risks of ESAs in CKD patients was reviewed at the September 2007 joint meeting between the FDA Cardiovascular and Renal Drugs Advisory Committee (CRDAC) & Drug Safety and Risk Management Advisory Committee, which included results from CHOIR as well as a review of the evidence regarding the role of ESA dose on outcomes. In the NHCT, higher ESA doses were required to achieve the higher target hemoglobin level[44]. This raised the concern that the risks seen in this high hemoglobin target study were, in part, attributable to ESA dose. Additional evidence suggesting that higher ESA doses increased mortality risk was provided by two different analyses of US hemodialysis patients using USRDS data and found that higher ESA doses were associated with a significantly elevated mortality

risk across all hemoglobin levels[47, 48]. Amgen undertook an extensive evaluation of the data from RCTs and observational studies to better understand the potential contribution of ESA dose on mortality and CV and/or thromboembolic risk. These analyses indicate that there are three important considerations when examining the relationship between ESA dose and clinical outcomes:

- ESA dose and hemoglobin are strongly correlated because ESA dose is titrated in response to specific hemoglobin levels.
- Hemoglobin response to ESAs is influenced by the patient's overall health status; sicker patients require higher doses of ESAs to maintain hemoglobin.
- Hemoglobin response to ESAs is not static, but rather, changes within each individual over time.

In the course of clinical management of dialysis patients, ESA dosing decisions are made based on a patient's preceding hemoglobin concentration[33]. Thus, there is a tight correlation between hemoglobin and ESA dose. This relationship is further complicated because each patient's overall health status influences their hemoglobin response to ESA dosing changes[49]. Since ESA dosing is administered chronically, the hemoglobin-dose relationship can change over time[50], and thus, the dose that is necessary to maintain a hemoglobin concentration varies over time. An analogous situation exists in the case of insulin dose 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[51], 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[52]. The authors of this latter investigation recognized the complexity of targeting blood glucose levels and considered that the control of glucose levels, rather than insulin doses, was the important determinant of the beneficial effects observed with lower target blood glucose levels.

This same conceptual view can be applied to ESA therapy and the clinical practice in which the physician attempts to maintain hemoglobin concentrations within a specified range over time. It was acknowledged at the 2007 CRDAC meeting that the excess mortality risk seen in patients receiving high ESA doses was likely related to their inability to respond to increased ESA doses (referred to as ESA hyporesponsiveness),

rather than the dose itself[53, 54]. Thus, in 2007 following the CRDAC meeting, the concept of hyporesponsiveness and its management was introduced into the USPI.

Following the 2007 CRDAC meeting, the EPOGEN® and Aranesp® labels were further revised:

- An update was made to the Boxed Warning
- The hemoglobin range of 10 to 12 g/dL was maintained
- Guidance was added for the treatment of patients who did not attain a hemoglobin level within the range of 10 to 12 g/dL despite the use of appropriate EPOGEN® dose titrations over a 12-week period

Since 2007, additional analyses have been conducted to further understand the inter-relationship between hyporesponsiveness, EPOGEN® dosing and adverse clinical outcomes in dialysis patients. It is now more widely understood that these initial observations of excess risk observed in patients who require greater EPOGEN® doses are largely attributable to patient characteristics, worsening clinical status and poor hemoglobin response rather than EPOGEN® dose[53-55]. Patients with the highest EPOGEN® doses are those most likely to have low hemoglobin levels, greater CV disease burden, more inflammation and malnutrition, increased hospitalization frequency, and are more likely to be dialyzing with a catheter (which promotes infection and is associated with increased mortality) rather than a permanent vascular access [55-57].

The prevalence of higher EPOGEN® doses in patients with worse overall prognosis results in confounding-by-indication and can produce biased results attributing risk to higher doses[50]. Several studies using different analytical techniques to address this confounding have shown that EPOGEN® dose is not an independent predictor of mortality[53, 58-60 60] (Table 1). Importantly, in subsequent analyses with more rigorous control for confounding, the lead investigators (Zhang, Thamer and Cotter) who originally suggested that higher EPOGEN® doses increase mortality risk[48], no longer demonstrated this association[59].

**Table 1. Results from the studies evaluating the association between EPOGEN® dose and mortality using methods to address confounding-by-indication**

| Author | N | Comparison | HR (95% CI) |
|---|---|---|---|
| **Limited baseline adjustment** | | | |

| | | | |
|---|---|---|---|
| Zhang 2004[48] | 94,569 | >22K vs. <7.9K U/wk | 2.3 (P < 0.05) |
| **Rigorous adjustment for time-dependent confounding** | | | |
| Zhang 2009[59] | 18,454 | >40K vs. 20-30K U/wk | 0.91 (0.67, 1.22) |
| Bradbury 2008[55] | 22,955 | Log EPO dose | 1.01 (0.99, 1.03) |
| Wang 2010[60] | 27,791 | >49K vs. <14K U/2wk | 0.98 (0.76, 1.74) |
| Bradbury 2009[53] | 5,974 | >37.5% vs. 0-12.5%^ | 0.86 (0.69, 1.08) |

^ Average monthly dose change over 3 months among patients with low hemoglobin levels

### 1.11 New Data from a CV Outcomes Trial Targeting Hemoglobin Levels above 12 g/dL

Since the review of the totality of the evidence at FDA CRDAC 2007, the results of TREAT, a large Amgen-sponsored phase III prospective randomized clinical trial, have become available[61]. TREAT was a study designed in 2002, and conducted between 2004 and 2009, to address the hypothesis that correction of anemia in CKD-NOD patients with mild anemia (hemoglobin < 11 g/dL at enrollment) and type 2 diabetes would improve CV morbidity and mortality. The detailed results for TREAT are described in the CKD-NOD section. In brief, the study did not meet the primary objective of showing an improvement in CV morbidity and mortality (HR = 1.05, 95% CI: 0.94 – 1.17). Patients in the Aranesp® treated arm experienced an almost two-fold increased risk of stroke compared with the placebo group (HR = 1.92, 95% CI: 1.38-2.68 with an annualized incidence rate of 1.1% in the placebo arm and 2.1% in the Aranesp® treated arm. Consistent with Amgen's previous response to safety signals identified in clinical trials, Amgen has proactively revised the EPOGEN® and Aranesp® labels to include this risk.

### 1.12 CONCLUSION: ESA THERAPY IS AN ESSENTIAL TREATMENT FOR DIALYSIS PATIENTS

ESAs are an essential therapy in the management of anemia in dialysis patients and have a positive benefit to risk profile when used according to the FDA-approved label. ESAs are effective at increasing hemoglobin levels in order to avoid transfusions and to improve physical function and exercise tolerance in dialysis patients. Transfusion avoidance protects against cumulative hazards—especially allo-sensitization to foreign antigens—and improves the eligibility for and outcome of renal transplant. This is a particularly relevant issue for many potential transplant candidates who often times spend many years on dialysis, thereby increasing both their exposure to the risks of transfusions as well as their mortality rates from having been on dialysis. A lower hemoglobin limit of 10.7 g/dL was studied in the original registrational clinical trials. Subsequently, additional clinical trials and observational data have demonstrated that the risk of transfusion increases substantially when hemoglobin levels fall below 10 g/dL; this supports 10 g/dL as the appropriate lower limit of the labeled range. The transfusion benefit continuously improves through the labeled hemoglobin range of 12 g/dL, and because of the intrinsic hemoglobin variability seen in dialysis patients; a 2 g/dL range is appropriate with an upper hemoglobin level of 12 g/dL. Additionally, the near-complete surveillance of the US dialysis population by USRDS has not provided evidence of an

increased rate of death when patients are treated to the FDA-approved ESA labeled hemoglobin range. Thus, the labeled hemoglobin range of 10 to 12 g/dL is necessary and prudent to maximize the benefit of transfusion avoidance and minimize the risk of CV events associated with high hemoglobin targets (≥ 13 g/dL), and allows physicians to effectively manage anemia in dialysis patients.

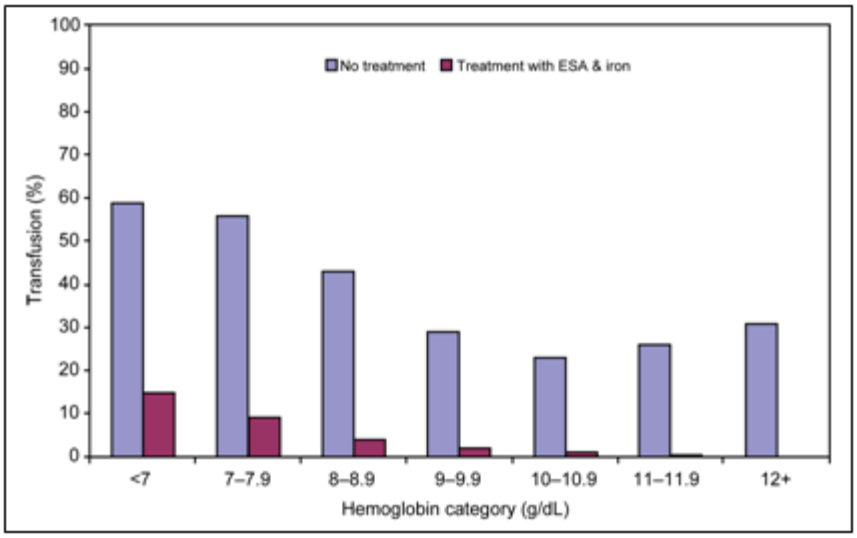
## 2. CKD PATIENTS NOT ON DIALYSIS (CKD-NOD)

There are an estimated 26 million people in the US with CKD-NOD, of which, approximately 22 million have moderate to severe loss of kidney function (estimated glomerular filtration rate [eGFR] 15 to 60 mL/min/1.73 $m^2$)[62]. As renal function decreases and endogenous erythropoietin production declines, anemia develops [7]. While anemia is ubiquitous and severe in dialysis patients (in the absence of treatment), the prevalence of anemia is lower in CKD-NOD. However, it is estimated that > 50% of Medicare CKD-NOD patients have some degree of anemia[2]; the prevalence of anemia increases with the stage of CKD[63]. The difference in the prevalence of anemia in CKD-NOD relative to dialysis is a key distinguishing clinical characteristic between these two populations.

### 2.1 Transfusion Therapy in CKD-NOD Patients

While the prevalence of anemia in CKD-NOD is lower than in patients who are on dialysis, the anemia in CKD-NOD can be severe and the transfusion burden in these patients is surprisingly high. In Medicare patients with CKD-NOD and chronic anemia, the annual transfusion rate ranged from 17% to 25% between 1992 and 2004, and the risk was three-fold higher than in CKD-NOD patients without anemia, and 10 fold higher than those without CKD[64]. In 2004 there were approximately 400,000 anemic CKD-NOD patients covered by Medicare; this roughly translates to 60,000 to 100,000 transfusion events annually in the Medicare population alone. In the Veteran's Administration (VA) healthcare system, transfusion rates are similarly elevated in the anemic CKD-NOD population[65]. Transfusions are significantly more common in non-treated patients when compared to patients receiving ESAs and iron, and increase markedly when hemoglobin levels fall below 10 g/dL[66] (Figure 14).

**Figure 14. The risk of transfusion by hemoglobin levels in anemic CKD-NOD patients treated with ESAs and iron and among those not receiving treatment (n = 97,636)[66]**




## 2.2 Adverse Sequelae of Transfusion Therapy

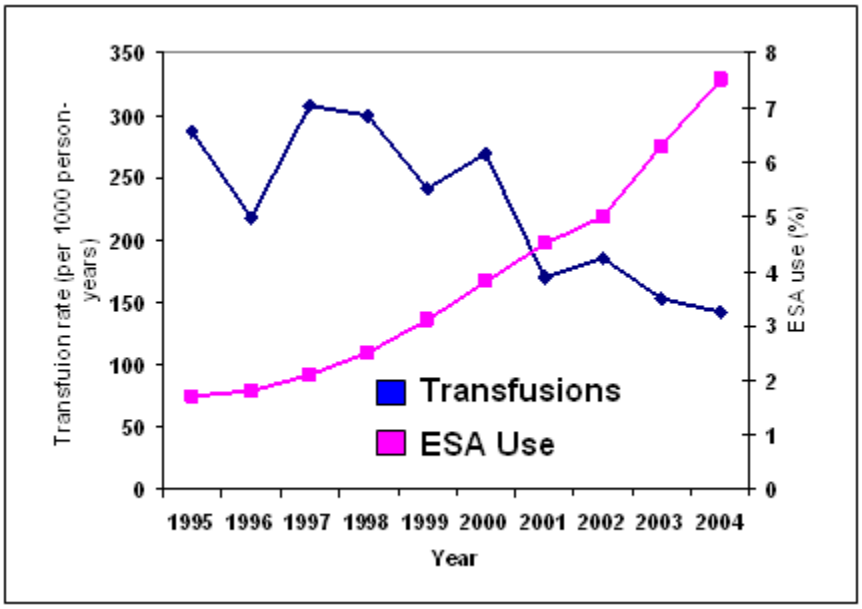
RBC transfusions carry a range of hazards including transmission of viral disease and transfusion reactions. As with dialysis patients, transfusion related complications such as acute volume and potassium overload, and more chronically, iron overload. can be problematic for CKD-NOD patients[10, 13-16]. Finally, and of unique importance to CKD patients, RBC transfusions can result in allo-sensitization to foreign antigens[2, 19] that can *delay* or *preclude* kidney transplantation[2] and impact overall graft survival in transplanted patients[20]. Currently, 15% of transplants occur in CKD-NOD patients before they initiate dialysis[2] and the numbers are growing. USRDS projects that ~700,000 patients will be receiving dialysis or be transplanted by the year 2020[2]. The largest group progressing to dialysis is projected to be 45-64 year-olds, all of whom will become Medicare beneficiaries upon developing ESRD; these patients will likely be prime candidates for renal transplantation. Avoidance of transfusion to maintain transplant eligibility is of critical importance because kidney transplant is the preferred treatment modality for ESRD. Successfully transplanted patients have superior survival and quality of life and incur lower health care costs[2].

## 2.3 Benefits of ESA Therapy in CKD-NOD Patients

The clinical benefit of transfusion avoidance in anemic dialysis patients was demonstrated by the registrational clinical trials with EPOGEN® and established hemoglobin as the key outcome for approval of ESAs in the non-dialysis setting. The Aranesp® clinical trial program evaluated hemoglobin response in CKD-NOD subjects

and demonstrated that hemoglobin levels could be raised and maintained within targeted hemoglobin range; approval for this indication was granted by the FDA in 2001[67]. In the original registration studies with EPOGEN® in dialysis patients, transfusion avoidance occurred when hemoglobin levels were raised above 10 g/dL[68], and the same efficacy was demonstrated in an open-label single-arm study of anemic CKD-NOD patients[69]. In this study, transfusion events were reduced by ~70% when hemoglobin levels were raised above 10 g/dL. This benefit has also been seen in general clinical practice. In the Medicare population with CKD-NOD and anemia, transfusion rates have declined from 30 to 15% among patients treated with ESAs between 1995 and 2004[64] (Figure 15).

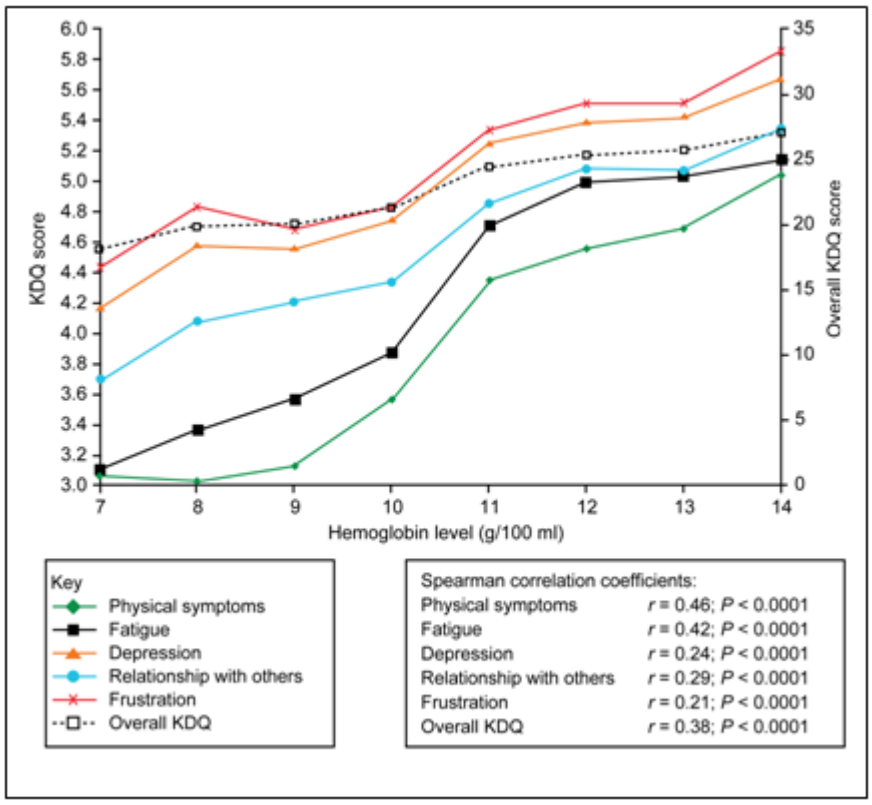
**Figure 15. Transfusion rate among ESA treated CKD-NOD patients with anemia over time[64]**




There has been, and continues to be, significant interest in the nephrology community toward better understanding the effects of treatment with ESAs to hemoglobin levels above 10 g/dL on CKD-NOD patients' symptoms and functioning from the patient's perspective; treatment of these patient reported domains is not an approved indication for Aranesp®. A number of trials, including double-blind placebo-controlled, open-label randomized controlled trials as well as single-arm and observational studies have been conducted to study this question. In summary, all of these studies suggest improvements in patient-reported outcomes, although the degree of benefit varies across studies. Studies which compare achieved hemoglobin levels below 10 g/dL to those above 10g/dL demonstrate more improvement than those which compare

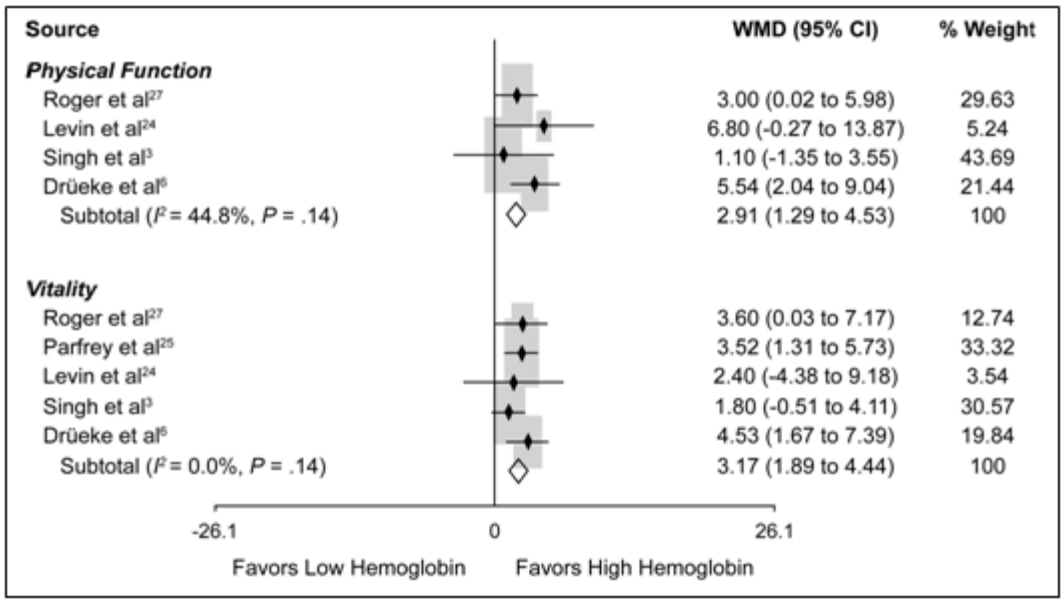
improvements in patient reported outcomes between high and low hemoglobin targets. For example, in an open-label RCT, SF-36 scores decreased in the untreated arm (achieved hemoglobin of 8.9 g/dL) for both physical function and energy while there was a significant increase in these subscale scores in the treated arm (achieved hemoglobin of 10.5 g/dL)[70]. Similar improvements have been demonstrated in fatigue, and activity levels[71-73]. A variety of studies have shown that there is a clinically meaningful improvement in physical function and vitality scores, as measured by various patient-reported outcome instruments, as hemoglobin levels rise above 10 g/dL[74] (Figure 16).

**Figure 16. Hemoglobin levels and associated Kidney Disease Questionnaire (KDQ) scores for physical symptoms, fatigue, depression, relationship with others, frustration, and overall KDQ[74] (Clinically meaningful change in KDQ is 0.2-0.5 [75])**




A recent meta-analysis showed that there was a modest difference in physical function and vitality scores in the SF-36 when scores for patients treated to higher hemoglobin targets (approximately 12.0 – 15 g/dL across studies) were compared to those treated to lower hemoglobin targets (approximately 9.5 – 11.5 g/dL across studies)[76] (Figure 17).

**Figure 17. A meta-analysis of the difference in SF-36 physical function and vitality scores between higher and lower hemoglobin levels in CKD-NOD patients; WMD = weighted mean difference[76]**




## 2.4 Anemia and CV Outcomes in CKD-NOD

As previously discussed, a number of observational studies demonstrated an association between anemia and an increased risk of adverse CV outcomes in CKD-NOD patients[77, 78]. Based on these studies, RCTs were undertaken to test the hypothesis that normalization or near normalization of hemoglobin levels in CKD-NOD patients would result in decreased CV morbidity and mortality. The NHCT in dialysis subjects with pre-existing CV disease or heart failure and anemia[44] and the CHOIR study in CKD-NOD subjects with anemia[45], addressed this question. Although NHCT was conducted in dialysis patients, it is described here as part of a full discussion of safety with respect to ESA use. The detailed results of these studies and the subsequent revisions to the ESA labels were discussed in the previous section. In brief, both studies evaluated higher-than-approved hemoglobin targets and found an excess of events in the high target arm: (1) NHCT hazard ratio [HR] = 1.3, 95% confidence interval [CI]: 0.9-1.8; (2) CHOIR HR = 1.34, 95%CI: 1.03 – 1.74). Based on the results of the NHCT trial, the USPI for ESAs were revised in 1996 to highlight the observed risks and to caution against normalization of hemoglobin levels in CKD. Following the publication of the CHOIR results in 2006, the USPI for ESAs was updated in 2007 to include the risks reported in the study including a Boxed Warning.

The totality of the evidence informing the benefit and risks of ESA in CKD patients was reviewed at the September 2007 joint meeting between the FDA CRDAC & Drug Safety

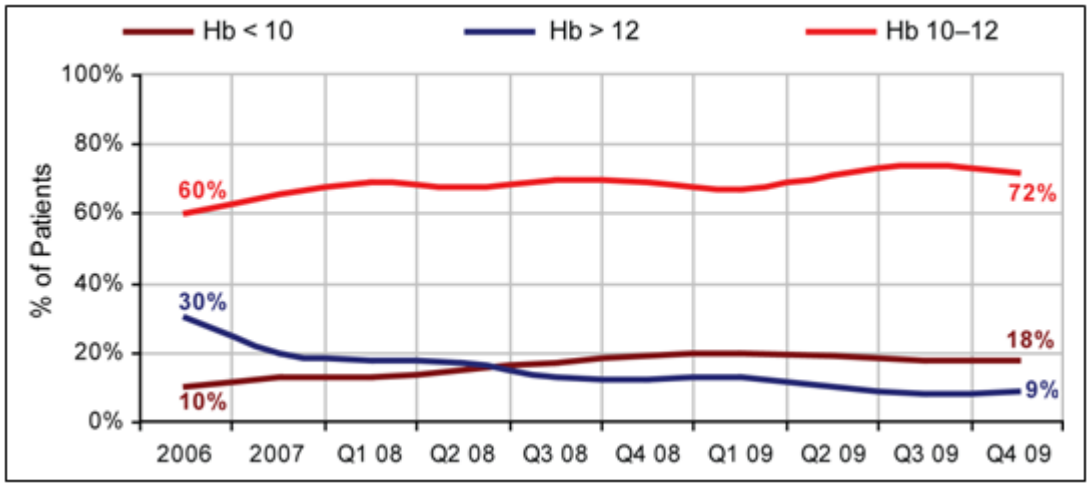
and Risk Management Advisory Committee, which included results from CHOIR. Following the CRDAC meeting, the ESA labels were further revised to highlight the following safety information:

- The Boxed Warning was updated
- The hemoglobin range of 10 to 12 g/dL was maintained
- Dosing guidance language was added on how to treat patients who did not attain a hemoglobin level within the range of 10 to 12 g/dL despite the use of appropriate Aranesp® dose titrations over a 12-week period

## 2.5 Overview of ESA use in General CKD-NOD Clinical Practice

Nephrologists have responded to the findings in these well-publicized clinical trials by treating to lower achieved hemoglobin levels; doses have also declined. The proportion of ESA-treated CKD-NOD patients with hemoglobin levels > 12 g/dL has dropped significantly (30% to 9%) and the proportion within the 10 to 12 g/dL hemoglobin range is nearly 70% (Amgen data on file) (Figure 18). As of June 2009, the average hemoglobin level among ESA-treated CKD-NOD patients was 10.7 g/dL[79]. Additionally, the average monthly Aranesp® dose in clinical practice in 2009 was 134 mcg.

**Figure 18. Percentage of hemoglobin measurements in specific ranges for the CKD-NOD patient population (Amgen data on file; these data are shared with CMS on an ongoing basis).**




## 2.6 Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT) Trial in Diabetic CKD-NOD Patients

In 2009, the results of TREAT, a large Amgen-sponsored phase III prospective randomized clinical trial, became available[61]. TREAT was designed in 2002, and conducted between 2004 and 2009, to explore whether there were benefits with ESA

treatment beyond the supportive care indication for which ESAs were approved. The rationale for this study was based on the observation that patients with higher achieved hemoglobin levels experienced lower CV morbidity and mortality[77, 78]. The specific objective of the study was to show that, when compared to placebo, treatment with Aranesp® could reduce time to first occurrence of death, CV morbidity or end-stage renal disease; although it also assessed other endpoints such as quality of life. TREAT enrolled diabetic, early-stage CKD-NOD patients (eGFR < 60 mL/min/1.73 $m^2$) with mild anemia (hemoglobin < 11 g/dL). TREAT was a 4,038 patient, randomized, double-blind, placebo-controlled study that examined treatment with ESA to a hemoglobin target of 13 g/dL compared to placebo (with Aranesp® as rescue therapy when hemoglobin fell below 9 g/dL). The median achieved hemoglobin in the Aranesp® treated arm was 12.5 g/dL and the median achieved hemoglobin in the placebo arm was 10.6 g/dL.

TREAT did not demonstrate a reduction in the risk of the primary composite endpoint (time to first event of death, myocardial infarction, hospitalization for congestive heart failure, stroke and myocardial ischemia) (HR = 1.05, 95% CI: 0.94-1.17). Patients in the Aranesp® treated arm experienced an almost two-fold increased risk of stroke compared with the placebo group (HR = 1.92, 95% CI: 1.38-2.68 with an annualized incidence rate of 1.1% in the placebo arm and 2.1% in the Aranesp® treated arm). In December 2009, consistent with Amgen's previous response to safety signals identified in clinical trials, Amgen proactively revised the ESA labels to include the risk of stroke observed in TREAT, including enhancement of the Boxed Warning language and the Warnings and Precautions section.

Amgen has undertaken a number of analyses to further understand the increased risk of stroke (Amgen data on file). To date, analyses did not identify an association between achieved hemoglobin or baseline characteristics (with the exception of a nominally significant interaction with baseline aspirin use), and the risk of stroke. Within either the Aranesp® or placebo group, there was no difference in mean hemoglobin between subjects who developed stroke and subjects who did not develop stroke. For subjects in both treatment groups, systolic and diastolic blood pressure was higher in subjects who developed stroke compared with subjects who did not develop stroke. Consistent with the post-hoc analyses of other RCTs (NHCT, CHOIR) and observational studies, higher achieved hemoglobin levels were associated with a lower risk of CV and mortality events.

TREAT also assessed the association of treatment with ESAs with patient reported outcomes in this mildly anemic CKD-NOD population. A modest improvement was seen in the mean change in the FACT-Fatigue subscale score for subjects in the Aranesp®-treated group from baseline to week 25 (4.2 points for the Aranesp®-treated group and 2.8 points for the placebo group), with a difference between the two groups of 1.33 (95% CI: 0.64, 2.02; $p < 0.0001$). No statistically significant changes were seen between the two groups in the SF-36 physical function and energy subscale scores.

While not an endpoint in the study, TREAT provides valuable information on the impact of ESAs on transfusions in CKD-NOD. Subjects randomized to the Aranesp® arm had approximately half the rate of RBC transfusions compared to placebo-treated patients (22.8 per 100 patient-years for placebo-treated *versus* 13.1 per 100 patient-years in the Aranesp®-treated arm; annualized rates). Additionally, analyses of the transfusion data in TREAT demonstrated a continuous increase in the risk of transfusion as hemoglobin levels decline (HR = 0.56, 95% CI 0.49-0.65)[61]. In general clinical practice, there is a strong relationship between declining hemoglobin levels and increased transfusion risk and this risk is particularly elevated when hemoglobin levels drop below 10 g/dL[65, 66].

TREAT was not a study designed to assess the optimal hemoglobin target range for treatment in CKD-NOD and does not provide evidence to support the use of ESAs beyond transfusion reduction in the population studied. During the treatment phase, the median hemoglobin in the arm randomized to receive Aranesp® was 12.5 g/dL and the median hemoglobin in the arm randomized to receive placebo with rescue therapy (at 9 g/dL) was 10.6 g/dL. TREAT only enrolled patients with hemoglobin < 11 g/dL; the median baseline hemoglobin in TREAT was 10.4 g/dL. In current clinical practice, most of the patients enrolled in TREAT would not receive ESA therapy; CKD-NOD patients are currently initiated on therapy when hemoglobin declines to below 10 g/dL (Amgen, data on file). Furthermore, the mean hemoglobin in anemic CKD-NOD patients who are currently receiving ESA therapy in the US is approximately 10.7 g/dL[79], which is similar to the placebo arm of TREAT and considerably less than the target hemoglobin of 13 g/dL.

### 2.7 CONCLUSION: ESA THERAPY IN CKD-NOD PATIENTS IS AN IMPORTANT TREATMENT OPTION IN THOSE FOR WHOM TRANSFUSION AVOIDANCE IS A MEANINGFUL CLINICAL BENEFIT

Although the prevalence of anemia is lower in CKD-NOD, anemia can be severe and transfusions are frequent. Anemic CKD-NOD patients are vulnerable to the risks of

transfusions, particularly the risk of allo-sensitization, and its potential impact on transplant eligibility and graft survival. ESA therapy should be initiated when hemoglobin declines below 10 g/dL because the demonstrated benefit of transfusion reduction with ESA use is observed when hemoglobin levels are treated to above 10 g/dL. ESA therapy should be individualized to achieve and maintain hemoglobin between 10 and 12 g/dL. As with dialysis patients, the intrinsic hemoglobin variability seen in CKD-NOD and the practical limitations of managing hemoglobin, require the use of a hemoglobin range to administer ESAs to maximize the clinical benefit for each patient. A hemoglobin level of 12.0 g/dL as the upper end of the hemoglobin range will allow physicians to manage patients so as to reduce transfusions. Avoiding a hemoglobin target > 12 g/dL provides a safety margin against the higher hemoglobin target (≥ 13.0 g/dL) in TREAT where risks have been identified. Evidence supports that ESAs are an important therapy for anemic CKD-NOD patients in whom transfusion avoidance is a meaningful clinical goal and believes that ESAs have a positive benefit to risk profile when used according to the FDA-approved label in these patients.

## REFERENCES


1. Go AS, Chertow GM, Fan D, McCulloch CE and Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. The New England journal of medicine. 2004;351: 1296-1305.
2. USRDS: USRDS 2009 Annual data report: atlas of end-stage renal disease in the United States. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive Kidney Diseases, 2009
3. Birmele B, Francois M, Pengloan J, et al.: Death after withdrawal from dialysis: the most common cause of death in a French dialysis population. Nephrol Dial Transplant. 2004;19: 686-691.
4. Karpinski M, Pochinco D, Dembinski I, Laidlaw W, Zacharias J and Nickerson P: Leukocyte reduction of red blood cell transfusions does not decrease allosensitization rates in potential kidney transplant candidates. J Am Soc Nephrol. 2004;15: 818-824.
5. Sargent JA and Acchiardo SR: Iron requirements in hemodialysis. Blood purification. 2004;22: 112-123.
6. Caro J, Brown S, Miller O, Murray T and Erslev AJ: Erythropoietin levels in uremic nephric and anephric patients. The Journal of laboratory and clinical medicine. 1979;93: 449-458.
7. Erslev AJ and Besarab A: Erythropoietin in the pathogenesis and treatment of the anemia of chronic renal failure. Kidney international. 1997;51: 622-630.
8. Cheung J, Yu A, LaBossiere J, Zhu Q and Fedorak RN: Peptic ulcer bleeding outcomes adversely affected by end-stage renal disease. Gastrointestinal endoscopy. 2010;71: 44-49.
9. Wasse H, Gillen DL, Ball AM, et al.: Risk factors for upper gastrointestinal bleeding among end-stage renal disease patients. Kidney international. 2003;64: 1455-1461.
10. Eschbach JW and Adamson JW: Anemia of end-stage renal disease (ESRD). Kidney international. 1985;28: 1-5.
11. Churchill DN, Taylor DW, Cook RJ, et al.: Canadian Hemodialysis Morbidity Study. Am J Kidney Dis. 1992;19: 214-234.
12. Eschbach JW, Egrie JC, Downing MR, Browne JK and Adamson JW: Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. The New England journal of medicine. 1987;316: 73-78.
13. Beauregard P and Blajchman MA: Hemolytic and pseudo-hemolytic transfusion reactions: an overview of the hemolytic transfusion reactions and the clinical conditions that mimic them. Transfusion medicine reviews. 1994;8: 184-199.
14. Despotis GJ, Zhang L and Lublin DM: Transfusion risks and transfusion-related pro-inflammatory responses. Hematol Oncol Clin North Am. 2007;21: 147-161.
15. Dodd RY, Notari EPt and Stramer SL: Current prevalence and incidence of infectious disease markers and estimated window-period risk in the American Red Cross blood donor population. Transfusion. 2002;42: 975-979.
16. Simon GE and Bove JR: The potassium load from blood transfusion. Postgraduate medicine. 1971;49: 61-64.
17. Hardy S, Lee S-H and Terasaki PI: Sensitization 2001, in PI, CJaT (ed): Clinical Transplants 2001, UCLA, 2001
18. USRDS: USRDS 2004 Annual data report: atlas of end-stage renal disease in the United States. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive Kidney Diseases, 2004
19. UNOS: United Network for Organ Sharing. Accessed at: 44Hhttp://www.unos.org/ . Accessed on Feb 12, 2010.,

20. Opelz G: Non-HLA transplantation immunity revealed by lymphocytotoxic antibodies. Lancet. 2005;365: 1570-1576.
21. Schold J, Srinivas TR, Sehgal AR and Meier-Kriesche HU: Half of kidney transplant candidates who are older than 60 years now placed on the waiting list will die before receiving a deceased-donor transplant. Clin J Am Soc Nephrol. 2009;4: 1239-1245.
22. CESG: Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. Canadian Erythropoietin Study Group. BMJ. 1990;300: 573-578.
23. Johansen KL, Finkelstein FO, Revicki DA, Gitlin M, Evans C and Mayne TJ: Systematic Review and Meta-analysis of Exercise Tolerance and Physical Functioning in Dialysis Patients Treated With Erythropoiesis-Stimulating Agents. Am J Kidney Dis. 2010;In press.
24. Pisoni RL, Bragg-Gresham JL, Young EW, et al.: Anemia management and outcomes from 12 countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis. 2004;44: 94-111.
25. USRDS: USRDS 2007 Annual data report: atlas of end-stage renal disease in the United States. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive Kidney Diseases, 2007
26. Ibrahim HN, Ishani A, Foley RN, Guo H, Liu J and Collins AJ: Temporal trends in red blood transfusion among US dialysis patients, 1992-2005. Am J Kidney Dis. 2008;52: 1115-1121. .
27. USRDS: USRDS 2003 Annual data report: atlas of end-stage renal disease in the United States. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive Kidney Diseases, 2003
28. Amgen: Background information for the joint meeting between the Cardiovascular and Renal Drugs Advisory Committee & Drug Safety and Risk Management Advisory Committee. Accessed at: 45Hhttp://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4315b1-04-AMGEN.pdf, 2007
29. Ebben JP, Gilbertson DT, Foley RN and Collins AJ: Hemoglobin level variability: associations with comorbidity, intercurrent events, and hospitalizations. Clin J Am Soc Nephrol. 2006;1: 1205-1210. .
30. Fishbane S and Berns JS: Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. Kidney Int. 2005;68: 1337-1343.
31. Lacson E, Jr., Ofsthun N and Lazarus JM: Effect of variability in anemia management on hemoglobin outcomes in ESRD. Am J Kidney Dis. 2003;41: 111-124.
32. Spiegel DM, Khan I, Krishnan M and Mayne TJ: Changes in hemoglobin level distribution in US dialysis patients from June 2006 to November 2008. Am J Kidney Dis. 2009;55: 113-120.
33. Collins AJ, Brenner RM, Ofman JJ, et al.: Epoetin alfa use in patients with ESRD: an analysis of recent US prescribing patterns and hemoglobin outcomes. Am J Kidney Dis. 2005;46: 481-488.
34. Medicare: Analysis conducted by the Chronic Disease Research Group of the Minneapolis Medical Research Foundation under DUA #16234 and #16235 with the Centers For Medicare and Medicaid Services,
35. Medicare: Dialysis facility compare. Accessed at: 46Hhttp://www.medicare.gov/Dialysis/Include/DataSection/Questions/SearchCriteria.asp?version=default&browser=IE%7C6%7CWin2000&language=English&defaultstatus=0&pagelist=Home,
36. Uehlinger DE, Gotch FA and Sheiner LB: A pharmacodynamic model of erythropoietin therapy for uremic anemia. Clinical pharmacology and therapeutics. 1992;51: 76-89.

37. Feng A and Comstock T: Within-subject hemoglobin variability in placebo-controlled Epoetin alfa studies of patients on hemodialysis with anemia. J Am Soc Nephrol [abstract]. 2009;20: 168A.
38. CMS: CMS Manuap System. Pub 100-04 Medicare Claims Processing. Transmittal 751, Change Request 4135, DHHS CMS 11-10-2005. National monitoring policy for EPO and Aranesp for end stage renal disease (ESRD) patients treated in renal dialysis facilities 2005
39. Cannella G, La Canna G, Sandrini M, et al.: Reversal of left ventricular hypertrophy following recombinant human erythropoietin treatment of anaemic dialysed uraemic patients. Nephrol Dial Transplant. 1991;6: 31-37.
40. Wizemann V, Kaufmann J and Kramer W: Effect of erythropoietin on ischemia tolerance in anemic hemodialysis patients with confirmed coronary artery disease. Nephron. 1992;62: 161-165.
41. Pascual J, Teruel JL, Moya JL, Liano F, Jimenez-Mena M and Ortuno J: Regression of left ventricular hypertrophy after partial correction of anemia with erythropoietin in patients on hemodialysis: a prospective study. Clinical nephrology. 1991;35: 280-287.
42. Collins AJ, Li S, St Peter W, et al.: Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. J Am Soc Nephrol. 2001;12: 2465-2473.
43. Volkova N and Arab L: Evidence-based systematic literature review of hemoglobin/hematocrit and all-cause mortality in dialysis patients. Am J Kidney Dis. 2006;47: 24-36.
44. Besarab A, Bolton WK, Browne JK, et al.: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998;339: 584-590.
45. Singh AK, Szczech L, Tang KL, et al.: Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355: 2085-2098.
46. Amgen: EPOGEN(R) (Epoetin alfa) Prescribing Information. Amgen Inc., Thousand Oaks, CA.
47. Cotter DJ, Stefanik K, Zhang Y, Thamer M, Scharfstein D and Kaufman J: Hematocrit was not validated as a surrogate end point for survival among epoetin-treated hemodialysis patients. Journal of clinical epidemiology. 2004;57: 1086-1095.
48. Zhang Y, Thamer M, Stefanik K, Kaufman J and Cotter DJ: Epoetin requirements predict mortality in hemodialysis patients. Am J Kidney Dis. 2004;44: 866-876.
49. Bradbury BD, Critchlow CW, Weir MR, Stewart R, Krishnan M and Hakim RH: Impact of elevated C-reactive protein levels on erythropoiesis- stimulating agent (ESA) dose and responsiveness in hemodialysis patients. Nephrol Dial Transplant. 2009;24: 919-925.
50. Bradbury BD, Brookhart MA, Winkelmayer WC, et al.: Evolving statistical methods to facilitate evaluation of the causal association between erythropoiesis-stimulating agent dose and mortality in nonexperimental research: strengths and limitations. Am J Kidney Dis. 2009;54: 554-560.
51. van den Berghe G, Wouters P, Weekers F, et al.: Intensive insulin therapy in the critically ill patients. The New England journal of medicine. 2001;345: 1359-1367.
52. Finney SJ, Zekveld C, Elia A and Evans TW: Glucose control and mortality in critically ill patients. JAMA. 2003;290: 2041-2047.
53. Bradbury BD, Danese MD, Gleeson M and Critchlow CW: Effect of epoetin alfa dose changes on hemoglobin and mortality in hemodialysis patients with hemoglobin levels persistently below 11 g/dL. Clin J Am Soc Nephrol. 2009;4: 630-637.

54. Kilpatrick RD, Critchlow CW, Fishbane S, et al.: Greater epoetin alfa responsiveness is associated with improved survival in hemodialysis patients. Clin J Am Soc Nephrol. 2008;3: 1077-1083.
55. Bradbury BD, Wang O, Critchlow CW, et al.: Exploring relative mortality and epoetin alfa dose among hemodialysis patients. Am J Kidney Dis. 2008;51: 62-70.
56. Kalantar-Zadeh K and Aronoff GR: Hemoglobin variability in anemia of chronic kidney disease. J Am Soc Nephrol. 2009;20: 479-487.
57. Solid CA, Foley RN, Gilbertson DT and Collins AJ: Perihospitalization hemoglobin-epoetin associations in U.S. hemodialysis patients, 1998 to 2003. Hemodial Int. 2007;11: 442-447.
58. Bradbury BD, Do TP, Winkelmayer WC, Critchlow CW and Brookhart MA: Greater Epoetin alfa (EPO) doses and short-term mortality risk among hemodialysis patients with hemoglobin levels less than 11 g/dL. Pharmacoepidemiol Drug Saf. 2009;18: 932-940.
59. Zhang Y, Thamer M, Cotter D, Kaufman J and Hernan MA: Estimated effect of epoetin dosage on survival among elderly hemodialysis patients in the United States. Clin J Am Soc Nephrol. 2009;4: 638-644.
60. Wang O, Kilpatrick RD, Critchlow CW, et al.: Relationship between Epoetin alfa dose and mortality: findings from a marginal structural model. Clin J Am Soc Nephrol. 2010;In press.
61. Pfeffer MA, Burdmann EA, Chen CY, et al.: A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. The New England journal of medicine. 2009;361: 2019-2032.
62. Coresh J, Selvin E, Stevens LA, et al.: Prevalence of chronic kidney disease in the United States. JAMA. 2007;298: 2038-2047.
63. Astor BC, Muntner P, Levin A, Eustace JA and Coresh J: Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994). Arch Intern Med. 2002;162: 1401-1408.
64. Ibrahim HN, Ishani A, Guo H and Gilbertson DT: Blood transfusion use in non-dialysis-dependent chronic kidney disease patients aged 65 years and older. Nephrol Dial Transplant. 2009;24: 3138-3143.
65. Lawler EV, Gagnon DR, Fink J, et al.: Initiation of anaemia management in patients with chronic kidney disease not on dialysis in the Veterans Health Administration. Nephrol Dial Transplant. 2010;In press.
66. Lawler EV, Bradbury BD, Fonda JR, Gaziano JM and Gagnon DR: Transfusion burden among patients with chronic kidney disease and anemia. Clin J Am Soc Nephrol. 2010;In press.
67. Amgen: Aranesp(R) (Epoetin alfa) Prescribing Information. Amgen Inc., Thousand Oaks, CA.
68. Eschbach JW, Abdulhadi MH, Browne JK, et al.: Recombinant human erythropoietin in anemic patients with end-stage renal disease. Results of a phase III multicenter clinical trial. Annals of internal medicine. 1989;111: 992-1000.
69. Provenzano R, Garcia-Mayol L, Suchinda P, et al.: Once-weekly epoetin alfa for treating the anemia of chronic kidney disease. Clin Nephrol. 2004;61: 392-405.
70. Revicki DA, Brown RE, Feeny DH, et al.: Health-related quality of life associated with recombinant human erythropoietin therapy for predialysis chronic renal disease patients. Am J Kidney Dis. 1995;25: 548-554.
71. Benz R, Schmidt R, Kelly K and Wolfson M: Epoetin alfa once every 2 weeks is effective for initiation of treatment of anemia of chronic kidney disease. Clin J Am Soc Nephrol. 2007;2: 215-221. .
72. Kleinman KS, Schweitzer SU, Perdue ST, Bleifer KH and Abels RI: The use of recombinant human erythropoietin in the correction of anemia in predialysis patients

and its effect on renal function: a double-blind, placebo-controlled trial. Am J Kidney Dis. 1989;14: 486-495.
73. Alexander M, Kewalramani R, Agodoa I and Globe D: Association of anemia correction with health related quality of life in patients not on dialysis. Curr Med Res Opin. 2007;23: 2997-3008.
74. Lefebvre P, Vekeman F, Sarokhan B, Enny C, Provenzano R and Cremieux PY: Relationship between hemoglobin level and quality of life in anemic patients with chronic kidney disease receiving epoetin alfa. Curr Med Res Opin. 2006;22: 1929-1937.
75. Jaeschke R, Singer J and Guyatt GH: Measurement of health status. Ascertaining the minimal clinically important difference. Controlled clinical trials. 1989;10: 407-415.
76. Clement FM, Klarenbach S, Tonelli M, Johnson JA and Manns BJ: The impact of selecting a high hemoglobin target level on health-related quality of life for patients with chronic kidney disease: a systematic review and meta-analysis. Archives of internal medicine. 2009;169: 1104-1112.
77. Al-Ahmad A, Rand WM, Manjunath G, et al.: Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. Journal of the American College of Cardiology. 2001;38: 955-962.
78. Sarnak MJ, Tighiouart H, Manjunath G, et al.: Anemia as a risk factor for cardiovascular disease in The Atherosclerosis Risk in Communities (ARIC) study. Journal of the American College of Cardiology. 2002;40: 27-33.
79. Regidor D, McClellan WM, Kewalramani R, Sharma A and Bradbury BD: Changes in erythropoiesis stimulating agent (ESA) dosing and hemoglobin levels in U.S. non-dialysis chronic kidney disease patients between 2005 and 2009. submitted (under review). 2010.

## Technical Appendix 1 – Evidence Tables

### Table 1a: Transfusion Burden in CKD Patients

| STUDY | OBJECTIVE | STUDY POPULATION | TRANSFUSION OUTCOME |
|---|---|---|---|
| **Retrospective observational** | | | |
| Gilbertson (2009)[1] | Describe the influence of anemia management interventions (ESA, Iron, and transfusions) on Hb variability | **HD** patients receiving ESAs<br>Hb variability groups:<br>• Patients with Hb < 11 for six months (L-L), **N**=2,165<br>• Patients with Hb 11-12.5 for six consecutive months (I-I), **N**=9,646<br>• Patients with Hb > 12.5 for six consecutive months (H-H), **N**=3,750<br>• Patients with Hb fluctuating between < 11 and 11-12.5 over six months (L-I), **N**=29,222<br>• Patients with Hb > 11 for six consecutive months (I-H), **N**=50,680<br>• Patients with Hb levels across Hb distribution (L-H), **N**=64,257 | • Increased time below 11 g/dL is associated with increased risk of transfusions<br>• Transfusion rate was 21.6 per 100 for patients with Hb fluctuating between < 11 g/dL and 11-12.5 g/dL over 6 months<br>• Transfusion rate was 121.7 per 100 for patients with Hb persistently below 11 g/dL for six consecutive months |
| Ibrahim (2008)[2] | Retrospective cohort study to address patterns and trends in red blood cell (RBC) transfusions in US hemodialysis patients (1992-2005) | All Medicare **HD** patients between 1992 and 2005<br>**N**=77,347 (1992)<br>**N**=164,933 (2005)<br>> 90% of hemodialysis received ESA treatment during this period | • Mean population hemoglobin increased from 9.7 g/dL in 1992 to 11.8 g/dL in 2004<br>• The total transfusion rate declined from 535.33 per 1000 patient-years in 1992 to 263.65 per 1000 patient-years in 2005<br>• For transfusions occurring in the outpatient setting only, transfusions declined from 225.63 per 1000 patient-years in 1992 to 66.66 per 1000 patient-years in 2005 |
| Ibrahim (2009)[3] | Retrospective cohort study to address patterns and trends in red blood cell (RBC) transfusions in the CKD and non-CKD population in Medicare between 1992 to 2004 | All Medicare beneficiaries with CKD between 1992 and 2004<br>**Total CKD N**=301,000<br>**N**=14,057 (1992)<br>**N**=42,225 (2004) | • The proportion of CKD patients receiving ESA therapy increased from 0.8% in 1992 to 7.5% in 2004<br>• The total transfusion among anemic CKD patients not receiving ESA therapy was 249.2 per 1000 patient-years in 1992 and 174.7 per 1000 patient-years in 2004 |

| STUDY | OBJECTIVE | STUDY POPULATION | TRANSFUSION OUTCOME |
|---|---|---|---|
| | | **Total CKD with anemia N**=118,895<br>**N**=4371 (1992)<br>**N**=18,579 | • The total transfusion among anemic CKD patients who received ESA therapy was 572.9 per 1000 patient-years in 1992 and 200.1 per 1000 patient-years in 2004 |
| Lawler (2010)[4] | Estimate the burden of transfusion by anemia treatment and Hb level in CKD-NOD patients | **CKD-NOD** (CKD ≥ Stage 3)<br>Hb< 11 g/dL<br>No anemia treatment, **N**=35,364<br>Iron treatment only, **N**=35,420<br>ESA treatment only, **N**=16,439<br>ESA + Iron treatment, **N**=10,413 | • Patients receiving anemia therapy were less likely to receive a transfusion at all Hb levels compared to patients who did not receive any anemia therapy<br>• Transfusion events were least for those who received by ESA + Iron treatment<br>o At Hb ≥ 10 g/dL, probability of transfusion was < 3% among treated, 23%-32% among treated<br>o Below 10 g/dL, probability of transfusion was 3%-20% among treated, 23%-59% among untreated |
| Lawler (2010)[5] | Examine initiation of anemia management among anemic CKD-NOD patients | **CKD-NOD** patients (eGFR 15-<60 ml/min/1.73 $m^2$) and Hb < 11 between January 2003 and December 2005<br>**N**=89,585 | • Among patients with Hb <9 g/dL and not receiving ESA treatment<br>• 15.6% received one or more transfusions during a 1-year baseline period<br>• 38.1% received one or more transfusions during 1 year of follow up<br>• Among patients with Hb 9-<10 g/dL and not receiving ESA treatment<br>• 8.6% received one or more transfusions during a 1-year baseline period<br>• 21.3% received one or more transfusions during 1 year of follow up<br>• Among patients with Hb 10-<11 g/dL and not receiving ESA treatment<br>• 5.6% received one or more transfusions during a 1-year baseline period<br>• 12.5% received one or more transfusions during 1 year of follow-up |

These evidence tables include the most commonly cited references; a systematic review was not conducted

1. Gilbertson DT, Peng Y, Bradbury B, Ebben JP and Collins AJ: Hemoglobin level variability: anemia management among variability groups. *American journal of nephrology*. 2009;30: 491-498.
2. Ibrahim HN, Ishani A, Foley RN, Guo H, Liu J and Collins AJ: Temporal trends in red blood transfusion among US dialysis patients, 1992-2005. *Am J Kidney Dis*. 2008;52: 1115-1121. .

3. Ibrahim HN, Ishani A, Guo H and Gilbertson DT: Blood transfusion use in non-dialysis-dependent chronic kidney disease patients aged 65 years and older. *Nephrol Dial Transplant*. 2009;24: 3138-3143.
4. Lawler EV, Bradbury BD, Fonda JR, Gaziano JM and Gagnon DR: Transfusion burden among patients with chronic kidney disease and anemia. *Clin J Am Soc Nephrol*. 2010;*In press*.
5. Lawler EV, Gagnon DR, Fink J, et al.: Initiation of anaemia management in patients with chronic kidney disease not on dialysis in the Veterans Health Administration. *Nephrol Dial Transplant*. 2010;*In press*.

## Table 1b: Cost of Red Blood Cell Transfusion

| STUDY | OBJECTIVE | STUDY POPULATION* | OUTCOME |
|---|---|---|---|
| **Prospective Observational** | | | |
| Agrawal et al, (2006)[1] (UK) | Assess direct costs of blood transfusion through a time and motion study | Hospital<br>Blood cost, staff time, blood-bank cost, disposables, overnight stay, transfusion related complications | Average blood transfusion of 2 units to £546.12. (2004) |
| Glenngard (2005)[12] (Sweden) | Assess direct costs of blood transfusion through interviews with hospital staff and published data | Societal<br>Acquisition, Typing, Testing, Preparation, Compatibility testing, Administration at the ward, Materials at the ward, Cell saver costs. | Swedish kronor (SEK) 6330 for filtered allogeneic RBCs and SEK 5394 for autologous<br>RBCs for surgery patients per 2-unit transfusion (2003) |
| Ueno et al (2006)[23] (US) | Assess direct and indirect costs of blood transfusion through interviews, prospective time and motion and retrospective chart review | Hospital<br>RBC acquisition/preparation, testing, and administration costs<br>**N**=20 | **Direct Costs:** One unit costs: US$582/RBC unit<br>Two unit costs: US$1,139/2-unit transfusion<br>(2005)<br><br>**Indirect Costs:** The mean (SD) time duration was 98.5 (12.7) and 92.5 (21.2) minutes for the first and second units, of blood transfusion, respectively.<br>Transfusions are also related to increased number of physician visits |
| Minuk et al (2008)[3] | Assess indirect costs of blood transfusion through a prospective, observational study | Patients receiving RBC transfusion in a tertiary-care cancer center.<br>**N**=1,279 | A patient receiving 1 RBC unit spent a total of 109 $\pm$ 19 minutes (mean $\pm$ SD) , independent of the time consumed by activities pre- and post- transfusion. |
| **Retrospective Observational** | | | |
| Amin (2004)[4] (Canada) | Assess direct costs of blood transfusion using a cost-structure analysis, observational | Societal<br>Cost of blood collection, production, and distribution<br>Cost of hospital transfusion service processing RBC transfusion. Transfusion reaction management<br>/RBC unit | US$264.81<br>(95% CI, $256.29-<br>$275.65)<br>(2002) |

| STUDY | OBJECTIVE | STUDY POPULATION* | OUTCOME |
|---|---|---|---|
| Cremieux (2000)[5] (US) | Assess direct costs of blood transfusion using retrospective chart review, observational | Provider<br>Total direct costs | Total: US$491.00/RBC unit (1998) |
| Norum (2008)[6] (Norway) | Assess direct costs of blood transfusion using retrospective, observational | Societal<br>Health care, infections, patient, family, other sectors | €1069<br>(2005) |

These evidence tables include the most commonly cited references; a systematic review was not conducted.

1. Agrawal S, Davidson N, Walker Mc, Gibson S, et al. Assessing the total costs of blood delivery to hospital oncology and haematology patients. *Current Medical Research and Opinion.* 2006. Vol. 22(10):1903–1909.
2. Glenngard AH, Persson U and Soderman C: Costs associated with blood transfusions in Sweden--the societal cost of autologous, allogeneic and perioperative RBC transfusion. *Transfus Med*. 2005;15: 295-306.
3. Ueno W, Beveridge RA and Kales AN: Costs of outpatient red blood cell transfusions. *J Support Oncol*. 2006;4: 494-495.
4. Minuk L, Chin-Yee I, Hibbert A, Chan D and Xenocostasn A: Red blood cell transfusion and chemotherapy administration: a study of resource utilization. *Community Oncology*;5: 598-603.
5. Cremieux PY, Barrett B, Anderson K and Slavin MB: Cost of outpatient blood transfusion in cancer patients. *J Clin Oncol*. 2000;18: 2755-2761.
6. Norum J and Moen MA: Practice and costs of red blood cell (RBC) transfusion in an oncological unit. *Anticancer Res*. 2008;28: 459-464.

## Table 2. Impact of Transfusion on Allo-Sensitization (Panel Reactive Antibodies [PRA]) and Transplantation

| STUDY | OBJECTIVE | STUDY POPULATION | STUDY RESULTS |
|---|---|---|---|
| **Retrospective observational** | | | |
| Bucin (1988)[1] | To determine the effect of pre-transplant transfusions on long-term transplant survival | Primary renal transplants, treated with azathioprine or prednisolone<br>Subgroups:<br>pre-transplant transfusions, **N**=79<br>no pre-transplant transfusions, **N**=37 | • Decreased 2-year graft survival in patients with pre-transplant transfusions.<br>• 2-year cumulative graft survival:<br>  • Transfused: 81%<br>  • No transfusion: 97% ($p < 0.05$) |
| Buscaroli (1992)[2] | To determine the association of intermediate PRA levels (30-60%) on transplant outcomes | 241 renal transplant patients with peak PRA 12 months prior to transplant<br>Low PRA <30%, **N**=174<br>Mod PRA 30-60%, **N**=63 | • Better graft survival 1 year post transplant for patients in the lower PRA group compared to the higher PRA group (90% vs. 79%, $p<0.05$)<br>• Better graft survival 3 years post transplant for patients in the lower PRA group compared to the higher PRA group (82% vs. 64%, $p<0.01$) |
| Cardarelli (2005)[3] | Examine the prevalence and significance of anti-HLA and donor-specific antibody (DSA) long term after renal transplantation | Transplant patients, 6 month post renal transplant<br>**N**=251 | • Among post-renal transplant patients<br>  • 11.2% had anti-HLA antibodies<br>  • 4.4% had DSA<br>• Post transplant Anti-HLA antibodies were significantly associated with<br>  • pre transplant sensitization<br>  • acute rejection<br>  • higher serum creatinine (2.15± 0.98 mg/dl vs. 1.57 ±0.69 mg/dl) |
| Cecka (1988)[4] | To determine effect of peak PRA on time to transplant | Renal transplant patients stratified by pre-transplant PRA levels<br>**N**=1,524 | • Increased peak PRA associated with longer time to transplant<br>  • 35-40% of nonsensitized patients (PRA = 0 – 10%) transplanted in <1 yr<br>  • <10% of patients with PRA >75% transplanted in <1 yr<br>  • >50% of patients with PRA >95% waited 4 yrs or more for transplant |
| Deierhoi (1989)[5] | Determine incidence of renal transplant by PRA pattern | Patients on the transplant wait list characterized by PRA level; all patients had a peak PRA level > 60%<br>1) Persistently high: sustaining high PRA (> 60%), **N**=46 | • Incidence of renal transplant in persistently high PRA group was 2%<br>• Incidence of renal transplant in persistently low PRA group was 32%<br>• Incidence of renal transplant in variable PRA group was 17% |

| STUDY | OBJECTIVE | STUDY POPULATION | STUDY RESULTS |
|---|---|---|---|
| | | 2) Persistently low: 1 peak and decline ≤ 30%, **N**=22<br>3) Variable PRA: ≥ 2 PRA peaks and decline ≤ 30%), **N**=24<br>Study follow-up period was not provided | |
| Hardy (2001)[6] | Describe graft survival by transfusion history and PRA level | Transplanted UNOS registrants<br>PRA ≤10%, **N**=27,787<br>PRA>10%, **N**=7,447 | • Lower 3-year kidney transplant survival as transfusion burden increased |
| Katznelson (1997)[7] | Describe association between highest pre-transplant PRA and transplant survival | Cadaveric transplants in UNOS registrants<br>Patients with PRA ≤20%, **N**=20,924<br>Patients with PRA >20%, **N**=5,570 | • At two years graft survival among patients with PRA>20% was 76%<br>• At two years graft survival among patients with PRA <20% was 82% (p<0.05) |
| Lietz (2003)[8] | Describe association between highest pre-transplant PRA and transplant survival | Transplanted kidney survival ≥ 6 months<br>Groups:<br>ESA, **N**=235<br>Transfusion, **N**=207<br>No treatment, **N**=60 | • Patients with a PRA <20% had a 2.1-fold higher probability of transplant than controls (p<0.001) |
| Nicol (1993)[9] | Determine effect of PRA, transfusions and other donor/recipient factors on transplant survival | Renal transplant patients<br>Graft failure attributed to rejection, **N**=48<br>Control (functioning graft at 3 years), **N**=300 | • Patients with a successful transplant were less likely to have historical PRA > 40% (17% vs. 46%, p<0.001)<br>• Patients with a successful transplant were less likely to have had pre-transplant transfusion(s) (24% vs 65%, p< 0.01) |
| Opelz (2005)[10] | Assess the association between the presence of lymphocytotoxic antibodies before transplantation and the outcome of kidney grafts for a) HLA identical sibling and b) cadaveric kidney transplants | PRA levels from the last pre-transplant serum level<br>HLA Living relative Subgroup:<br>PRA 0 **N**=3001<br>PRA 1-50 **N**=803<br>PRA > 50 **N**=244 | • At 10 years graft survival among patient with PRA 0 was 72.4%<br>• At 10 years graft survival among patient with PRA 1-50 was 63.3%<br>• At 10 years graft survival among patient with PRA > 50 was 55.5%<br>• The difference in survival across the three groups was statistically significant (P<0.0001) |
| | | PRA levels from the last pre-transplant serum level<br>Cadaveric Kidney Transplant Subgroup:<br>No PRA **N**=116562<br>PRA 1-50 **N**=36314 | • At 10 years graft survival among patient with PRA 0 was 50%<br>• At 10 years graft survival among patient with PRA 1-50 was 42%<br>• At 10 years graft survival among patient with PRA > 50 was 35% |

| STUDY | OBJECTIVE | STUDY POPULATION | STUDY RESULTS |
|---|---|---|---|
| | | PRA > 50 **N**=7610 | |
| Soosay (2003)[11] | Characterize the impact of transfusion on sensitization and time to transplant | Patients on renal transplant wait list stratified by PRA<br>**N**=244<br>PRA categorized as:<br>PRA 0−9%<br>PRA 10−59%<br>PRA 60−79%<br>PRA 80−100% | • Transfusions associated with elevated PRA levels<br>• Patients with PRA 0 – 9% received 5.6 units of blood on average<br>• Patients with PRA 80 – 100% received 37.8 units of blood on average<br>• Higher PRA levels increase time to transplant<br>• Patients with PRA 0 – 9% waited 7 months on average<br>• Patients with PRA 80 – 100% waited >35 months on average |
| UNOS[12] | **Transplant registry**<br>Scientific Registry of Transplant Recipients (SRTR), annual report for transplant patients. | CKD patients receiving a living donor kidney transplant by PRA level.<br>PRA levels by graft survival 3 months, 1 year, 5 years, and 10 years. | • Despite graft survival being highest in recipients of living donor kidneys, 2006 survival rates at 3 months, 1 year, 5 years, and 10 years show marked reduction in survival as PRA level increases<br>• PRA = 0-9% graft survival was 97.9% at 3 mos, 96% at 1 yr, 81% at 5 years and 57.5% at 10 years<br>• PRA = 10-79% graft survival was 97.4% at 3 mos, 95.2% at 1 yr, 76.3% at 5 years and 51.6% at 10 years<br>• PRA > 80% graft survival was 93.8% at 3 mos, 90.9% at 1 yr, 67.4% at 5 years and 45.4% at 10 years |
| USRDS (2009)[13] | Surveillance data assessing treatment patterns among ESRD patients | ESRD patients<br>Patients 18 and older listed for a first-time kidney-only transplant in the given year. | • Wait time for transplant continues to increase nationwide<br>• Higher sensitized patients (PRA ≥ 10%) wait twice as long (>4 yrs vs. >2 yrs) as patients with PRA < 10%<br>• Patients on the transplant waitlist longer have a higher likelihood of death |
| Vella (1998)[14] | Determine transfusion burden, PRA levels, and reason for sensitization in patients on the renal transplant waitlist in the pre compared to post ESA era (1989 compared 1994) | Patients on renal transplant waitlist<br>Year 1989, patients **N**=205 (pre ESA)<br>Year 1994 patients **N**=126 (post ESA)<br>Nonsensitized=PRA <10%<br>Moderately sensitized=PRA 10-59%<br>Highly sensitized=PRA≥60% | • PRA levels were lower the in 1994 cohort vs. 1989 cohort in each of the three different PRA categories (p=0.008)<br>• 49.8% of 1989 cohort had PRA = 0-9% compared to 63.5% in the 1994 cohort<br>• 25.9% of the 1989 cohort had PRA = 10-79% compared to 12.7% in the 1994 cohort<br>• 24.4% of the 1989 cohort had PRA > 80% compared to 23.8% of the 1994 cohort |
| Zhou (1991)[15] | Describe effects of sensitization on waiting time and graft survival | UCLA and UNOS registry data on patients with peak PRA values pre-transplant: | • At one year graft survival among patients with PRA 0-10% was 79%<br>• At one year graft survival among patients with PRA 10-50% |

| STUDY | OBJECTIVE | STUDY POPULATION | STUDY RESULTS |
|---|---|---|---|
| | | PRA 0-10%, **N=**15,615<br>PRA 11-50%, **N**=4,824<br>PRA >50%, **N**=2,615 | was 78%<br>• At one year graft survival among patients with PRA > 50% was 72% |

These evidence tables include the most commonly cited references; a systematic review was not conducted.


1. Besarab A, Bolton WK, Browne JK, et al.: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med*. 1998;339: 584-590.
2. Pfeffer MA, Burdmann EA, Chen CY, et al.: A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *The New England journal of medicine*. 2009;361: 2019-2032.
3. Provenzano R, Garcia-Mayol L, Suchinda P, et al.: Once-weekly epoetin alfa for treating the anemia of chronic kidney disease. *Clin Nephrol*. 2004;61: 392-405.
4. Boelaert JR, Daneels RF, Schurgers ML, Matthys EG, Gordts BZ and Van Landuyt HW: Iron overload in haemodialysis patients increases the risk of bacteraemia: a prospective study. *Nephrol Dial Transplant*. 1990;5: 130-134.
5. Churchill DN, Taylor DW, Cook RJ, et al.: Canadian Hemodialysis Morbidity Study. *Am J Kidney Dis*. 1992;19: 214-234.
6. Ibrahim HN, Ishani A, Foley RN, Guo H, Liu J and Collins AJ: Temporal trends in red blood transfusion among US dialysis patients, 1992-2005. *Am J Kidney Dis*. 2008;52: 1115-1121. .
7. Ibrahim HN, Ishani A, Guo H and Gilbertson DT: Blood transfusion use in non-dialysis-dependent chronic kidney disease patients aged 65 years and older. *Nephrol Dial Transplant*. 2009;24: 3138-3143.
8. Seliger: Timing of ESA initiation and adverse outcomes in non-dialysis dependent CKD: a propensity matched observational cohort study. *Clin J Am Soc Nephrol*. 2010;*In press*.

## Table 3: Transfusion Reduction with ESA Treatment

| STUDY | OBJECTIVE | STUDY POPULATION | OUTCOMES |
|---|---|---|---|
| **Randomized trial** | | | |
| Amgen study 8701 (data on file) | **Double-blind, partial cross over**<br>Correction of anemia with intravenous EPOGEN® in HD patients and estimate reduction in transfusions.<br>**Treatment duration** 24 weeks<br>Correction phase, 12 weeks<br>Maintenance phase: 12 weeks | **HD** patients, Hb ≤ 10 g/dL<br>Target Hb 10.7-12.7 g/dL<br>**N**=68<br>Placebo, **N**=32<br>EPOGEN® treated, **N**=36 | • For patients randomized to receive EPOGEN®, transfusions were reduced from 58% at baseline to 17% at 12 weeks and to 0% at 24 weeks.<br>• 72% of patients randomized to placebo received transfusion at baseline and this persisted at 12 weeks (63%). At this point, patients were switched to EPOGEN® and by 24 weeks only 17% were receiving transfusion. |
| Amgen 8904 (data on file) | **Double-blind, partial cross over**<br>Estimate correction of anemia with subcutaneous EPOGEN® and reduction in transfusions, PRO<br>Target Hb 10.7-12.7<br>**Treatment duration** 24 weeks<br>Correction phase, 12 weeks<br>Maintenance phase: 12 weeks | **PD** patients, Hb ≤ 10 g/dL<br>Target Hb 10 10.7-12.7 g/dL<br>**N**=152<br>Placebo, **N=**74<br>EPOGEN® treated, **N**=78 | • Patients receiving SC EPOGEN® were able to achieve target Hb with almost complete elimination of need of transfusion by 12 weeks. |
| Besarab (1998)[1] | **Open label**<br>To examine the risks and benefits of normalizing the hematocrit in patients with cardiac disease who were undergoing hemodialysis. | **HD** Patients with congestive heart failure or ischemic heart disease; serum transferring saturation of ≥ 20%. Patients treated to:<br>High target Hb arm (14 g/dL), **N**=618<br>Low target Hb arm (10 g/dL), **N**=615<br>**Median treatment duration:** 14 months | • Over the course of the study, 21% of the patients in the high Hb target arm received a transfusions compared to 31% in the low Hb target arm received transfusion (p<0.001) |
| Pfeffer (2009)[2] and Amgen data on file | **Randomized, double-blind, placebo-controlled**<br>In patients with Type 2 Diabetes and Chronic Kidney Disease that does not require dialysis and concomitant anemia, increasing Hb levels with the use of Darbepoetin alfa to lower the rates of death, cardiovascular events and end-stage renal disease | Diabetic **CKD-NOD** patients (20 to 60 mL/min/1.73 $m^2$) with anemia (Hb ≤ 11 g/dL).<br>Treated arm, **N**=2012<br>Placebo arm, **N**=2025 | • Exposure adjusted transfusion rate in the treated arm (11.6 per 100 patient years)<br>• Exposure adjusted transfusion rate in the placebo-treated arm (22.9 per 100 patient-years)<br>• HR=0.56, 95% CI: 0.49-0.65 |
| **Single Arm Trial** | | | |
| Provenzano | **Prospective, multi-center, open-label** | Anemic **CKD-NOD** patients | • Before treatment initiation, 11.1% of patients received a |

| STUDY | OBJECTIVE | STUDY POPULATION | OUTCOMES |
|---|---|---|---|
| (2004)[3] | **study**<br>To study the safety and efficacy with changes in health-related quality of life. | **N**=1557 (enrolled)<br>**N**=1338 (efficacy)<br>16-week study<br>Mean baseline Hb=9.1 g/dL<br>Mean follow-up Hb=11.6 g/dL (at 16 weeks) | transfusion during the baseline period and at 16 weeks, the declined to 3.7% (p<0.0001). |
| **Prospective observational** | | | |
| Boelaert (1990)[4] | Examine the increased risk of bacteremia with transfusional iron overload in patients on hemodialysis | **HD** adult patients who have received transfusion in the past, and stratified by iron level:<br>Ferretin < 500<br>Ferritin 500-1000<br>Ferritin ≥1000<br>**N**=158 | • Acquired transfusional iron overload in hemodialysis patients is associated with a greater risk of bacteremia<br>• The bacterimic incidence was 2.92 times higher in the Ferritin > 1000 than in the Ferritin < 1000 and was independent of age or dialysis vintage |
| Churchill (1992)[5] | Determine the transfusion practices prior to the availability of EPOGEN® | Incident **HD** patients (after one month on dialysis) and prevalent patients who remained on dialysis for 6 months<br>**N**=1158 | • Mean pre-transfusion Hb 6.87 g/dL<br>• 639 patients (55.2%) received at least 1 unit RBC transfusion (8.1 units/pt yr)<br>o 7% had at least one transfusion reaction<br>o The probability of surviving 12 months without receiving a blood transfusion was 47.2% for males and 27.5% for females |
| **Retrospective observational** | | | |
| Ibrahim (2008)[6] | Retrospective cohort study to address patterns and trends in red blood cell (RBC) transfusions in US hemodialysis patients (1992-2005) | All Medicare **HD** patients between 1992 and 2005<br>**N**=77,347 (1992)<br>**N**=164,933 (2005)<br>> 90% of hemodialysis received ESA treatment during this period | • Mean population Hb increased from 9.7 g/dL in 1992 to 11.8 g/dL in 2004<br>• The total transfusion rate declined from 535.33 per 1000 patient-years in 1992 to 263.65 per 1000 patient-years in 2005<br>• For transfusions occurring in the outpatient setting only, transfusions declined from 225.63 per 1000 patient-years in 1992 to 66.66 per 1000 patient-years in 2005 |
| Ibrahim (2009)[7] | Retrospective cohort study to address patterns and trends in red blood cell (RBC) transfusions in the CKD and non-CKD population in Medicare between 1992 to 2004 | All Medicare beneficiaries with **CKD** between 1992 and 2004<br>**Total CKD N**=301,000<br>**N**=14,057 (1992)<br>**N**=42,225 (2004)<br>**Total CKD with anemia N**=118,895 | • The proportion of CKD patients receiving ESA therapy increased from 0.8% in 1992 to 7.5% in 2004<br>• The total transfusion among anemic CKD patients not receiving ESA therapy was 249.2 per 1000 patient-years in 1992 and 174.7 per 1000 patient-years in 2004<br>• The total transfusion among anemic CKD patients who |

| STUDY | OBJECTIVE | STUDY POPULATION | OUTCOMES |
|---|---|---|---|
| | | **N**=4371 (1992)<br>**N**=18,579 | received ESA therapy was 572.9 per 1000 patient-years in 1992 and 200.1 per 1000 patient-years in 2004 |
| Seliger (2010)[8] | Determine the association of timing of ESA initiation with clinical outcomes among CKD-NOD population | Patient with **CKD-NOD** (CKD < 60 mL/min/1.73 $m^2$) and anemia (excluded patients with ESRD, hematological malignancy, on chemotherapy, hospitalized for have gastrointestinal bleeding)<br><br>Early ESA treatment initiation (Hb 10-11 g/dL)<br>**N**=705<br>Delayed ESA treatment initiation (Hb < 10 g/dL)<br>**N**=705<br>Early and delayed treatment patients were propensity score matched | • Transfusion incidence rate was 19.5 per 100 person-years among the delayed ESA treatment initiation patients and 13.4 per 100 person-years among the early ESA treatment initiation patients (HR=0.71, 95% CI: 0.59-0.97) |

These evidence tables include the most commonly cited references; a systematic review was not conducted


1. Besarab A, Bolton WK, Browne JK, et al.: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med*. 1998;339: 584-590.
2. Pfeffer MA, Burdmann EA, Chen CY, et al.: A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *The New England journal of medicine*. 2009;361: 2019-2032.
3. Provenzano R, Garcia-Mayol L, Suchinda P, et al.: Once-weekly epoetin alfa for treating the anemia of chronic kidney disease. *Clin Nephrol*. 2004;61: 392-405.
4. Boelaert JR, Daneels RF, Schurgers ML, Matthys EG, Gordts BZ and Van Landuyt HW: Iron overload in haemodialysis patients increases the risk of bacteraemia: a prospective study. *Nephrol Dial Transplant*. 1990;5: 130-134.
5. Churchill DN, Taylor DW, Cook RJ, et al.: Canadian Hemodialysis Morbidity Study. *Am J Kidney Dis*. 1992;19: 214-234.
6. Ibrahim HN, Ishani A, Foley RN, Guo H, Liu J and Collins AJ: Temporal trends in red blood transfusion among US dialysis patients, 1992-2005. *Am J Kidney Dis*. 2008;52: 1115-1121. .
7. Ibrahim HN, Ishani A, Guo H and Gilbertson DT: Blood transfusion use in non-dialysis-dependent chronic kidney disease patients aged 65 years and older. *Nephrol Dial Transplant*. 2009;24: 3138-3143.
8. Seliger: Timing of ESA initiation and adverse outcomes in non-dialysis dependent CKD: a propensity matched observational cohort study. *Clin J Am Soc Nephrol*. 2010;*In press*.

## Table 4: Patient Reported Outcomes (PROs) in Dialysis Patients

| STUDY | PRO INSTRUMENT | TREATMENT | N | BASELINE Hb MEAN (SD) or Mean (95% CI) (g/dL) | BASELINE PRO | Hb (g/dL)/Hct(%) LEVELS or CHANGE IN Hb (g/dL)/Hct (%) LEVELS | CHANGE IN PRO | STAT SIGNIF |
|---|---|---|---|---|---|---|---|---|
| **RCT** | | | | | | | | |
| Furuland (2003)[1] 48-76 weeks **N**=416 | KDQ-physical symptoms | Normal Hb with EA | 129 | 10.9±1.1 | 3.83 (1.67–7.00) | 2.2-3.7 | **Median (Min-Max)** 0.66 (–1.17–3.00) | 0.02 |
| | | Sub normal Hb with EA | 124 | 11.0±0.9 | 4.00 (1.00–7.00) | 0.3-0.8 | 0.25 (–1.17–2.66) | |
| | KDQ- Fatigue | Normal Hb with EA | 129 | 10.9±1.1 | 4.67 (1.17–7.00) | 2.2-3.7 | 0.16 (–2.50–2.34) | 0.05 |
| | | Sub normal Hb with EA | 124 | 11.0±0.9 | 5.00 (1.00–7.00) | 0.3-0.8 | -0.33 (-3.17–2.00) | |
| | KDQ- Depression | Normal Hb with EA | 129 | 10.9±1.1 | 5.40 (1.40–7.00) | 2.2-3.7 | 0.00 (-4.00–2.60) | 0.01 |
| | | Sub normal Hb with EA | 124 | 11.0±0.9 | 5.60 (1.60–7.00) | 0.3-0.8 | -0.40 (-2.40–2.20) | |
| | KDQ- Frustration | Normal Hb with EA | 129 | 10.9±1.1 | 6.00 (3.00–7.00) | 2.2-3.7 | 0.00 (-1.67–2.34) | 0.05 |
| | | Sub normal Hb with EA | 124 | 11.0±0.9 | 6.00 (1.00–7.00) | 0.3-0.8 | 0.00 (-2.00–2.00) | |
| | KDQ- Relations | Normal Hb with EA | 129 | 10.9±1.1 | 5.17 (1.83–6.67) | 2.2-3.7 | 0.00 (-2.66–2.67) | 0.19 |
| | | Sub normal Hb with EA | 124 | 11.0±0.9 | 5.00 (1.17–6.83) | 0.3-0.8 | 0.00 (-2.67–2.33) | |
| Foley (2001)[2] 48 weeks **N**=104 (13.5 g/dL arm, **n**=60; 10 g/dL arm, **n**=54) | KDQ-fatigue | EA target 13.5 g/dL (Concentric LV hypertrophy) | 34 | 12.2 (11.9,12.5) | 4.41 (4.10,4.73) | NR | **Mean (95%CI)** to week 24: 0.46 (0.17,0.75) to week 48: 0.25 (-0.05,0.55) | To week 24: *P*=0.004 To week 48: *P*=0.22 |
| | | EA target 13.5 g/dL (LV dilation) | 39 | 12.3 (12.0,12.5) | | | | |
| | | EA target 10 g/dL (Concentric LV hypertrophy) | 36 | 10.4 (10.2,10.6) | 4.53 (4.15,4.91) | NR | To week 24: -0.04 (-0.22,0.14) To week 48: | |

| STUDY | PRO INSTRUMENT | TREATMENT | N | BASELINE Hb MEAN (SD) or Mean (95% CI) (g/dL) | BASELINE PRO | Hb (g/dL)/Hct(%) LEVELS or CHANGE IN Hb (g/dL)/Hct (%) LEVELS | CHANGE IN PRO | STAT SIGNIF |
|---|---|---|---|---|---|---|---|---|
| | KDQ-depression | EA target 10 g/dL (LV dilation) | 36 | 10.4 (10.2,10.6) | 5.02 (4.69,5.35) | NR | -0.01 (-0.30,0.29) | Week 24: *P*=0.083 Week 48: *P*=0.49 |
| | | EA target 13.5 g/dL (Concentric LV hypertrophy) | 34 | 12.2 (11.9,12.5) | | | To week 24: 0.30 (0.06,0.53) To week 48: 0.05 (-0.28,0.37) | |
| | | EA target 13.5 g/dL (LV dilation) | 39 | 12.3 (12.0,12.5) | | | | |
| | | EA target 10 g/dL (Concentric LV hypertrophy) | 36 | 10.4 (10.2,10.6) | 5.20 (4.81,5.59) | NR | To week 24: 0.00 (-0.23,0.24) To week 48: 0.20 (-0.11,0.51) | |
| | | EA target 10 g/dL (LV dilation) | 36 | 10.4 (10.2,10.6) | | | | |
| | KDQ-relationships | EA target 13.5 g/dL (Concentric LV hypertrophy) | 34 | 12.2 (11.9,12.5) | 5.04 (4.78,5.29) | NR | To week 24: 0.31 (0.15,0.48) To week 48: -0.07 (-0.38,0.24) | Week 24: *P*=0.025 Week 48: *P*=0.31 |
| | | EA target 13.5 g/dL (LV dilation) | 39 | 12.3 (12.0,12.5) | | | | |
| | | EA target 10 g/dL (Concentric LV hypertrophy) | 36 | 10.4 (10.2,10.6) | 4.96 (4.49,5.32) | NR | To week 24: -0.04 (-0.31,0.23) To week 48: 0.20 (-0.15,0.46) | |
| | | EA target 10 g/dL(LV dilation) | 36 | 10.4 (10.2,10.6) | | | | |
| | KDQ-physical symptoms | EA target 13.5 g/dL (Concentric LV hypertrophy) | 34 | 12.2 (11.9,12.5) | 3.49 (3.17,3.81) | NR | To week 24: 0.79 (0.39,1.20) To week 48: 1.10 (0.55,1.64) | Week 24: *P*=0.76 WEEK 48: *P*=0.84 |
| | | EA target 13.5 g/dL (LV dilation) | 39 | 12.3 (12.0,12.5) | | | | |
| | | EA target 10 g/dL (Concentric LV hypertrophy) | 36 | 10.4 (10.2,10.6) | 3.68 (3.28,4.08) | NR | To week 24: 0.71 (0.38,1.04) To week 48: 1.17 (0.76,1.57) | |
| | | EA target 10 g/dL(LV | 36 | 10.4 (10.2,10.6) | | | | |

| STUDY | PRO INSTRUMENT | TREATMENT | N | BASELINE Hb MEAN (SD) or Mean (95% CI) (g/dL) | BASELINE PRO | Hb (g/dL)/Hct(%) LEVELS or CHANGE IN Hb (g/dL)/Hct (%) LEVELS | CHANGE IN PRO | STAT SIGNIF |
|---|---|---|---|---|---|---|---|---|
| | KDQ—Frustration | dilation)<br>EA target 13.5 g/dL (Concentric LV hypertrophy) | 34 | 12.2 (11.9,12.5) | 4.93 (4.57,5.30) | NR | To week 24: 0.16 (-0.08,0.39)<br>To week 48: -0.07 (-0.38,0.24) | Week 24: *P*=0.36<br>Week 48: *P*=0.31 |
| | | EA target 13.5 g/dL (LV dilation) | 39 | 12.3 (12.0,12.5) | | | | |
| | | EA target 10 g/dL (Concentric LV hypertrophy) | 36 | 10.4 (10.2,10.6) | 5.07 (4.66,5.08) | NR | To week 24: -0.01 (-0.31,0.27)<br>To week 48: 0.15 (-0.15,0.46) | |
| | | EA target 10 g/dL (LV dilation) | 36 | 10.4 (10.2,10.6) | | | | |
| Muirhead (1992)[3] (SC Epoetin alfa vs IV Epoetin alfa) 24 weeks | Physical | SC | 45 | After run-in: 8.01±1.37 | 4.3±1.2 | **Mean (SD)**<br>After stabilization: 11.8±0.81;<br>24 week: 10.93±1.05 | After stabilization: 0.53±0.890*;<br>week 8 0.70±1.0*;<br>week 16 0.55±1.1*;<br>week 24 0.69±1.2*<br>(*p<0.005) | |
| | | IV | 36 | After run-in:7.74 ±1.53 | 4.3±1.1 | After stabilization 11.5±0.8<br>24 week: 11.2±1.1 | | |
| | Fatigue | SC | 45 | After run-in: 8.01±1.37 | 4.5±1.4 | After stabilization: 11.7±0.81;<br>24 week: 10.93±1.05 | 0.45±0.90<br>0.46±1.1* | |
| | | IV | 36 | After run-in:7.74 ±1.53 | 4.3±1.4 | After stabilization 11.5±0.8<br>24 week: 11.2±1.1 | 0.24±1.2<br>0.34±14**<br>(*p<0.005; **p<0.05) | |
| | Relationship | SC | 45 | After run-in: 8.01±1.37 | 5.2±1.0 | After stabilization: 11.7±0.81; | 0.14±0.71<br>0.10±0.77 | |

| STUDY | PRO INSTRUMENT | TREATMENT | N | BASELINE Hb MEAN (SD) or Mean (95% CI) (g/dL) | BASELINE PRO | Hb (g/dL)/Hct(%) LEVELS or CHANGE IN Hb (g/dL)/Hct (%) LEVELS | CHANGE IN PRO | STAT SIGNIF |
|---|---|---|---|---|---|---|---|---|
| | | | | | | 24 week: 10.93±1.05 | 0.06±0.88 | |
| | | | | | | | 0.15±0.93 | |
| | | IV | 36 | After run-in:7.74 ±1.53 | 4.9±1.2 | After stabilization 11.5±0.8 24 week: 11.2±1.1 | | |
| | Depression | SC | 45 | After run-in: 8.01±1.37 | 5.1±1.4 | After stabilization: 11.7±0.81; 24 week: 10.93±1.05 | 0.14±0.79 0.15±0.94 | |
| | | IV | 36 | After run-in:7.74 ±1.53 | 5.0±1.4 | After stabilization 11.5±0.8 24 week: 11.2±1.1 | 0.00±0.97 0.07±0.98 | |
| | Frustration | SC | 45 | After run-in: 8.01±1.37 | 5.3±1.3 | After stabilization: 11.7±0.81; 24 week: 10.93±1.05 | 0.07±0.86 0.03±0.94 | |
| | | IV | 36 | After run-in:7.74 ±1.53 | 4.9±1.5 | After stabilization 11.5±0.8 24 week: 11.2±1.1 | -0.06±0.98 -0.02±0.98 | |
| | Global physical | SC | 45 | After run-in: 8.01±1.37 | 4.5±1.2 | After stabilization: 11.7±0.81; 24 week: 10.93±1.05 | 0.46±0.75* 0.54±0.92* | |
| | | IV | 36 | After run-in:7.74 ±1.53 | 4.4±1.2 | After stabilization 11.5±0.8 24 week: | 0.35±1.1* 0.46±1.1* | |

| STUDY | PRO INSTRUMENT | TREATMENT | N | BASELINE Hb MEAN (SD) or Mean (95% CI) (g/dL) | BASELINE PRO | Hb (g/dL)/Hct(%) LEVELS or CHANGE IN Hb (g/dL)/Hct (%) LEVELS | CHANGE IN PRO | STAT SIGNIF |
|---|---|---|---|---|---|---|---|---|
| | | | | | | 11.2±1.1 | | |
| | Global emotional | SC | 45 | After run-in: 8.01±1.37 | 5.2±1.1 | After stabilization: 11.7±0.81; 24 week: 10.93±1.05 | 0.12±0.69<br>0.11±0.76 | |
| | | IV | 36 | After run-in:7.74 ±1.53 | 4.9±1.2 | After stabilization 11.5±0.8 24 week: 11.2±1.1 | 0.01±0.83<br>0.08±0.82 | |
| **Non-randomized controlled studies** | | | | | | | | |
| Barany (1993)[4] | Physical activities, physical symptoms, sleep, sexual adjustment, emotional wellbeing | NR | 24(EPO) 8 (control) | NR | NR | NR | NR | P<0.05 |
| **Open-label single arm studies** | | | | | | | | |
| | Kamotsky Index | EA | 333 | NR | 3.30 (1.33) | Average hematocrit 1st follow-up (mean 4.4 months): 0.35; 2nd follow-up(mean 10.3 months): 0.34 | Mean at 1st follow-up: 2.77(1.28); mean at 2nd follow-up: 2.75(1.24) | P<0.001 |
| Evans (1990)[5] | pain | EA | 333 | NR | 64.8% | Average hematocrit 1st follow-up (mean 4.4 months): 0.35; 2nd follow-up (mean 10.3 months): 0.34 | 1st:55.6%; 2nd: 57.2% | 0.142 |
| | No energy | | | | 83.6% | | 50.8%; 58.1% | 0.001 |
| | weak | | | | 76.7% | | 55.5%; 53.1% | 0.001 |
| | Aches, swelling, sick feeling | | | | 54.7% | | 36%; 42.7% | 0.008 |
| | dizziness | | | | 22.9% | | 13.5%; 11.9% | 0.012 |
| | anxiety | | | | 53.1% | | 33.7%; 37.3% | 0.001 |

| STUDY | PRO INSTRUMENT | TREATMENT | N | BASELINE Hb MEAN (SD) or Mean (95% CI) (g/dL) | BASELINE PRO | Hb (g/dL)/Hct(%) LEVELS or CHANGE IN Hb (g/dL)/Hct (%) LEVELS | CHANGE IN PRO | STAT SIGNIF |
|---|---|---|---|---|---|---|---|---|
| | Shortness of breath | | | | 38% | | 19%; 21.2% | 0.001 |
| | depression | | | | 40.4% | | 23.3%;37.9% | 0.496 |
| | tremors | | | | 15.9% | | 12.3%; 13.6% | 0.134 |
| | Muscle weakness | | | | 54.2% | | 37.1%; 36.9% | 0.001 |
| | Leg cramps | | | | 53.6% | | 51.1%; 42.2% | 0.034 |
| | Muscle spasms | | | | 31.8% | | 22.6%; 25.1% | 0.144 |
| | Shaky hands | | | | 31.3% | | 25.3%; 27.4% | 0.151 |
| | energy | | | | 50.4% | | 24.2%;23.4% | 0.001 |
| | pain | | | | 14.6% | | 12.5%; 15.7% | 0.253 |
| | Emotional reactions | | | | 20.3% | | 12.2%; 13.1% | 0.001 |
| | sleep | | | | 33.5% | | 26.3%; 28.1% | 0.124 |
| | Social isolation | | | | 19.3% | | 13.6%; 14.2% | 0.032 |
| | mobility | | | | 21.1% | Average hematocrit 1st follow-up (mean 4.4 months): 0.35; 2nd follow-up (mean 10.3 months): 0.34 | 16.3%;19.0% | 0.263 |
| | Job or work | EA | 333 | NR | 37.1% | | 24.4%; 28.9% | 0.080 |
| | home | | | | 55.0% | | 41.6%; 42.4% | 0.010 |
| | Social life | | | | 46.9% | | 36%; 40.8% | 0.160 |
| | Personal relationship | | | | 28.4% | | 21%; 21.3% | 0.160 |
| | Sex life | | | | 49.2% | | 40.9%; 35.7% | 0.004 |
| | hobbies | | | | 51.1% | | 33.1%; 32.9% | 0.001 |
| | Holidays | | | | 63.6% | | 57.9%; 64.6% | 0.780 |
| | Well-being | EA | 333 | NR | 11.24 (3.13) | Average hematocrit 1st follow-up (mean 4.4 months): 0.35; 2nd follow-up (mean 10.3 months): 0.34 | 11.81 (2.66); 11.87 (2.70) | 0.004 |
| | Psychological affect | | | | 5.05 (1.35) | | 5.30 (1.07); 5.25 (1.20) | 0.003 |
| | Life satisfaction | | | | 5.63 (1.77) | | 5.92 (1.61); 6.02 (1.59) | 0.017 |

These evidence tables include the most commonly cited references; a systematic review was not conducted

1. Furuland H, Linde T, Ahlmen J, Christensson A, Strombom U and Danielson BG: A randomized controlled trial of haemoglobin normalization with epoetin alfa in pre-dialysis and dialysis patients. *Nephrol Dial Transplant*. 2003;18: 353-361.
2. Foley RN, Parfrey PS, Morgan J, et al.: Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney international*. 2000;58: 1325-1335.
3. Muirhead N, Laupacis A and Wong C: Erythropoietin for anaemia in haemodialysis patients: results of a maintenance study (the Canadian Erythropoietin Study Group). *Nephrol Dial Transplant*. 1992;7: 811-816.
4. Barany P, Pettersson E and Konarski-Svensson JK: Long-term effects on quality of life in haemodialysis patients of correction of anaemia with erythropoietin. *Nephrol Dial Transplant*. 1993;8: 426-432.
5. Evans RW, Rader B and Manninen DL: The quality of life of hemodialysis recipients treated with recombinant human erythropoietin. Cooperative Multicenter EPO Clinical Trial Group. *JAMA*. 1990;263: 825-830.

## Table 5: Cardiovascular and All-cause Morbidity/Mortality Outcomes Related to Target and Achieved Hemoglobin Levels

| STUDY | OBJECTIVE | STUDY POPULATION | OUTCOMES |
|---|---|---|---|
| **Randomized trials** | | | |
| Besarab (1998)[1] | **Open label**<br>To examine the risks and benefits of normalizing the hematocrit in patients with cardiac disease who were undergoing hemodialysis. | Patients with congestive heart failure or ischemic heart disease who were undergoing **HD**; serum transferring saturation of ≥ 20%.<br>Patients treated to:<br>High target Hb arm (14 g/dL), **N**=618<br>Low target Hb arm (10 g/dL), **N**=615<br>**Median treatment duration:** 14 months | • Trend towards increased risk of CV morbidity and mortality in higher target group: RR(95%CI) = 1.3(0.9-1.9)<br>• Within each treatment arm, a higher Hct was associated with lower risk of death |
| Drueke (2006)[2] | **Open label**<br>Determine effect of treating with ESA to a high Hb target of 13-15 g/dL compared to a low Hb target of 10.5 – 11.5 g/dL on CV events on patients with Stage IV CKD patients. | Patients with **CKD-NOD** and anemia: eGFR 15-35 ml/min/1.73m$^2$, Hb 11-12.5 g/dL<br>26% had type 2 diabetes<br>Treatment groups- Treated with ESA to a target of:<br>High target arm: 13-15 g/dL, **N**=301<br>Low target arm: 10.5-11.5 g/dL, **N**=302 | • Slightly elevated (not statistically significant) occurrence of cardiovascular events in higher target group. HR=0.78 (0.53 – 1.14)<br>• Time to initiation of ESRD 1.04 (0.66 - 1.65) |
| Singh (2006)[3] | **Open label**<br>Determine effect of treating with ESA to a high Hb target of 13.5 g/dL compared to a low Hb target of less than 11.3 g/dL on CV events and mortality | Patients with **CKD-NOD** and anemia: eGFR 115-50 mL/min/1.73 m2, Hb <11 g/dL<br>~50% had type 2 diabetes<br><br>Treatment groups- Treated with ESA to a target of:<br>High arm: 13.5 g/dL, **N**=715<br>Low arm: 11.3 g/dL, **N**=717 | • Interim analysis: Higher risk of composite endpoint (CV events and mortality) in higher target group, RR 1.34(1.03 - 1.74)<br>• Trial was stopped early |
| Parfrey (2005)[9] | **Randomized double blind**<br>Determine effect of treating with ESA to a high Hb target of 13.5 – 14.5 g/dL compared to a low Hb target of less than 9.5 - 11.5 g/dL on left ventricular volume index | ncident dialysis patients<br><br>Treatment groups- Treated with ESA to a target of:<br>High arm: 13.5 – 14.5 g/dL, **N**=300<br>Low arm: 9.5 - 11.5 g/dL, **N**=296 | • No difference in percentage increase in left ventricular volume index 16.8 versus 14.2 % high versus low |
| Pfeffer (2009)[4] | **Randomized, double-blind, placebo-controlled**<br>Determine effect of treating with ESA to a target of 13 g/dL on composite CV | Patients with **CKD-NOD**, anemia and diabetes<br><br>Treatment groups:<br>Treated with ESA to target of Hb = 13 g/dL, | • No difference in risk of composite endpoint (CV events and mortality), HR(95%CI) = 1.05(0.94-1.17) compared to placebo with rescue (ESA treatment only when Hb<9 g/dL)<br>• Target to Hb of 13g/dL associated with increased risk of |

| STUDY | OBJECTIVE | STUDY POPULATION | OUTCOMES |
|---|---|---|---|
| | morbidity and mortality compared to placebo (with rescue at Hb<9g/dL) | **N**=2012 – median achieved Hb =12.5 g/dL Rescue-only ESA treatment when Hb <9 g/dL<br>**N**=2026 – median achieved Hb = 10.6 g/dL | stroke, HR(95%CI) = 1.92(1.38-2.68) compared to placebo with rescue (ESA treatment only when Hb<9g/dL) |
| **Retrospective observational studies** | | | |
| Collins (2001)[5] | To assess mortality, hospitalization, and Medicare allowable expenditures in incident hemodialysis patients | Incident **HD** patients<br>Time frame: January 1, 1996 and June 30, 1998<br>**N:** 66,761 | • Relative risk of death and all-cause, cardiovascular, and infectious hospitalizations increased significantly with declining Hb (HCT). |
| Ofsthun (2003)[6] | To determine the association between hemoglobin level and risk of mortality and hospitalization. | **HD** patients in Fresenius Medical Care-North America facilities<br>**N:**44,550<br>**Time frame:** July 1, 1998~June 30, 2000 | • There is an increased risk of death with decreasing Hb, comparing Hb <9g/dL with 9-12 g/dL<br>• No decreased risk with Hb 12-13 g/dL |
| Li (2004)[7] | To determine the association between Hct and cardiac risk | Incident **HD** patients<br>At least 9 months f/u<br>**N:** 50,579<br>**Time frame:** Jan 1, 1998 ~Dec 31, 1999. | • These is a decrease in risk of CV hospitalizations and mortality with increasing Hct, when comparing Hct 36-39% and >39% to 33-36% |
| Regidor (2006)[8] | Determine the association between achieved hemoglobin level and CV/all cause mortality | **HD** patients in DaVita database<br>**N**=58,058<br>Twelve categories of blood hemoglobin (< 9 g/dL, ≥ 14 g/dl, and 10 g/dL, increments of 0.5 g/dL in between) | • Compared to a time-varying hemoglobin of 11.5-12 g/dL, a time-varying hemoglobin of 9.5-<10 g/dL was associated with<br>o Increased risk of all-cause mortality (HR=1.50, 95% CI: 1.37-1.64)<br>o Increased risk of CV-specific mortality (HR=1.42, 95% CI: 1.23-1.63) |

These evidence tables include the most commonly cited references; a systematic review was not conducted.


1. Besarab A, Bolton WK, Browne JK, et al.: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med*. 1998;339: 584-590.
2. Drueke TB, Locatelli F, Clyne N, et al.: Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med*. 2006;355: 2071-2084.
3. Singh AK, Szczech L, Tang KL, et al.: Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med*. 2006;355: 2085-2098.
4. Pfeffer MA, Burdmann EA, Chen CY, et al.: A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *The New England journal of medicine*. 2009;361: 2019-2032.
5. Collins AJ, Li S, St Peter W, et al.: Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. *J Am Soc Nephrol*. 2001;12: 2465-2473.
6. Ofsthun N, Labrecque J, Lacson E, Keen M and Lazarus JM: The effects of higher hemoglobin levels on mortality and hospitalization in hemodialysis patients. *Kidney Int*. 2003;63: 1908-1914.

7. Li S and Collins AJ: Association of hematocrit value with cardiovascular morbidity and mortality in incident hemodialysis patients. *Kidney international*. 2004;65: 626-633.
8. Regidor DL, Kopple JD, Kovesdy CP, et al.: Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. *J Am Soc Nephrol*. 2006;17: 1181-1191.
9. Pafrey PS,Foley RN, Wittreich BH et al : Double blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. J Am Soc Nephrol. 2005;16: 2180-2189

**Table 6: Relationship Between Achieved Hemoglobin (Hematocrit) and the Risk of Hospitalization and Healthcare Resource Utilization (HRU)**

| STUDY | OBJECTIVE | STUDY POPULATION | HOSPITALIZATION AND HRU OUTCOME SUMMARY |
|---|---|---|---|
| **Retrospective data analysis** | | | |
| Xia (1999)[1] | To evaluate the association between hematocrit level and risk of hospitalization | US **HD** patients<br>**N=**71,717<br>**Time frame:** July 1993-December 1994 | • Hct and hospitalization during follow-up period: Hospital days in follow-up period monotonically decreased as Hct rose to 36%.<br>• Steady decrease in admission rates and hospital days as patient Hct increased to 33 to <36%<br>• Baseline Hct and future hospitalization: Increased risk of future hospitalization with decreasing Hct |
| Collins (2001)[2] | To evaluate the association between baseline hematocrit level and the risk of hospitalization and death | Incident US **HD** patients<br>**N**=66,761<br>**Time frame:** 1996 - 1998<br>Follow-up period: 1 year | • Compared to patients with hematocrit between 33 and 36%, those with a hematocrit < 30% had<br>  • An elevated risk of hospitalization (RR=1.42, p<0.05)<br>  • An elevated risk of cardiac hospitalization (RR=1.3, p<0.05)<br>  • An elevated risk of infectious hospitalization (RR=1.76, p<0.05)<br>  • 32.8% higher Per patient per month (PMPM) expenditures |
| Ofsthun (2003)[3] | To evaluate the association between hemoglobin level and hospitalization burden and length of stay | US **HD** patients<br>**N=**44,550<br>**Time frame:** July 1998-June 2000. | • Hospitalizations decreased monotonically from the group of Hb<9 g/dL to the group with Hb≥13 g/dL.<br>• Length of stay decreased monotonically from for the group with Hb<9 g/dL to the group with Hb≥13 g/dL. |
| Li (2004)[4] | To evaluate the association between hematocrit and risk of hospitalization | Incident US **HD** patients with at least 9 months of follow-up.<br>**N=**50,579<br>**Time frame:** January, 1998- December, 1999. | • Increasing Hct is associated with lower risk of CV-related hospitalizations<br>• Compared to pts with >33% to ≤36%, pts with Hct >36-≤39% and >39% had RR of 0.92 (95% CI 0.88-0.97) and 0.79 (95% CI 0.72 to 0.87), respectively.<br>• Trend was similar for first hospitalization due to cardiac cause and hospitalization/death in patients with pre-existing cardiac disease |
| Seliger (2010)[5] | To evaluate the association between the timing of ESA treatment initiation and the risk of hospitalization | **CKD-NOD** patients<br>(eGFR 15-<60cc/min/1.73m$^2$)<br>ESA treatment initiation at:<br>Hb 10-11 g/dL (**N**=705)<br>Hb 6-9.9 g/dL (**N**=705)<br>Propensity-score matched analysis | • Patients initiated on an ESA at Hb 10-11 g/dL had a 17% lower risk of hospitalization compared to those patients initiated on an ESA at Hb 6-9.9g/dL |

| STUDY | OBJECTIVE | STUDY POPULATION | HOSPITALIZATION AND HRU OUTCOME SUMMARY |
|---|---|---|---|
| **Prospective Data Analysis** | | | |
| Churchill (1995)[6] | To evaluate the effect of ESA use on utilization of hospital resources in hemodialysis patients | Multicenter Canadian prospective cohort study in **HD** patients<br>**N**=67 EPO treated hemodialysis patients<br>Baseline Hb 78.6 g/L<br>**N**=67 non-treated matched patient<br>Baseline Hb 74.0 g/L | • There were 58 hospitalizations in the EPO group vs. 97 in the non-treated group.<br>• Average days hospitalized per admission: 15.3 days (EPO treated) vs. 23.2 (non-treated) |

These evidence tables include the most commonly cited references; a systematic review was not conducted


1. Xia H, Ebben J, Ma JZ and Collins AJ: Hematocrit levels and hospitalization risks in hemodialysis patients. *J Am Soc Nephrol*. 1999;10: 1309-1316.
2. Collins AJ, Li S, St Peter W, et al.: Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. *J Am Soc Nephrol*. 2001;12: 2465-2473.
3. Ofsthun N, Labrecque J, Lacson E, Keen M and Lazarus JM: The effects of higher hemoglobin levels on mortality and hospitalization in hemodialysis patients. *Kidney Int*. 2003;63: 1908-1914.
4. Li S, Foley RN and Collins AJ: Anemia, hospitalization, and mortality in patients receiving peritoneal dialysis in the United States. *Kidney Int*. 2004;65: 1864-1869.
5. Seliger: Timing of ESA initiation and adverse outcomes in non-dialysis dependent CKD: a propensity matched observational cohort study. *Clin J Am Soc Nephrol*. 2010;*In press*.
6. Churchill DN, Muirhead N, Goldstein M, et al.: Effect of recombinant human erythropoietin on hospitalization of hemodialysis patients. *Clinical nephrology*. 1995;43: 184-188.

**Table 7: Hemoglobin Variability in CKD Patients**

| STUDY | OBJECTIVE | STUDY POPULATION | OUTCOMES |
|---|---|---|---|
| **Randomized prospective trial** | | | |
| West (2007)[1] | **Open-label, single-center**<br>To characterize Hb variability using functional data analysis | Ad-hoc analysis of data from prevalent **HD** patients, iron-replete<br>**N**=151 | • For majority of patients, Hb instability was small, typified by the overall mean value of 0.63 g/dL per mo<br>• The data show trajectories that vary widely and form a continuum, rather than obvious subsets<br>• The quantitative analysis of individual responses within the system revealed a continuous spectrum of measurable Hb instability, overlapping for each treatment group |
| **Retrospective data analysis** | | | |
| Fishbane (2005)[2] | To describe hemoglobin cycling in ESA-treated HD patients; to analyze etiologic factors; assess Hb fluctuations on iron storage; and to study factors associated with a greater degree of cycling. | **HD** Patients on chronic maintenance outpatient hemodialysis in a single center<br>**N**=281<br>**Time frame:** 1998-2003 | • Greater than 90% of patients experienced Hb cycling defined as one or more annual, full, extended cycle of amplitude >1.5 Hb g/dL of a duration more than 8 weeks<br>• A subpopulation of patients was identified with more frequent cycling (>2 cycles per year). No clinical factors were identified in this group other than they were more responsive to ESA than other patients (ERI 1036 ± 659 U/week/g Hb compared to 1992 ± 701 U/week/g Hb respectively) (p=0.02) |
| Lacson (2003)[3] | To quantify Hb level variability and the likelihood of falling within the Hb level goal range of 11 to 12 g/dL. | US **HD** patients in Fresenius Medical Care<br>**N=**65,009<br>**Time frame**: Jan 1-Dec 31, 2000 | • 38.4% patients had Hb 11~12 g/dL. In only 8% did Hb levels consistently remain less than 11 g/dL, and in 18%, greater than 12 g/dL all year. 29% (18,633 patients) moved from below to above target range or vice versa. The average individual patient is expected to have a±1.4-g/dL fluctuation in 3-month rolling average Hgb levels per year.<br>• Greater mean facility Hb level correlated with a greater percentage of patients with Hb levels greater than 10 g/dL ($R^2$=0.49) and greater than 12.5 g/dL ($R^2$=0.61).<br>• Despite increased mean Hb levels and EPO and iron use, the spread of the Hb distribution curve remained unchanged in the last 6 years. |
| Ebben (2006)[4] | To characterize hemoglobin level variability in US dialysis patients | US **HD** patients<br>**N**=159,720<br>Assess variability of 6-month period based on patterns of hemoglobin change using the | • 1.8% of patients had Hb < 11 for six consecutive months<br>• 6.5% of patients had Hb 11-12.5 for six consecutive months<br>• 2.0% of patients had Hb > 12.5 for six consecutive months |

| STUDY | OBJECTIVE | STUDY POPULATION | OUTCOMES |
|---|---|---|---|
| | | categories<br>• < 11 g/dL<br>• 11-12.5 g/dL<br>• > 12.5 g/dL | • 21.3% of patients had Hb fluctuations between < 11 and 11-12.5 over six months<br>• 28.9% of patients had Hb fluctuations between 11-12.5 and > 12.5 g/dL over six months<br>• 39.5% of patients had Hb < 11 and > 12.5 g/dL over six months<br>• Hospitalization events, comorbidity and intercurrent events were association with persistently low (Hb < 11 for six months) and transiently low (Hb < 11 and between 11 and 12.5) hemoglobin levels |
| Gilbertson (2008)[5] | To evaluate association between hemoglobin variability groups and mortality | US **HD** patients receiving ESAs<br>**N**=159,720<br>**Time frame**: 2004<br>Hemoglobin variability groups:<br>• Patients with Hb < 11 for six months<br>• Patients with Hb 11-12.5 for six consecutive months<br>• Patients with Hb > 12.5 for six consecutive months<br>• Patients with Hb fluctuating between < 11 and 11-12.5 over six months<br>• Patients with Hb > 11 for six consecutive months<br>• Patients with Hb levels across Hb distribution | • Patients with Hb < 11 for six consecutive months had significantly elevated risk of mortality compared to those with Hb 11-12.5 for six months (HR 2.18; 95%CI:1.93-2.45)<br>• Patients with Hb < 11 and 11-12.5 had an elevated risk of death (HR=1.44, 95% CI: 1.33-1.56) |
| Spiegel (2009)[6] | To evaluate the impact of recent events on ESA dosing patterns and consequently on hemoglobin (Hb) distribution characteristics in dialysis patients. | **HD** patients from ~87% of dialysis centers in the US.<br>**N:** 743,000<br>**Time frame:** June 2006-November 2008 | • Mean Hb level decreased by 0.37 g/dL during the indicated period<br>• standard deviation (SD) of the population Hb level distribution decreased by 0.14 g/dL and skewness increased by -0.10<br>• Hb measurements in specific ranges changed as follows: >12 g/dL, decreased by 11.3 percentage points; 10-12 g/dL, increased by 9.4 percentage points; and <10 g/dL, increased by 1.9 percentage points. The percentage of patients with Hb level >13 g/dL for ≥3 months decreased by 2.9 percentage points |
| Yang (2007)[7] | To evaluate the association between hemoglobin variability and mortality | **HD** patients have ≥3 Hb measurements, no drop-out in exposure window<br>**N**=19,150<br>Hb variability measured by:<br>• absolute level of Hb (intercept), | • Survival analyses indicated that each 1g/dL increase in the residual standard deviation was associated with a 33% increase in rate of death, even after adjusting for multiple baseline covariates<br>• Patient characteristics accounted for very little of the variation in |

| STUDY | OBJECTIVE | STUDY POPULATION | OUTCOMES |
|---|---|---|---|
| | | • temporal trend in Hb (slope)<br>• Hb variability (residual standard deviation). | hemoglobin variability metric<br>• Limitation: hospitalizations and other acute events were not included in the model used |
| Minutolo (2009)[8] | To evaluate whether intensity of epoetin therapy affects hemoglobin variability and renal survival in CKD-NOD patients. | Adult **CKD-NOD** patients with anemia patients receiving epoetin<br>**N:** 137 patients (1,198 visits)<br>**Time frame:** April 30, 2002~October 31, 2005 | • Lower hemoglobin response to first epoetin dosage was an independent predictor of higher therapeutic index(TI) (difference between rates of visits that required EPO dosage change and those with effective EPO change) (P = 0.002)<br>• From lower to higher tertile of TI, Hb variability increased, as shown by the reduction of time with Hb at target (time in target, from 9.2 ±2.0 to 3.0±2.2 mo; p < 0.0001) and the wider values of within-patient Hb standard deviation (from 0.70 to 0.96; P = 0.005) and Hb fluctuations across target (p < 0.0001)<br>• Lack of adjustment of EPO worsens Hb variability in CKD. Hb variability may be associated with renal survival, but further studies are needed to explore the association versus causal relationship |

These evidence tables include the most commonly cited references; a systematic review was not conducted.


1. West RM, Harris K, Gilthorpe MS, Tolman C and Will EJ: Functional data analysis applied to a randomized controlled clinical trial in hemodialysis patients describes the variability of patient responses in the control of renal anemia. *J Am Soc Nephrol*. 2007;18: 2371-2376.
2. Fishbane S and Berns JS: Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. *Kidney Int*. 2005;68: 1337-1343.
3. Lacson E, Jr., Ofsthun N and Lazarus JM: Effect of variability in anemia management on hemoglobin outcomes in ESRD. *Am J Kidney Dis*. 2003;41: 111-124.
4. Ebben JP, Gilbertson DT, Foley RN and Collins AJ: Hemoglobin level variability: associations with comorbidity, intercurrent events, and hospitalizations. *Clin J Am Soc Nephrol*. 2006;1: 1205-1210. .
5. Gilbertson DT, Ebben JP, Foley RN, Weinhandl ED, Bradbury BD and Collins AJ: Hemoglobin level variability: associations with mortality. *Clin J Am Soc Nephrol*. 2008;3: 133-138.
6. Spiegel DM, Khan I, Krishnan M and Mayne TJ: Changes in hemoglobin level distribution in US dialysis patients from June 2006 to November 2008. *Am J Kidney Dis*. 2009;55: 113-120.
7. Yang W, Israni RK, Brunelli SM, Joffe MM, Fishbane S and Feldman HI: Hemoglobin variability and mortality in ESRD. *J Am Soc Nephrol*. 2007;18: 3164-3170.
8. Minutolo R, Chiodini P, Cianciaruso B, et al.: Epoetin therapy and hemoglobin level variability in nondialysis patients with chronic kidney disease. *Clin J Am Soc Nephrol*. 2009;4: 552-559.

## Table 8: Patient Reported Outcomes (PROs) in CKD-NOD Patients

| STUDY | DESIGN | CHANGE IN PRO Mean (SD) | STAT SIG[§] | EFFECT SIZE | MCID | BASELINE Hb OR HCT | Hb OR Hct AT STUDY END | CHANGE IN Hb OR Hct | PER UNIT CHANGE IN ENERGY / VITALITY / ACTIVITY** |
|---|---|---|---|---|---|---|---|---|---|
| **Double-blind RCT – Energy/Vitality/Activity** | | | | | | | | | |
| Kleinman (1989)[1] ***** **Energy (Single item VAS)** N = 14 PRO FU=12 weeks | Treated (target Hct: 38 – 40 % | NR | NR* | NE | NE | NR | NR | 7.7% (Hct) | NE |
| | Placebo | NR | | NE | NE | NR | NR | -0.1% (Hct) | NE |
| Pfeffer (2009)[2] **Energy/Vitality subscale of the SF-36** N= 4047 PRO FU= 25 weeks | DA (High Hb Target: 13 g/dL) | +2.6(9.9) | p = 0.20 | 0.234 | No | 10.4 (9.8-10.8) | 12.5 g/dL | 2.1 g/dL | 1.2 |
| | Placebo | +2.1(9.7) | | 0.190 | No | 10.4 (9.8-10.8) | 10.6 g/dL | 0.2 g/dL | 10.5 |
| Singh (2006)[3] **LASA Energy score** N= 1432 PRO FU= NR | High Hb Target (13.5 g/dL) | +16.6 (23.7)* | P = 0.7 | 0.70 (Moderate) | Yes | 10.1 (0.9) g/dL | 12.6 g/dL | 2.5 g/dL | 6.6 |
| | Low Hb Target (11.3 g/dL) | +15.5 (23.1)* | | 0.67 (Moderate) | Yes | 10.1 (0.9) g/dL | 11.3 g/dL | 1.2 g/dL | 12.9 |
| The US Recombinant Human Erythropoietin Predialysis Study Group (1991)[4] *** **Energy (5-point Likert Scale)** N= 117 PRO FU=8 weeks | Anemia corrected [Target Hct: 40% (men) and 37% (women)] | +1.45 (NR) | p<0.05 | NE | NE | Range: Male = 93 to 97 g/L Female = 88 to 93 g/L | NR | NR**** | NE |
| **Open-label RCTs - Energy/Vitality/Activity** | | | | | | | | | |
| Drueke (2006)[5] **Energy/Vitality subscale of the SF-36** N =603 PRO FU= 12 months | High Hb Target (13.0 – 15.0 g/dL) | +3.8 (NR) | p< 0.001 | NE | No | 11.6 (0.6) g/dL | 13.5 g/dL | 1.9 g/dL | 2.0 |
| | Low Hb Target (10.5 – 11.5 g/dL) | -0.5 (NR) | | NE | No | 11.6 (0.6) g/dL | 11.6 g/dL | 0.0 g/dL | NE |
| MacDougall (2008)[6] **Energy/Vitality subscale of the SF-36** | Darbepoetin alfa | +7.5 (NR) | NR *** | NE | Yes | 10.2 (0.7) g/dL | 12.2 g/dL | 2.02 g/dL | 3.7 |
| | CERA | +11.2 | | NE | Yes | 10.2 (0.6) g/dL | 12.3 g/dL | 2.12 g/dL | 5.3 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| N = 297<br>PRO FU=29 weeks | | (NR) | | | | | | | |
| **STUDY** | **DESIGN** | **CHANGE IN PRO Mean (SD)** | **STAT SIG[§]** | **EFFECT SIZE** | **MCID** | **BASELINE Hb OR HCT** | **Hb OR Hct AT STUDY END** | **CHANGE IN Hb OR HCT** | **PER UNIT CHANGE IN ENERGY / VITALITY / ACTIVITY**** |
| Revicki (1995)[7]<br>**Energy/Vitality subscale of the SF-36**<br>**N**= 83<br>Untreated **N**=40<br>ESA treated **N**=43<br>PRO FU= 48 weeks | Treated (target Hct: 36 % | +5.8 (3.6)* | p = 0.04 | 1.90 (Large) | Yes | 26.8%(4.5) | 31.5% | 4.7 % (Hct) | 1.2 |
| | Untreated | -3.1 (2.0) | | -0.84 (Large) | No | 26.8% (3.6) | 25.8% | -1.0 % (Hct) | 3.1 |
| Rossert (2006)[8]<br>**Energy/Vitality subscale of the SF-36**<br>N= 224<br>PRO FU=16 weeks | High Hb Target (13.0 – 15.0 g/dL) | NR | p = 0.04 | NE | NE | 11.5 (1.0) g/dL | 13.9 g/dL | 2.4 g/dL | NE |
| | Low Hb Target (11.0 – 12.0 g/dL) | | | NE | NE | 11.6 (0.9) g/dL | 11.8 g/dL | 0.2 g/dL | NE |
| Singh (2006)[3]<br>**Energy/Vitality subscale of the SF-36**<br>N= 1432<br>PRO FU= NR | High Hb Target (13.5 g/dL) | +10.0 (22.6)* | p = 0.6 | 0.44 (Moderate) | Yes | 10.1 (0.9) g/dL | 12.6 g/dL | 2.5 g/dL | 4.0 |
| | Low Hb Target (11.3 g/dL) | +8.2 (22.4)* | | 0.36 (Moderate) | Yes | 10.1 (0.9) g/dL | 11.3 g/dL | 1.2 g/dL | 6.8 |
| Singh (2006)[3]<br>**LASA Activity Score**<br>N=1432<br>PRO FU= NR | High Hb Target (13.5 g/dL) | +15.0(39.9)* | p<0.001 to 0.02 | NE | Yes | 10.1 (0.9) g/dL | 12.6 g/dL | 2.5 g/dL | 6.0 |
| | Low Hb Target (11.3 g/dL) | +13.3(29.8)* | | NE | Yes | 10.1 (0.9) g/dL | 11.3 g/dL | 1.2 g/dL | 11.1 |
| **Open-label single-arm studies – Energy/Vitality/Activity** | | | | | | | | | |
| Alexander (2007)[9]<br>**Energy/Vitality subscale of the SF-36**<br>N= 48<br>PRO FU=16 weeks | | +14.9 (3.2) | p< 0.001 | 5.0 (Large) | Yes | 9.1 (0.1) g/dL | 12.6 g/dL | 3.5 g/dL | 4.3 |
| Benz (2007)[10]<br>**Energy/Vitality subscale of the SF-36**<br>**N**= 67<br>PRO FU=16 weeks | | +14.1 (23.9) | p< 0.05 | SRM 0.59 (Moderate) | Yes | 9.8 (0.9) g/dL | 11.7 g/dL | 1.9 g/dL | 7.4 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Benz (2007)[10]<br>**LASA Activity Score**<br>**N**=67<br>PRO FU=16 weeks | | +17.0(21.9) | p<0.05 | 0.78 SRM (Moderate) | Yes | 9.8 (0.9) g/dL | 11.7 g/dL | 1.9 g/dL | 8.9 |

| STUDY | DESIGN | CHANGE IN PRO Mean (SD) | STAT SIG§ | EFFECT SIZE | MCID | BASELINE Hb OR HCT | Hb OR Hct AT STUDY END | CHANGE IN Hb OR HCT | PER UNIT CHANGE IN ENERGY / VITALITY / ACTIVITY** |
|---|---|---|---|---|---|---|---|---|---|
| Benz (2007)[10]<br>**LASA Energy Score**<br>**N**= 67<br>PRO FU=16 weeks | | +20.6 (21.8) | p< 0.05 | SRM 0.94 (Large) | Yes | 9.8 (0.9) g/dL | 11.7 g/dL | 1.9 g/dL | 10.8 |
| Provenzano (2004)[11]<br>**LASA Activity Score**<br>**N**=1184<br>PRO FU=16 weeks | | +24.5(24.9) | p<0.0001 | 0.98 SRM (Large) | Yes | 9.1 (0.7) g/dL | 11.8 g/dL | 2.7 g/dL | 9.1 |
| Provenzano (2004)[11]<br>**LASA Energy Score**<br>**N**= 1184<br>PRO FU=16 weeks | | +27.9 (23.4) | p< 0.0001 | SRM 1.15 (Large) | Yes | 9.1 (0.7) g/dL | 11.8 g/dL | 2.7 g/dL | 10.3 |
| Provenzano (2005)[12]<br>**LASA Activity Score**<br>N= 519<br>PRO FU=16 weeks | Parallel groups | +5.4 (22.3) | p< 0.0001 | 0.24 (Small) | No | Range: 11.8 to 11.9 g/dL | Range: 11.2 to 12.0 g/dL | Range: -0.7 to +0.3 g/dL | NE |
| **Double-blind RCT – Physical Function** | | | | | | | | | |
| Pfeffer (2009)[2]<br>**Subscale of the SF-36**<br>N= 4047<br>PRO FU= 25 weeks | DA (High Hb Target: 13 g/dL) | +1.3 (9.2) | p = 0.51 | 0.12 | No | 10.4 (9.8-10.8) | 12.5 g/dL | 2.1 g/dL | 0.62 |
| | Placebo | +1.1(8.8) | | 0.10 | No | 10.4 (9.8-10.8) | 10.6 g/dL | 0.2 g/dL | 5.5 |
| **Open-label RCTs - Physical Function, Activity or Role Limitation** | | | | | | | | | |
| Drueke (2006)[5]<br>**Subscale of the SF-36**<br>N=603<br>PRO FU=12 months | High Hb Target (13.0 – 15.0 g/dL) | +3.3 (NR) | p<0.001 | NE | No | 11.6 (0.6) g/dL | 13.5 g/dL | 1.9 g/dL | 1.7 |
| | Low Hb Target (10.5 – 11.5 g/dL) | -2.2 (NR) | | NE | No | 11.6 (0.6) g/dL | 11.6 g/dL | 0.0 g/dL | NE |
| MacDougall (2008)[6]<br>**Subscale of the SF-36** | DA | +3.5 (NR) | NR | NE | No | 10.2 (0.7) g/dL | 12.2 g/dL | 2.02 g/dL | 1.7 |
| | CERA | +4.2 (NR) | | NE | No | 10.2 (0.6) g/dL | 12.3 g/dL | 2.12 g/dL | 2.0 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| N=297<br>PRO FU=29 weeks | | | | | | | | | |
| Revicki (1995)[7]<br>**Subscale of the SF-36**<br>**N**=83; PRO FU 48 weeks<br>Untreated **N**=40<br>ESA treated **N**=43 | Treated (target Hct: 36 %<br><br>Untreated | +7.8(3.8)*<br><br>-4.8 (2.1)* | p < 0.006 | 2.52 (Large)<br><br>-1.0 (Large) | Yes<br><br>Yes | 26.8%(4.5)<br><br>26.8% (3.6) | 31.5%<br><br>25.8% | 4.7 % (Hct)<br><br>-1.0 % (Hct) | 1.7<br><br>4.8 |
| **STUDY** | **DESIGN** | **CHANGE IN PRO Mean (SD)** | **STAT SIG§** | **EFFECT SIZE** | **MCID** | **BASELINE Hb OR HCT** | **Hb OR Hct AT STUDY END** | **CHANGE IN Hb OR HCT** | **PER UNIT CHANGE IN ENERGY / VITALITY / ACTIVITY**** |
| Roger (2004)[13]<br>**SF-36 Physical Composite Score**<br>N=155<br>PRO FU=24 months | High Hb target (12.0 13.0 g/dL) | -2 (14) | NR | -0.18 (-0.14 SRM) | No | 11.2 (0.9) g/L | 11.2 (0.8) g/L | 0.9 g/dL | 2.2 |
| | Low Hb target (12.0 13.0 g/dL) | -1 (13) | | -0.09 (-0.077 SRM) | No | 11.2 (0.8) g/L | 10.8 (1.3) g/L | -0.4 g/dL | 2.5 |
| Rossert (2006)[8]<br>**Subscale of the SF-36**<br>N=224<br>PRO FU=16 weeks | High Hb Target (13.0 – 15.0 g/dL) | NR | p = 0.08 | NE | NE | 11.5 (1.0) g/dL | 13.9 g/dL | 2.4 g/dL | NE |
| | Low Hb Target (11.0 – 12.0 g/dL) | NR | | NE | NE | 11.6 (0.9) g/dL | 11.8 g/dL | 0.2 g/dL | NE |
| **Open-label single-arm studies – Physical Function, Activity or Role Limitation** | | | | | | | | | |
| Abu-Alfa (2008)[14]<br>**SF-36 Physical Composite Score**<br>N=277<br>PRO FU=52 weeks | Single arm | +3.3 (8.7) | P<0.001 | 0.308 (0.379) (Small) | No | 10 (0.9) g/dL | 11.8 (1.1) g/dL | 1.8 (1.3) g/dL | 1.8 |
| Alexander (2007)[9]<br>**Subscale of the SF-36**<br>**N**=48<br>PRO FU=16 weeks | | +9.5 (2.9) | p<0.05 | 2.38 (Large) | Yes | 9.1 (0.1) g/dL | 12.6 g/dL | 3.5 g/dL | 2.7 |
| Benz (2007)[10]<br>**Subscale of the SF-36**<br>**N**=67<br>PRO FU=16 weeks | | +7.8 (20.9) | p<0.05 | *SRM* 0.37 (Small) | Yes | 9.8 (0.9) g/dL | 11.7 g/dL | 1.9 g/dL | 4.1 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Islam (2005)[15]<br>**Nottingham Scale**<br>N=45<br>PRO FU=6 months | Single arm | _9 (68.8) | P<0.001 | 0.13 | NE | 27.85% (1.5) | 32.81% (3.92) | 4.95% (Hct) | 1.8 |
| Kleinman (1989)[16]<br>**Single item VAS**<br>N=14<br>PRO FU=12 weeks | Treatment (target Hct: 38 – 40 %) | NR | NR | NE | NE | NR | NR | 7.7% Hct | NE |
| | Placebo | NR | | NE | NE | NR | NR | -0.1% Hct | NE |

| STUDY | DESIGN | CHANGE IN PRO Mean (SD) | STAT SIG[§] | EFFECT SIZE | MCID | BASELINE Hb OR HCT | Hb OR Hct AT STUDY END | CHANGE IN Hb OR HCT | PER UNIT CHANGE IN ENERGY / VITALITY / ACTIVITY** |
|---|---|---|---|---|---|---|---|---|---|
| The US Recombinant Human Erythropoietin Predialysis Study Group (1991)[4] ***<br>**5 Point Likert**<br>N=117<br>PRO FU=8 weeks | Anemia corrected [Target Hct: 40% (men) and 37% (women)] | 92 (NR) **** | p<0.05 | NE | NE | Range: Male = 93 to 97 g/L Female = 88 to 93 g/L | NR | NR***** | NE |
| | Anemia not corrected | 32 (NR) | | NE | NE | Male = 99 (16) g/L Female = 94 (8) g/L | NR | NR | NE |

*RCT = Randomized control trial, PRO FU = Follow up, NR = Not Reported, NE = Not Evaluable, SF-36 = Short Form 36*
*[*] Represents significant within-group changes from baseline*
[§]Statistical significance reported for randomized control trials is the between-groups comparison of change from baseline.
**Change in PRO divided by change in Hb (or change in Hematocrit)
*PRO FU = Follow up, NR = Not Reported, NE = Not Evaluable, VAS = Visual Analogue Scale, KDQ = Kidney Disease Questionnaire, FACT = Functional Assessment of Cancer Therapy*
[§]Statistical significance reported for randomized control trials is the between-groups comparison of change from baseline.
** Change in PRO divided by change in Hb (or change in Hematocrit)
***The US Recombinant Human Erythropoietin Predialysis Study Group (1991) randomized patients to one of four treatment groups, including placebo. Quality of life results were reported by two groups, anemia corrected and anemia not corrected.
****The US Recombinant Human Erythropoietin Predialysis Study Group (1991) reports the percent of patients in each arm showing at least 6% change in hematocrit.
***** Kleinman (1989) reports “quality of life improvement” in treated patients, but not in patients in placebo group.

These evidence tables include the most commonly cited references; a systematic review was not conducted.

1. Kleinman KS, Schweitzer SU, Perdue ST, Bleifer KH and Abels RI: The use of recombinant human erythropoietin in the correction of anemia in predialysis patients and its effect on renal function: a double-blind, placebo-controlled trial. *Am J Kidney Dis*. 1989;14: 486-495.
2. Pfeffer MA, Burdmann EA, Chen CY, et al.: A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *The New England journal of medicine*. 2009;361: 2019-2032.
3. Singh AK, Szczech L, Tang KL, et al.: Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med*. 2006;355: 2085-2098.
4. The US Recombinant Human Erythropoietin Predialysis Study Group. Double-blind, placebo-controlled study of the therapeutic use of recombinant human erythropoietin for anemia associated with chronic renal failure in predialysis patients. *Am J Kidney Dis*. 1991;18: 50-59.
5. Drueke TB, Locatelli F, Clyne N, et al.: Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med*. 2006;355: 2071-2084.
6. Macdougall IC, Walker R, Provenzano R, et al.: C.E.R.A. corrects anemia in patients with chronic kidney disease not on dialysis: results of a randomized clinical trial. *Clin J Am Soc Nephrol*. 2008;3: 337-347.
7. Revicki DA, Brown RE, Feeny DH, et al.: Health-related quality of life associated with recombinant human erythropoietin therapy for predialysis chronic renal disease patients. *Am J Kidney Dis*. 1995;25: 548-554.
8. Rossert J, Levin A, Roger SD, et al.: Effect of early correction of anemia on the progression of CKD. *Am J Kidney Dis*. 2006;47: 738-750.
9. Alexander M, Kewalramani R, Agodoa I and Globe D: Association of anemia correction with health related quality of life in patients not on dialysis. *Curr Med Res Opin*. 2007;23: 2997-3008.
10. Benz R, Schmidt R, Kelly K and Wolfson M: Epoetin alfa once every 2 weeks is effective for initiation of treatment of anemia of chronic kidney disease. *Clin J Am Soc Nephrol*. 2007;2: 215-221. .
11. Provenzano R, Garcia-Mayol L, Suchinda P, et al.: Once-weekly epoetin alfa for treating the anemia of chronic kidney disease. *Clin Nephrol*. 2004;61: 392-405.
12. Provenzano R, Bhaduri S and Singh AK: Extended epoetin alfa dosing as maintenance treatment for the anemia of chronic kidney disease: the PROMPT study. *Clinical nephrology*. 2005;64: 113-123.
13. Roger SD, McMahon LP, Clarkson A, et al.: Effects of early and late intervention with epoetin alpha on left ventricular mass among patients with chronic kidney disease (stage 3 or 4): results of a randomized clinical trial. *J Am Soc Nephrol*. 2004;15: 148-156.
14. Abu-Alfa AK, Sloan L, Charytan C, et al.: The association of darbepoetin alfa with hemoglobin and health-related quality of life in patients with chronic kidney disease not receiving dialysis. *Curr Med Res Opin*. 2008;24: 1091-1100.
15. Islam S, Rahman H and Rashid HU: Effect rHuEpo on predialysis CRF patients: study of 45 cases. *Bangladesh Medical Research Council bulletin*. 2005;31: 83-87.
16. Kleinman KS, Schweitzer SU, Perdue ST, Bleifer KH and Abels RI: The use of recombinant human erythropoietin in the correction of anemia in predialysis patients and its effect on renal function: a double-blind, placebo-controlled trial. *Am J Kidney Dis*. 1989;14: 486-495.

## Technical Appendix 2 – Literature References

## Technical Appendix 3 – Package Inserts for Aranesp and EPOGEN

**Aranesp®**
**(darbepoetin alfa)**
**For Injection**

**WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR EVENTS, THROMBOEMBOLIC EVENTS, STROKE and INCREASED RISK OF TUMOR PROGRESSION OR RECURRENCE**

***Chronic Renal Failure:***

- **In clinical studies, patients experienced greater risks for death, serious cardiovascular events, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target hemoglobin levels of 13 g/dL and above.**
- **Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL.**

***Cancer:***

- **ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers (see WARNINGS: Table 1).**
- **To decrease these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusion.**
- **Because of these risks, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense Aranesp® to patients with cancer. To enroll in the ESA APPRISE Oncology Program, visit www.esa-apprise.com or call 1-866-284-8089 for further assistance.**
- **Use ESAs only for treatment of anemia due to concomitant myelosuppressive chemotherapy.**
- **ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.**
- **Discontinue following the completion of a chemotherapy course.**

**(See WARNINGS: Increased Mortality, Serious Cardiovascular Events, Thromboembolic Events, and Stroke, WARNINGS: Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence, INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION.)**

### 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 or subcutaneous 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 receiving or not receiving dialysis and cancer patients receiving chemotherapy.

Following intravenous administration in CRF patients receiving dialysis, 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 administration of Aranesp® to CRF patients (receiving or not receiving dialysis), absorption was slow and peak concentrations occurred at 48 hours (range: 12 to 72 hours). In CRF patients receiving dialysis, the average half-life was 46 hours (range: 12 to 89 hours), and in CRF patients not receiving dialysis, the average half-life was 70 hours (range: 35 to 139 hours). Aranesp® apparent clearance was approximately 1.4 times faster on average in patients receiving dialysis compared to patients not receiving dialysis. The bioavailability of Aranesp® in CRF patients receiving dialysis after subcutaneous administration was 37% (range: 30% to 50%).

Following the first subcutaneous 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 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 intravenously or subcutaneously on a once weekly schedule and 4.5 to 15 mcg/kg administered subcutaneously on a once every 3 week 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 intravenous or subcutaneous Aranesp® dose, Cmax and half-life were similar to those obtained in adult CRF patients on dialysis. Following a single subcutaneous dose, the average bioavailability was 54% (range: 32% to 70%), which was higher than that obtained in adult CRF patients on dialysis.

**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®**

*Once Weekly Aranesp® Starting Dose*

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. In both studies, the starting dose of Aranesp® was 0.45 mcg/kg administered once weekly. The starting dose of Epoetin alfa was 50 Units/kg 3 times weekly in Study N1 and 50 Units/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** for recommended clinical hemoglobin target.) The primary efficacy endpoint was the proportion of patients who experienced at least a 1 g/dL increase in hemoglobin concentration to a level of at least 11 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 1.1 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).

*Once Every 2 Week Aranesp® Starting Dose*

In two single arm studies (N3 and N4), Aranesp® was administered for the correction of anemia in CRF patients not receiving dialysis. In both studies, the starting dose of Aranesp® was 0.75 mcg/kg administered once every 2 weeks.

In Study N3 (study duration of 18 weeks), the hemoglobin goal (hemoglobin concentration $\geq$ 11 g/dL) was achieved by 92% (95% CI: 86%, 96%) of the 128 patients treated with Aranesp®.

In Study N4 (study duration of 24 weeks), the hemoglobin goal (hemoglobin concentration of 11-13 g/dL) was achieved by 85% (95% CI: 77%, 93%) of the 75 patients treated with Aranesp®.

**Conversion From Other Recombinant Erythropoietins**

Two adult studies (N5 and N6) and one pediatric study (N7) 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** 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 N5 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 N6 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 N5, 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 N6, 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 N7 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 (subcutaneously or intravenously) 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***

Efficacy in patients with anemia due to concomitant chemotherapy was demonstrated based on reduction in the requirement for RBC transfusions.

*Once Weekly 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 Dosing*

The safety and effectiveness of once every 3 week 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 once every 3 weeks (n = 353) or 2.25 mcg/kg (n = 352) administered weekly as a subcutaneous 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 once every 3 week group and 1.35 mcg/kg in the once weekly 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 once every 3 week group, 254 patients (72%) required dose reductions (median time to first reduction at 6 weeks). In the once weekly 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 once every 3 week group and 337 patients in the once weekly 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 once every 3 week group and 34% (95% CI: 29%, 39%) in the weekly group required a RBC transfusion. The observed difference in the transfusion rates (once every 3 week-once weekly) was -6.7% (95% CI: -13.8%, 0.4%).

**INDICATIONS AND USAGE**

**Anemia With Chronic Renal Failure**

Aranesp® is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis.

**Anemia With Non-Myeloid Malignancies Due to Chemotherapy**

Aranesp® is indicated for the treatment of anemia due to the effect of concomitantly administered chemotherapy based on studies that have shown a reduction in the need for RBC transfusions in patients with metastatic, non-myeloid malignancies. Studies to determine whether Aranesp® increases mortality or decreases progression-free/recurrence-free survival are ongoing.

- Aranesp® is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy.
- Aranesp® is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure due to the absence of studies that adequately characterize the impact of Aranesp® on progression-free and overall survival (see **WARNINGS: Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence**).
- Aranesp® use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.

**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 Events, Thromboembolic Events, and Stroke**

Patients with chronic renal failure experienced greater risks for death, serious cardiovascular events, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target hemoglobin levels of 13 g/dL and above in clinical studies. Patients with chronic renal failure and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular events and mortality than other patients. Aranesp® and other ESAs increased the risks for death and serious cardiovascular events in controlled clinical trials of patients with cancer. These events included myocardial infarction, stroke, congestive heart failure, and hemodialysis vascular access thrombosis. A rate of hemoglobin rise of > 1 g/dL over 2 weeks may contribute to these risks.

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]

In a randomized, double-blind, placebo-controlled study of 4038 patients, there was an increased risk of stroke when Aranesp® was administered to patients with anemia, type 2 diabetes, and CRF who were not on dialysis. Patients were randomized to Aranesp® treatment targeted to a hemoglobin level of 13 g/dL or to placebo. Placebo patients received Aranesp® only if their hemoglobin levels were less than 9 g/dL. A total of 101 patients receiving Aranesp® experienced stroke compared to 53 patients receiving placebo (5% vs. 2.6%; HR 1.92, 95% CI: 1.38, 2.68; p < 0.001).

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 $14 \pm 1$ g/dL or $10 \pm 1$ 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 5**).

In a randomized controlled study (referred to as Cancer Study 1 - 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).[4]

A systematic review of 57 randomized controlled trials (including Cancer Studies 1 and 5 - 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.

**Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence**

Erythropoiesis-stimulating agents resulted in decreased locoregional control/progression-free survival and/or overall survival (see Table 1). These findings were observed in studies of patients with advanced head and neck cancer receiving radiation therapy (Cancer Studies 5 and 6), in patients receiving chemotherapy for metastatic breast cancer (Cancer Study 1) or lymphoid malignancy (Cancer Study 2), and in patients with non-small cell lung cancer or various malignancies who were not receiving chemotherapy or radiotherapy (Cancer Studies 7 and 8).

**Table 1: Randomized, Controlled Trials with Decreased Survival and/or Decreased Locoregional Control**

| Study / Tumor / (n) | Hemoglobin Target | Achieved Hemoglobin (Median Q1,Q3) | Primary Endpoint | Adverse Outcome for ESA-containing Arm |
|---|---|---|---|---|
| **Chemotherapy** | | | | |
| **Cancer Study 1**<br>Metastatic breast cancer<br>(n=939) | 12-14 g/dL | 12.9 g/dL<br>12.2, 13.3 g/dL | 12-month overall survival | Decreased 12-month survival |
| **Cancer Study 2**<br>Lymphoid malignancy<br>(n=344) | 13-15 g/dL (M)<br>13-14 g/dL (F) | 11.0 g/dL<br>9.8, 12.1 g/dL | Proportion of patients achieving a hemoglobin response | Decreased overall survival |
| **Cancer Study 3**<br>Early breast cancer<br>(n=733) | 12.5-13 g/dL | 13.1 g/dL<br>12.5, 13.7 g/dL | Relapse-free and overall survival | Decreased 3 yr. relapse-free and overall survival |

| | | | | |
|---|---|---|---|---|
| **Cancer Study 4**<br>Cervical Cancer<br>(n=114) | 12-14 g/dL | 12.7 g/dL<br>12.1, 13.3 g/dL | Progression-free and overall survival and locoregional control | Decreased 3 yr. progression-free and overall survival and locoregional control |
| **Radiotherapy Alone** | | | | |
| **Cancer Study 5**<br>Head and neck cancer<br>(n=351) | ≥15 g/dL (M)<br>≥14 g/dL (F) | Not available | Locoregional progression-free survival | Decreased 5-year locoregional progression-free survival<br>Decreased overall survival |
| **Cancer Study 6**<br>Head and neck cancer<br>(n=522) | 14-15.5 g/dL | Not available | Locoregional disease control | Decreased locoregional disease control |
| **No Chemotherapy or Radiotherapy** | | | | |
| **Cancer Study 7**<br>Non-small cell lung cancer<br>(n=70) | 12-14 g/dL | Not available | Quality of life | Decreased overall survival |
| **Cancer Study 8**<br>Non-myeloid malignancy<br>(n=989) | 12-13 g/dL | 10.6 g/dL<br>9.4, 11.8 g/dL | RBC transfusions | Decreased overall survival |

*Decreased overall survival:*

Cancer Study 1 (the 'BEST' study) was previously described (see **WARNINGS: Increased Mortality, Serious Cardiovascular Events, Thromboembolic Events, and Stroke**). 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. Survival at 12 months was significantly lower in the Epoetin alfa arm (70% vs. 76%, HR 1.37, 95% CI: 1.07, 1.75; p = 0.012).[4]

Cancer Study 2 was a Phase 3, double-blind, randomized (Aranesp® vs. placebo) study conducted in 344 anemic patients with lymphoid malignancy receiving chemotherapy. With a median follow-up of 29 months, overall mortality rates were significantly higher among patients randomized to Aranesp® as compared to placebo (HR 1.36, 95% CI: 1.02, 1.82).

Cancer Study 7 was a Phase 3, multicenter, randomized (Epoetin alfa vs. placebo), double-blind study, in which patients with advanced non-small cell lung cancer receiving only palliative radiotherapy or no active therapy were treated with Epoetin alfa to achieve and maintain hemoglobin levels between 12 and 14 g/dL. Following an interim analysis of 70 of 300 patients planned, a significant difference in survival in favor of the patients on the placebo arm of the trial was observed (median survival 63 vs. 129 days; HR 1.84; p = 0.04).

Cancer Study 8 was 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. The median survival was shorter in the Aranesp® treatment group (8 months) compared with the placebo group (10.8 months); HR 1.30, 95% CI: 1.07, 1.57.

*Decreased progression-free survival and overall survival:*

Cancer Study 3 (the 'PREPARE' study) was a randomized controlled study in which Aranesp® was administered to prevent anemia conducted in 733 women receiving neo-adjuvant breast cancer treatment. After a median follow-up of approximately 3 years the survival rate (86% vs. 90%, HR 1.42, 95% CI: 0.93, 2.18) and relapse-free survival rate were lower (72% vs. 78%, HR 1.33, 95% CI: 0.99, 1.79) in the Aranesp®-treated arm compared to the control arm.

Cancer Study 4 (protocol GOG 191) was a randomized controlled study that enrolled 114 of a planned 460 cervical cancer patients receiving chemotherapy and radiotherapy. Patients were randomized to receive Epoetin alfa to maintain hemoglobin between 12 and 14 g/dL or to transfusion support as needed. The study was terminated prematurely due to an increase in thromboembolic events in Epoetin alfa-treated patients compared to control (19% vs. 9%). Both local recurrence (21% vs. 20%) and distant recurrence (12% vs. 7%) were more frequent in Epoetin alfa-treated patients compared to control. Progression-free survival at 3 years was lower in the Epoetin alfa-treated group compared to control (59% vs. 62%, HR 1.06, 95% CI: 0.58, 1.91). Overall survival at 3 years was lower in the Epoetin alfa-treated group compared to control (61% vs. 71%, HR 1.28, 95% CI: 0.68, 2.42).

Cancer Study 5 (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. Overall survival was significantly shorter in patients receiving Epoetin beta (HR 1.39, 95% CI: 1.05, 1.84; p = 0.02).

*Decreased locoregional control:*

Cancer Study 6 (DAHANCA 10) was conducted in 522 patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy randomized to Aranesp® with radiotherapy or radiotherapy alone. An interim analysis on 484 patients demonstrated that locoregional control at 5 years was significantly shorter in patients receiving Aranesp® (RR 1.44, 95% CI: 1.06, 1.96; p = 0.02). Overall survival was shorter in patients receiving Aranesp® (RR 1.28, 95% CI: 0.98, 1.68; p = 0.08).

**ESA APPRISE Oncology Program**

Prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense Aranesp® to patients with cancer. To enroll, visit www.esa-apprise.com or call 1-866-284-8089 for further assistance. Additionally, prescribers and patients must provide written acknowledgment of a discussion of the risks associated with Aranesp®.

**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 ESAs by subcutaneous administration. PRCA has also been reported in patients receiving ESAs while undergoing treatment for hepatitis C with interferon and ribavirin. 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 ESAs. 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 ESAs 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**). See **DOSAGE AND ADMINISTRATION: *Chronic Renal Failure Patients*, Dose Adjustment** for management of patients with an insufficient hemoglobin response to Aranesp® therapy.

**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 range (10 to 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 CRF patients not on dialysis generally receive less frequent monitoring of blood pressure and laboratory parameters than dialysis patients, CRF patients not on dialysis 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.

**Patients Transitioning to Dialysis**

During the transition period onto dialysis, hemoglobin and blood pressure should be monitored carefully and patients may need to have their maintenance doses adjusted to maintain hemoglobin levels within the range of 10 to 12 g/dL (see **DOSAGE AND ADMINISTRATION: Maintenance Dose**).

**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 increased risk of tumor progression or recurrence (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.

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. Patients should be instructed to read the Aranesp® Medication Guide and Patient Instructions for Use and should be informed that the Medication Guide is not a disclosure of all possible side effects. 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 1801 CRF patients in clinical studies of Aranesp®, 44% were age 65 and over, while 17% 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 events with Aranesp® were infection, congestive heart failure, angina pectoris/cardiac chest pain, thrombosis vascular access, and cardiac arrhythmia/cardiac arrest. The most frequently reported adverse events 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 infection, hypertension, hypotension, and muscle spasm. See **WARNINGS: Increased Mortality, Serious Cardiovascular Events, Thromboembolic Events, and Stroke** and **Hypertension**.

The data described below reflect exposure to Aranesp® in 1801 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 = 978). These data include a pooled analysis of CRF patients not on dialysis and dialysis patients who were studied for the correction of anemia and maintenance of hemoglobin.

The population encompassed an age range from 18 to 94 years. Fifty-five percent of the patients were male. The percentages of Caucasian, Black, Asian, and Hispanic patients were 80%, 13%, 3%, and 2%, respectively. The median weekly dose of Aranesp® for patients who received either

once weekly or once every 2 week administration was 0.44 mcg/kg (25th, 75th percentiles: 0.30, 0.64 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 2 reflect those adverse events occurring in at least 5% of patients treated with Aranesp®.

**Table 2. Adverse Events Occurring in ≥ 5% of CRF Patients**

| Event | Patients Treated with Aranesp® (n = 1801) |
|---|---|
| APPLICATION SITE | |
| Injection Site Pain | 6% |
| BODY AS A WHOLE | |
| Peripheral Edema | 10% |
| Fatigue | 9% |
| Fever | 7% |
| Death | 6% |
| Chest Pain, Unspecified | 7% |
| Fluid Overload | 6% |
| Access Infection | 6% |
| Influenza-like Symptoms | 6% |
| Access Hemorrhage | 7% |
| Asthenia | 5% |
| CARDIOVASCULAR | |
| Hypertension | 20% |
| Hypotension | 20% |
| Cardiac Arrhythmias/Cardiac Arrest | 8% |
| Angina Pectoris/Cardiac Chest Pain | 8% |
| Thrombosis Vascular Access | 6% |
| Congestive Heart Failure | 5% |
| CNS/PNS | |
| Headache | 15% |
| Dizziness | 7% |
| GASTROINTESTINAL | |
| Diarrhea | 14% |
| Vomiting | 14% |
| Nausea | 11% |
| Abdominal Pain | 10% |
| Constipation | 5% |
| MUSCULO-SKELETAL | |
| Muscle Spasm | 17% |
| Arthralgia | 9% |
| Limb Pain | 8% |
| Back Pain | 7% |

(Continued)

**Table 2. Adverse Events Occurring in ≥ 5% of CRF Patients (Continued)**

| Event | Patients Treated with Aranesp® (n = 1801) |
|---|---|
| RESISTANCE MECHANISM | |
| Infection[a] | 24% |
| RESPIRATORY | |
| Upper Respiratory Infection | 15% |
| Dyspnea | 10% |
| Cough | 9% |
| Bronchitis | 5% |
| SKIN AND APPENDAGES | |
| Pruritus | 6% |

[a] Infection includes sepsis, bacteremia, pneumonia, peritonitis, and abscess.

The incidence rates for other clinically significant events are shown in Table 3.

**Table 3. Percent Incidence of Other Clinically Significant Events in CRF Patients**

| Event | Patients Treated with Aranesp® (n = 1801) |
|---|---|
| Acute Myocardial Infarction | 2% |
| Stroke | 2% |
| Seizure | 1% |
| Transient Ischemic Attack | ≤1% |

*Pediatric Patients*

In Study N7, 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 events with Aranesp® were catheter sepsis, fever, catheter related infection, chronic renal failure, and vascular access complication. The most commonly reported adverse events were fever, headache, nasopharyngitis, hypertension, hypotension, injection site pain, cough, peritonitis, and vomiting. 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® once weekly (547, 63%), once every 2 weeks (128, 16%), and once every 3 weeks (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 4**). Except for those events listed in Tables 4 and 5, 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 4. 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 5. 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 once every 3 weeks (n = 353) and Aranesp® 2.25 mcg/kg once weekly (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**

**IMPORTANT: See BOXED WARNINGS and WARNINGS: Increased Mortality, Serious Cardiovascular Events, Thromboembolic Events, and Stroke.**

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 needlesticks.

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® may be administered either intravenously or subcutaneously as a single weekly injection. ***In patients on hemodialysis, the intravenous 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. During therapy, hematological parameters should be monitored regularly. Doses must be individualized to ensure that hemoglobin is maintained at an appropriate level for each patient.

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.

Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL.

**Starting Dose**

**Correction of Anemia**

The initial dose by subcutaneous or intravenous administration is 0.45 mcg/kg body weight, as a single injection once weekly. Alternatively, in patients not receiving dialysis, an initial dose of 0.75 mcg/kg may be administered subcutaneously as a single injection once every 2 weeks. If hemoglobin excursions outside the recommended range occur, the Aranesp® dose should be adjusted as described below.

The use of Aranesp® in pediatric CRF patients as the initial treatment to correct anemia has not been studied.

**Maintenance Dose**

The dose should be individualized to maintain hemoglobin levels within the range of 10 to 12 g/dL (see Dose Adjustment). If hemoglobin excursions outside the recommended range occur, the Aranesp® dose should be adjusted as described below. For many patients, the appropriate maintenance dose will be lower than the starting dose. CRF patients not on dialysis, in particular, may require lower maintenance doses. In the maintenance phase, Aranesp® may continue to be administered as a single injection once weekly or once every 2 weeks.

**Dose Adjustment**

The dose should be adjusted for each patient to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL. If hemoglobin excursions outside the recommended range occur, the Aranesp® dose should be adjusted as described below. 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.

For patients whose hemoglobin does not attain a level within the range of 10 to 12 g/dL despite the use of appropriate Aranesp® dose titrations over a 12-week period:

- do not administer higher Aranesp® doses and use the lowest dose that will maintain a hemoglobin level sufficient to avoid the need for recurrent RBC transfusions,
- evaluate and treat for other causes of anemia (see **PRECAUTIONS: Lack or Loss of Response to Aranesp®**), and
- thereafter, hemoglobin should continue to be monitored and if responsiveness improves, Aranesp® dose adjustments should be made as described above; discontinue Aranesp® if responsiveness does not improve and the patient needs recurrent RBC transfusions.

**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 6**). 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. Because of variability, doses should be titrated to achieve and maintain hemoglobin levels within the range of 10 to 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 (intravenous or subcutaneous) should be maintained.

**Table 6. 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***

Only prescribers enrolled in the ESA APPRISE Oncology Program may prescribe and/or dispense Aranesp® (see **WARNINGS: ESA APPRISE Oncology Program)**.

For pediatric patients, see **PRECAUTIONS: Pediatric Use**.

The recommended starting dose for Aranesp® administered weekly is 2.25 mcg/kg as a subcutaneous injection.

The recommended starting dose for Aranesp® administered once every 3 weeks is 500 mcg as a subcutaneous injection.

Therapy should not be initiated at hemoglobin levels≥ 10 g/dL. For both dosing schedules, the dose should be adjusted for each patient to maintain the lowest hemoglobin level sufficient to

avoid RBC transfusion. If the rate of hemoglobin increase is more than 1 g/dL per 2-week period or when the hemoglobin reaches a level needed to avoid transfusion, the dose should be reduced by 40% of the previous dose. If the hemoglobin exceeds a level needed to avoid transfusion, Aranesp® should be temporarily withheld until the hemoglobin approaches a level where transfusions may be required. 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.

Discontinue Aranesp® if after 8 weeks of therapy there is no response as measured by hemoglobin levels or if transfusions are still required.

Discontinue Aranesp® following the completion of a chemotherapy course (see **BOXED WARNINGS: *Cancer***).

**Preparation and Administration of Aranesp®**

Do not shake Aranesp® or leave vials, syringes, or prefilled SureClick™ autoinjectors exposed to light. After removing the vials, prefilled syringes, or autoinjectors from the refrigerator, 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 “Patient Instructions for Use” insert 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.**

**REFERENCES**

1. Egrie JC, Browne JK. Development and characterization of novel erythropoiesis stimulating protein (NESP). *Br J Cancer*. 2001; 84 (suppl 1): 3-10.
2. Singh AK, Szczech L, Tang KL, et al. Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease. *N Engl J Med.* 2006; 355: 2085-98.
3. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med*. 1998; 339: 584-590.
4. Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining Normal Hemoglobin Levels With Epoetin Alfa in Mainly Nonanemic Patients With Metastatic Breast Cancer Receiving First-Line Chemotherapy: A Survival Study. *JCO.* 2005; 23(25): 1-13.
5. Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant Human Erythropoietins and Cancer Patients: Updated Meta-Analysis of 57 Studies Including 9353 Patients. *J Natl Cancer Inst.* 2006; 98: 708-14.

**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.

AMGEN®

**Manufactured by:**

Amgen Manufacturing, Limited, a subsidiary of Amgen Inc.

One Amgen Center Drive

Thousand Oaks, CA 91320-1799



* UltraSafe® is a registered trademark of Safety Syringes, Inc.

1xxxxxx – v23

Revised: 02/2010

**EPOGEN®**
**(Epoetin alfa)**
**FOR INJECTION**

**WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR EVENTS, THROMBOEMBOLIC EVENTS, STROKE and INCREASED RISK OF TUMOR PROGRESSION OR RECURRENCE**

***Chronic Renal Failure:***

- **In clinical studies, patients experienced greater risks for death, serious cardiovascular events, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target hemoglobin levels of 13 g/dL and above.**
- **Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL.**

***Cancer:***

- **ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers (see WARNINGS: Table 1).**
- **To decrease these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusion.**
- **Because of these risks, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense EPOGEN® to patients with cancer. To enroll in the ESA APPRISE Oncology Program, visit www.esa-apprise.com or call 1-866-284-8089 for further assistance.**
- **Use ESAs only for treatment of anemia due to concomitant myelosuppressive chemotherapy.**
- **ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.**
- **Discontinue following the completion of a chemotherapy course.**

***Perisurgery:*** **EPOGEN® increased the rate of deep venous thromboses in patients not receiving prophylactic anticoagulation. Consider deep venous thrombosis prophylaxis.**

**(See WARNINGS: Increased Mortality, Serious Cardiovascular Events, Thromboembolic Events, and Stroke, WARNINGS: Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence, INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION.)**

## 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.[4-12] 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.[13-15] 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.[16] 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.[39]

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 ($13.3 \pm 12.4$ vs. $14.2 \pm 6.7$ hours, and $20.2 \pm 15.9$ vs. $23.6 \pm 9.5$ 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 $T_{max}$ ($38 \pm 18$ hours) and lower clearance ($9.2 \pm 4.7$ mL/h/kg) during Week 1 when patients were receiving chemotherapy (n = 18) compared with those ($22 \pm 4.5$ hours, $13.9 \pm 7.6$ 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 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.

### *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® use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.

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 ≤ 500 mUnits/mL and when patients are receiving a dose of zidovudine ≤ 4200 mg/week.

***Treatment of Anemia in Cancer Patients on Chemotherapy***

EPOGEN® is indicated for the treatment of anemia due to the effect of concomitantly administered chemotherapy based on studies that have shown a reduction in the need for RBC transfusions in patients with metastatic, non-myeloid malignancies receiving chemotherapy for a minimum of 2 months. Studies to determine whether EPOGEN® increases mortality or decreases progression-free/recurrence-free survival are ongoing.

- EPOGEN® is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy.
- EPOGEN® is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure due to the absence of studies that adequately characterize the impact of EPOGEN® on progression-free and overall survival (see WARNINGS: Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence).
- 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 (see PRECAUTIONS: Lack or Loss of Response).
- EPOGEN® use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.

***Reduction of Allogeneic Blood Transfusion in Surgery Patients***

EPOGEN® is indicated for the treatment of anemic patients (hemoglobin > 10 to ≤ 13 g/dL) who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions.[17-19] 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**

When dosed with EPOGEN®, patients responded with an increase in hematocrit.[5] After 3 months on study, more than 95% of patients were transfusion-independent.

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 (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 |

In a 26 week, double-blind, placebo-controlled trial, 118 anemic dialysis patients with an average hemoglobin of approximately 7 g/dL were randomized to either EPOGEN® or placebo. By the end of the study, average hemoglobin increased to approximately 11 g/dL in the EPOGEN®-treated patients and remained unchanged in patients receiving placebo. EPOGEN®-treated patients experienced improvements in exercise tolerance and patient-reported physical functioning at month 2 that was maintained throughout the study.

*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.[20]

*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.[21-22]

***Zidovudine-treated HIV-infected Patients***

Efficacy in HIV-infected patients with anemia related to therapy with zidovudine was demonstrated based on reduction in the requirement for RBC transfusions.

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.[23]

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.[23-25]

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**

Efficacy in patients with anemia due to concomitant chemotherapy was demonstrated based on reduction in the requirement for RBC transfusions.

**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. [23]

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,[19,26] 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.[17] All patients received oral iron and a low-dose post-operative warfarin regimen.[17]

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.[17] 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®.[17]

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.[18] 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.[18] The mean increase in absolute reticulocyte count was smaller in the weekly group (0.11 x $10^6$/$mm^3$) compared to the daily group (0.17 x $10^6$/$mm^3$). 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].[18] 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 Events, Thromboembolic Events, and Stroke

Patients with chronic renal failure experienced greater risks for death, serious cardiovascular events, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target hemoglobin levels of 13 g/dL and above in clinical studies. Patients with chronic renal failure and an insufficient hemoglobin response to ESA therapy may

be at even greater risk for cardiovascular events and mortality than other patients. EPOGEN® and other ESAs increased the risks for death and serious cardiovascular events in controlled clinical trials of patients with cancer. These events included myocardial infarction, stroke, congestive heart failure, and hemodialysis vascular access thrombosis. A rate of hemoglobin rise of > 1 g/dL over 2 weeks may contribute to these risks.

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).[40]

In a randomized, double-blind, placebo-controlled study of 4038 patients, there was an increased risk of stroke when darbepoetin alfa was administered to patients with anemia, type 2 diabetes, and CRF who were not on dialysis. Patients were randomized to darbepoetin alfa treatment targeted to a hemoglobin level of 13 g/dL or to placebo. Placebo patients received darbepoetin alfa only if their hemoglobin levels were less than 9 g/dL. A total of 101 patients receiving darbepoetin alfa experienced stroke compared to 53 patients receiving placebo (5% vs. 2.6%; HR 1.92, 95% CI: 1.38, 2.68; p < 0.001).

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%.[37] 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 Cancer Study 1 - 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).[43]

A systematic review of 57 randomized controlled trials (including Cancer Studies 1 and 5 - 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.[41]

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. Deep venous thrombosis 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.[42] ESAs are not approved for reduction of allogeneic red blood cell transfusions in patients scheduled for cardiac surgery.

**Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence**

Erythropoiesis-stimulating agents resulted in decreased locoregional control/progression-free survival and/or overall survival (see Table 1). These findings were observed in studies of patients with advanced head and neck cancer receiving radiation therapy (Cancer Studies 5 and 6), in patients receiving chemotherapy for metastatic breast cancer (Cancer Study 1) or lymphoid malignancy (Cancer Study 2), and in patients with non-small cell lung cancer or various malignancies who were not receiving chemotherapy or radiotherapy (Cancer Studies 7 and 8).

**Table 1: Randomized, Controlled Trials with Decreased Survival and/or Decreased Locoregional Control**

| Study / Tumor / (n) | Hemoglobin Target | Achieved Hemoglobin (Median Q1,Q3) | Primary Endpoint | Adverse Outcome for ESA-containing Arm |
|---|---|---|---|---|
| **Chemotherapy** | | | | |
| **Cancer Study 1** Metastatic breast cancer (n=939) | 12-14 g/dL | 12.9 g/dL 12.2, 13.3 g/dL | 12-month overall survival | Decreased 12-month survival |

| | | | | |
|---|---|---|---|---|
| **Cancer Study 2**<br>Lymphoid malignancy<br>(n=344) | 13-15 g/dL (M)<br>13-14 g/dL (F) | 11.0 g/dL<br>9.8, 12.1 g/dL | Proportion of patients achieving a hemoglobin response | Decreased overall survival |
| **Cancer Study 3**<br>Early breast cancer<br>(n=733) | 12.5-13 g/dL | 13.1 g/dL<br>12.5, 13.7 g/dL | Relapse-free and overall survival | Decreased 3 yr. relapse-free and overall survival |
| **Cancer Study 4**<br>Cervical Cancer<br>(n=114) | 12-14 g/dL | 12.7 g/dL<br>12.1, 13.3 g/dL | Progression-free and overall survival and locoregional control | Decreased 3 yr. progression-free and overall survival and locoregional control |
| **Radiotherapy Alone** | | | | |
| **Cancer Study 5**<br>Head and neck cancer<br>(n=351) | ≥15 g/dL (M)<br>≥14 g/dL (F) | Not available | Locoregional progression-free survival | Decreased 5-year locoregional progression-free survival<br>Decreased overall survival |
| **Cancer Study 6**<br>Head and neck cancer<br>(n=522) | 14-15.5 g/dL | Not available | Locoregional disease control | Decreased locoregional disease control |
| **No Chemotherapy or Radiotherapy** | | | | |
| **Cancer Study 7**<br>Non-small cell lung cancer<br>(n=70) | 12-14 g/dL | Not available | Quality of life | Decreased overall survival |
| **Cancer Study 8**<br>Non-myeloid malignancy<br>(n=989) | 12-13 g/dL | 10.6 g/dL<br>9.4, 11.8 g/dL | RBC transfusions | Decreased overall survival |

*Decreased overall survival:*

Cancer Study 1 (the 'BEST' study) was previously described (see WARNINGS: Increased Mortality, Serious Cardiovascular Events, Thromboembolic Events, and Stroke). 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. Survival at 12 months was significantly lower in the Epoetin alfa arm (70% vs. 76%, HR 1.37, 95% CI: 1.07, 1.75; p = 0.012).[43]

Cancer Study 2 was a Phase 3, double-blind, randomized (darbepoetin alfa vs. placebo) study conducted in 344 anemic patients with lymphoid malignancy receiving chemotherapy. With a median follow-up of 29 months, overall mortality rates were significantly higher among patients randomized to darbepoetin alfa as compared to placebo (HR 1.36, 95% CI: 1.02, 1.82).

Cancer Study 7 was a Phase 3, multicenter, randomized (Epoetin alfa vs. placebo), double-blind study, in which patients with advanced non-small cell lung cancer receiving

only palliative radiotherapy or no active therapy were treated with Epoetin alfa to achieve and maintain hemoglobin levels between 12 and 14 g/dL. Following an interim analysis of 70 of 300 patients planned, a significant difference in survival in favor of the patients on the placebo arm of the trial was observed (median survival 63 vs. 129 days; HR 1.84; p = 0.04).

Cancer Study 8 was 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. The median survival was shorter in the darbepoetin alfa treatment group (8 months) compared with the placebo group (10.8 months); HR 1.30, 95% CI: 1.07, 1.57.

*Decreased progression-free survival and overall survival:*
Cancer Study 3 (the 'PREPARE' study) was a randomized controlled study in which darbepoetin alfa was administered to prevent anemia conducted in 733 women receiving neo-adjuvant breast cancer treatment. After a median follow-up of approximately 3 years, the survival rate (86% vs. 90%, HR 1.42, 95% CI: 0.93, 2.18) and relapse-free survival rate (72% vs. 78%, HR 1.33, 95% CI: 0.99, 1.79) were lower in the darbepoetin alfa-treated arm compared to the control arm.

Cancer Study 4 (protocol GOG 191) was a randomized controlled study that enrolled 114 of a planned 460 cervical cancer patients receiving chemotherapy and radiotherapy. Patients were randomized to receive Epoetin alfa to maintain hemoglobin between 12 and 14 g/dL or to transfusion support as needed. The study was terminated prematurely due to an increase in thromboembolic events in Epoetin alfa-treated patients compared to control (19% vs. 9%). Both local recurrence (21% vs. 20%) and distant recurrence (12% vs. 7%) were more frequent in Epoetin alfa-treated patients compared to control. Progression-free survival at 3 years was lower in the Epoetin alfa-treated group compared to control (59% vs. 62%, HR 1.06, 95% CI: 0.58, 1.91). Overall survival at 3 years was lower in the Epoetin alfa-treated group compared to control (61% vs. 71%, HR 1.28, 95% CI: 0.68, 2.42).

Cancer Study 5 (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. Overall survival was significantly shorter in patients receiving Epoetin beta (HR 1.39, 95% CI: 1.05, 1.84; p = 0.02).[38]

*Decreased locoregional control:*
Cancer Study 6 (DAHANCA 10) was conducted in 522 patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy randomized to darbepoetin alfa with radiotherapy or radiotherapy alone. An interim analysis on 484 patients demonstrated that locoregional control at 5 years was significantly shorter in patients receiving darbepoetin alfa (RR 1.44, 95% CI: 1.06, 1.96; p = 0.02). Overall survival was shorter in patients receiving darbepoetin alfa (RR 1.28, 95% CI: 0.98, 1.68; p = 0.08).

**ESA APPRISE Oncology Program**

Prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense EPOGEN® to patients with cancer. To enroll, visit www.esa-apprise.com or call 1-866-284-8089 for further assistance. Additionally, prescribers and patients must provide written acknowledgement of a discussion of the risks associated with EPOGEN®.

**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 ESAs by subcutaneous administration. PRCA has also been reported in patients receiving ESAs while undergoing treatment for hepatitis C with interferon and ribavirin. 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 ESAs. 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 ESAs 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. 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 dose of EPOGEN® should be carefully adjusted to achieve and maintain hemoglobin levels between 10-12 g/dL (see WARNINGS: Increased Mortality, Serious

Cardiovascular Events, Thromboembolic Events, and Stroke, 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).

See DOSAGE AND ADMINISTRATION: Chronic Renal Failure Patients for management of patients with an insufficient hemoglobin response to EPOGEN® therapy.

**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[27-30] provides supportive evidence of the safety and effectiveness of EPOGEN® in pediatric CRF patients on dialysis.*

Pediatric Patients Not Requiring Dialysis: Published literature30,31 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 literature32,33 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 increased risk of tumor progression or recurrence (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 instructed to read the EPOGEN® Medication Guide and Patient Instructions for Use and should be informed that the Medication Guide is not a disclosure of all possible side 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.

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 hemoglobin 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[8,9] or the efficiency of high flux hemodialysis.[10] 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®.[23]

***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 Events, Thromboembolic Events, and Stroke).

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.[34-36]

**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.[23] In 71 patients from this group treated with EPOGEN® at 150 Units/kg TIW, serum p24 antigen levels did not appear to increase.[25] Preliminary data showed no enhancement of HIV replication in infected cell lines in vitro.[23]

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.[23] 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.[17,19,26] 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.[18]

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: SEE BOXED WARNINGS AND WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR EVENTS, THROMBOEMBOLIC EVENTS, AND STROKE.

***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. Individualize dosing to achieve and maintain hemoglobin levels between 10-12 g/dL. 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. If hemoglobin excursions outside the recommended range occur, the EPOGEN® dose should be adjusted as described below.

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). 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:

Individually titrate to achieve and maintain hemoglobin levels between 10 to 12 g/dL.

| | |
|---|---|
| Starting Dose: | |
| Adults | 50 to 100 Units/kg TIW; IV or SC |
| Pediatric Patients | 50 Units/kg TIW; IV or SC |
| Increase Dose by 25% If: | 1. Hemoglobin is < 10 g/dL and has not increased by 1 g/dL after 4 weeks of therapy or<br>2. Hemoglobin decreases below 10 g/dL |
| Reduce Dose by 25% When: | 1. Hemoglobin approaches 12 g/dL or,<br>2. Hemoglobin increases > 1 g/dL in any 2-week period |

During therapy, hematological parameters should be monitored regularly. Doses must be individualized to ensure that hemoglobin is maintained at an appropriate level for each patient.

*For patients whose hemoglobin does not attain a level within the range of 10 to 12 g/dL despite the use of appropriate EPOGEN® dose titrations over a 12-week period:*

- do not administer higher EPOGEN® doses and use the lowest dose that will maintain a hemoglobin level sufficient to avoid the need for recurrent RBC transfusions,
- evaluate and treat for other causes of anemia (see PRECAUTIONS: Lack or Loss of Response), and
- thereafter, hemoglobin should continue to be monitored and if responsiveness improves, EPOGEN® dose adjustments should be made as described above; discontinue EPOGEN® if responsiveness does not improve and the patient needs recurrent RBC transfusions.

**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 hemoglobin levels between 10 to 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 dose should also be individualized to maintain hemoglobin levels between 10 to 12 g/dL. 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 the upper safety limit of 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 the upper safety limit of 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***

Only prescribers enrolled in the ESA APPRISE Oncology Program may prescribe and/or dispense EPOGEN® (see **WARNINGS: ESA APPRISE Oncology Program)**.

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. Therapy should not be initiated at hemoglobin levels ≥ 10 g/dL. 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 (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. The initial recommended dose of EPOGEN® in pediatric patients is 600 Units/kg IV weekly. Discontinue EPOGEN® following the completion of a chemotherapy course (see BOXED WARNINGS: *Cancer*).

**Dose Modification**

**TIW Dosing**

| | |
|---|---|
| Starting Dose: | |
| Adults | 150 Units/kg SC TIW |
| Reduce Dose by 25% when: | Hemoglobin reaches a level needed to avoid transfusion or increases > 1 g/dL in any 2-week period. |
| Withhold Dose if: | Hemoglobin exceeds a level needed to avoid transfusion. Restart at 25% below the previous dose when the hemoglobin approaches a level where transfusions may be required. |
| Increase Dose to 300 Units/kg TIW if: | Response is not satisfactory (no reduction in transfusion requirements or rise in hemoglobin) after 4 weeks to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion. |
| Discontinue: | If after 8 weeks of therapy there is no response as measured by hemoglobin levels or if transfusions are still required. |

**Weekly Dosing**

| | |
|---|---|
| Starting Dose: | |
| Adults | 40,000 Units SC |
| Pediatrics | 600 Units/kg IV (maximum 40,000 Units) |
| Reduce Dose by 25% when: | Hemoglobin reaches a level needed to avoid transfusion or increases > 1 g/dL in any 2-weeks. |
| Withhold Dose if: | Hemoglobin exceeds a level needed to avoid transfusion and restart at 25% below the previous dose when the hemoglobin approaches a level where transfusions may be required. |
| Increase Dose if:<br>For Adults: 60,000 Units SC Weekly<br>For Pediatrics: 900 Units/kg IV (maximum 60,000 Units) if: | Response is not satisfactory (no increase in hemoglobin by ≥ 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. |
| Discontinue: | If after 8 weeks of therapy there is no response as measured by hemoglobin levels or if transfusions are still required. |

***Surgery Patients***

Prior to initiating treatment with EPOGEN® a hemoglobin should be obtained to establish that it is > 10 to ≤ 13 g/dL.[17] 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.[18]

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. Deep venous thrombosis 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. Protect the solution from light. 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. Protect from light.**

**REFERENCES**

1. Egrie JC, Strickland TW, Lane J, et al. Characterization and Biological Effects of Recombinant Human Erythropoietin. *Immunobiol*. 1986;72:213-224.
2. Graber SE, Krantz SB. Erythropoietin and the Control of Red Cell Production. *Ann Rev Med*. 1978;29:51-66.
3. Eschbach JW, Adamson JW. Anemia of End-Stage Renal Disease (ESRD). *Kidney Intl.* 1985;28:1-5.
4. Eschbach JW, Egrie JC, Downing MR, et al. Correction of the Anemia of End-Stage Renal Disease with Recombinant Human Erythropoietin. *NEJM*. 1987;316:73-78.
5. Eschbach JW, Abdulhadi MH, Browne JK, et al. Recombinant Human Erythropoietin in Anemic Patients with End-Stage Renal Disease. *Ann Intern Med*. 1989;111:992-1000.
6. Eschbach JW, Egrie JC, Downing MR, et al. The Use of Recombinant Human Erythropoietin (r-HuEPO): Effect in End-Stage Renal Disease (ESRD). In: Friedman, Beyer, DeSanto, Giordano, eds. *Prevention of Chronic Uremia.* Philadelphia, PA: Field and Wood Inc; 1989: 148-155.
7. Egrie JC, Eschbach JW, McGuire T, Adamson JW. Pharmacokinetics of Recombinant Human Erythropoietin (r-HuEPO) Administered to Hemodialysis (HD) Patients. *Kidney Intl*. 1988;33:262.
8. Paganini E, Garcia J, Ellis P, et al. Clinical Sequelae of Correction of Anemia with Recombinant Human Erythropoietin (r-HuEPO); Urea Kinetics, Dialyzer Function and Reuse. *Am J Kid Dis*. 1988;11:16.
9. Delano BG, Lundin AP, Golansky R, et al. Dialyzer Urea and Creatinine Clearances Not Significantly Changed in r-HuEPO Treated Maintenance Hemodialysis (MD) Patients. *Kidney Intl*. 1988;33:219.
10. Stivelman J, Van Wyck D, Ogden D. Use of Recombinant Erythropoietin (r-HuEPO) with High Flux Dialysis (HFD) Does Not Worsen Azotemia or Shorten Access Survival. *Kidney Intl*. 1988;33:239.
11. Lim VS, DeGowin RL, Zavala D, et al. Recombinant Human Erythropoietin Treatment in Pre-Dialysis Patients: A Double-Blind Placebo Controlled Trial. *Ann Int Med*.
1989;110:108-114.
12. Stone WJ, Graber SE, Krantz SB, et al. Treatment of the Anemia of Pre-Dialysis Patients with Recombinant Human Erythropoietin: A Randomized, Placebo-Controlled Trial*. Am J Med Sci*. 1988;296:171-179.

13. Braun A, Ding R, Seidel C, Fies T, Kurtz A, Scharer K. Pharmacokinetics of recombinant human erythropoietin applied subcutaneously to children with chronic renal failure. *Pediatr Nephrol*. 1993;7:61-64.

14. Geva P, Sherwood JB. Pharmacokinetics of recombinant human erythropoietin (rHuEPO) in pediatric patients on chronic cycling peritoneal dialysis (CCPD). *Blood*. 1991;78 (Suppl 1):91a.

15. Jabs K, Grant JR, Harmon W, *et al.* Pharmacokinetics of Epoetin alfa (rHuEPO) in pediatric hemodialysis (HD) patients. *J Am Soc Nephrol*. 1991;2:380.

16. Kling PJ, Widness JA, Guillery EN, Veng-Pedersen P, Peters C, DeAlarcon PA. Pharmacokinetics and pharmacodynamics of erythropoietin during therapy in an infant with renal failure. *J Pediatr*. 1992;121:822-825.

17. deAndrade JR and Jove M. Baseline Hemoglobin as a Predictor of Risk of Transfusion and Response to Epoetin alfa in Orthoperdic Surgery Patients. *Am. J. of Orthoped*. 1996;25 (8):533-542.

18. Goldberg MA and McCutchen JW. A Safety and Efficacy Comparison Study of Two Dosing Regimens of Epoetin alfa in Patients Undergoing Major Orthopedic Surgery. *Am. J. of Orthoped*. 1996;25 (8):544-552.

19. Faris PM and Ritter MA. The Effects of Recombinant Human Erythropoietin on Perioperative Transfusion Requirements in Patients Having a Major Orthopedic Operation. *J. Bone and Joint surgery*. 1996;78-A:62-72.

20. Amgen Inc., data on file.

21. Eschbach JW, Kelly MR, Haley NR, et al. Treatment of the Anemia of Progressive Renal Failure with Recombinant Human Erythropoietin. *NEJM*. 1989;321:158-163.

22. The US Recombinant Human Erythropoietin Predialysis Study Group. Double-Blind, Placebo-Controlled Study of the Therapeutic Use of Recombinant Human Erythropoietin for Anemia Associated with Chronic Renal Failure in Predialysis Patients. *Am J Kid Dis*. 1991;18:50-59.

23. Ortho Biologics, Inc., data on file.

24. Danna RP, Rudnick SA, Abels RI. Erythropoietin Therapy for the Anemia Associated with AIDS and AIDS Therapy and Cancer. In: MB Garnick, ed. *Erythropoietin in Clinical Applications - An International Perspective*. New York, NY: Marcel Dekker; 1990:301-324.

25. Fischl M, Galpin JE, Levine JD, et al. Recombinant Human Erythropoietin for Patients with AIDS Treated with Zidovudine. *NEJM*. 1990;322:1488-1493.

26. Laupacis A. Effectiveness of Perioperative Recombinant Human Eyrthropoietin in Elective Hip Replacement. *Lancet*. 1993;341:1228-1232.

27. Campos A, Garin EH. Therapy of renal anemia in children and adolescents with recombinant human erythropoietin (rHuEPO). *Clin Pediatr* (Phila). 1992;31:94-99.

28. Montini G, Zacchello G, Baraldi E, et al. Benefits and risks of anemia correction with recombinant human erythropoietin in children maintained by hemodialysis. *J Pediatr*. 1990;117:556-560.

29. Offner G, Hoyer PF, Latta K, Winkler L, Brodehl J, Scigalla P. One year's experience with recombinant erythropoietin in children undergoing continuous ambulatory or cycling peritoneal dialysis. *Pediatr Nephrol*. 1990;4:498-500.

30. Muller-Wiefel DE, Scigalla P. Specific problems of renal anemia in childhood. *Contrib Nephrol.* 1988;66:71-84.

31. Scharer K, Klare B, Dressel P, Gretz N. Treatment of renal anemia by subcutaneous erythropoietin in children with preterminal chronic renal failure. *Acta Paediatr.* 1993;82:953-958.

32. Mueller BU, Jacobsen RN, Jarosinski P, et al. Erythropoietin for zidovudine-associated anemia in children with HIV infection. *Pediatr AIDS and HIV Infect: Fetus to Adolesc.* 1994;5:169-173.

33. Zuccotti GV, Plebani A, Biasucci G, et al. Granulocyte-colony stimulating factor and erythropoietin therapy in children with human immunodeficiency virus infection. *J Int Med Res.* 1996;24:115-121.

34. Raskin NH, Fishman RA. Neurologic Disorders in Renal Failure (First of Two Parts). *NEJM*. 1976;294:143-148.

35. Raskin NH and Fishman RA. Neurologic Disorders in Renal Failure (Second of Two Parts). *NEJM*. 1976;294:204-210.

36. Messing RO, Simon RP. Seizures as a Manifestation of Systemic Disease. *Neurologic Clinics*. 1986;4:563-584.

37. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *NEJM.* 1998;339:584-90.

38. Henke, M, Laszig, R, Rübe, C., et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomized, double-blind, placebo-controlled trial. *The Lancet.* 2003; 362:1255-1260.

39. Widness JA, Veng-Pedersen P, Peters C, Pereira LM, Schmidt RL, Lowe SL. Erythropoietin Pharmacokinetics in Premature Infants: Developmental, Nonlinearity, and Treatment Effects. *J Appl Physiol.* 1996;80 (1):140-148.

40. Singh AK, Szczech L, Tang KL, et al. Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease, *N Engl j Med.* 2006; 355:2085-98.

41. Bohlius J, Wilson J, Seidenfeld J, et at. Recombinant HumanErythropoietins and Cancer Patients: Updated Meta-Analysis of 57 Studies Including 9353 Patients. *J Natl Cancer Inst.* 2006; 98:708-14.

42. D'Ambra MN, Gray RJ, Hillman R, et al. Effect of Recombinant Human Erythropoietin on Transfusion Risk in Coronary Bypass Patients. *Ann Thorac Surg.* 1997; 64: 1686-93.

43. Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining Normal Hemoglobin Levels With Epoetin Alfa in Mainly Nonanemic Patients With Metastatic Breast Cancer Receiving First-Line Chemotherapy: A Survival Study. *JCO.* 2005; 23(25): 1-13.

This product's label may have been revised after this insert was used in production. For further product information and the current package insert, please visit www.amgen.com or call our medical information department toll-free at 1-800-77AMGEN (1-800-772-6436).

**Manufactured by:**
Amgen Manufacturing, Limited, a subsidiary of Amgen Inc.
One Amgen Center Drive

Thousand Oaks, CA 91320-1799



1xxxxxx – v24
Revised: 02/2010