BACKGROUND INFORMATION

FOR

THE ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

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KEY POINTS:

Overview:

- Amgen and Johnson & Johnson Pharmaceutical Research & Development (J&JPRD) are committed to robust risk management to optimize the safety of our products.
- The purpose of the forthcoming Oncologic Drugs Advisory Committee (ODAC) meeting is to discuss the benefit:risk profile of erythropoiesis stimulating agents (ESAs) in patients with cancer, particularly within the licensed indication of chemotherapy-induced anemia (CIA). As such, this briefing document addresses the following:
    - all available data pertaining to ESA safety, including new data from studies that have been provided to the FDA for review
    - updates on the ongoing pharmacovigilance studies and proposals for further large, definitive, placebo-controlled studies evaluating the safety of ESAs within the labeled CIA indication
    - ongoing and proposed risk management and risk minimization action plans to promote informed benefit:risk discussions and decisions between patients and their physicians (particularly, oncologists):
        - labeling changes
        - risk communication to healthcare professionals through physician, patient, and patient advocacy group initiatives designed to ensure awareness of the risks of ESA use
        - Medication Guide, including an enhanced distribution system to ascertain distribution and receipt by patients
        - formal assessment of appropriateness of ESA use
        - formal evaluation of these activities, with regular reporting to FDA

Benefits of ESAs in CIA

- ESAs offer the only alternative to RBC transfusions in patients with CIA.
- RBC transfusions, which are primarily administered to treat symptomatic anemia, are associated with significant inherent risks and increase the burden on the US blood supply.

- ESAs have been proven to reduce RBC transfusions in patients with CIA in well-controlled clinical studies, supported by comprehensive meta-analyses.
- An extensive published literature of placebo-controlled studies supports the benefits of ESAs in improving anemia symptoms such as fatigue, which is recognized in practice guidelines and product labeling outside the US. Although these data do not meet FDA's current guidance for the registration of patient-reported outcome (PRO) endpoints, they are consistent with the expected clinical benefit of correcting anemia.

Safety Concerns in Patients With Cancer Receiving ESAs

- Over 50 randomized, controlled studies have reported data for mortality and/or tumor progression in patients with cancer.
- Data from 8 individual studies that have become available over the last 5 years have suggested a potential negative effect of ESAs on survival and/or tumor progression in patients with cancer. Two of these studies (PREPARE and GOG-191) were recently included in proposed labeling after the data became available in November 2007. All 8 studies were conducted in treatment settings not approved for ESAs; however, legitimate concerns remain that these risks have not been adequately excluded in the labeled setting.
- Other controlled studies of ESAs also performed outside of the labeled indication, but considered to be informative with respect to mortality and/or tumor progression, have not suggested an increased risk of these events.
- Meta-analyses in over 8000 subjects do not indicate a clear effect of ESAs on mortality or tumor progression. This is in contrast to the well-documented risk of vascular thrombotic events (VTE), which has consistently been detected in individual studies and meta-analyses.
- Amgen and J&JPRD believe that the results of meta-analyses must be considered in light of the significant safety signals that were observed in the individual studies noted. However, the lack of a consistent effect of ESAs on the risk of mortality or tumor progression in CIA across individual studies indicates that further research in the labeled indication is needed.

- Amgen and J&JPRD are working closely with FDA to design additional large, well-controlled, definitive studies to specifically explore the effect of ESAs on mortality and tumor progression when administered in accordance with approved labeling.
- The companies continue to proactively evaluate and accelerate the communication of all studies (including those for which Amgen and J&JPRD are not the sponsor) that could contribute useful information to the assessment of ESA safety in CIA.
- The observed risks in individual studies are prominently communicated in the BOXED WARNING and WARNINGS AND PRECAUTIONS sections of the current product labeling for epoetin alfa and darbepoetin alfa.

Potential Mechanisms for an Increased Risk of Mortality

- Hypotheses for a true biologic effect of ESAs on survival include the following:
  - Increased risk of cardiovascular and thromboembolic events with ESAs:

    VTEs are common in cancer patients, and certain chemotherapy regimens increase this risk. VTEs are also a recognized complication of ESA treatment. It is known that VTEs are underdiagnosed as a proximate cause of death in cancer patients. Thus, it is plausible that VTE could represent a mechanism for increased mortality with ESAs in cancer patients.
  - Increased risk of tumor promotion and/or angiogenesis through the erythropoietin receptor (EPO-R):

    A logical and theoretically testable hypothesis is that the expression of EPO-R on cancer cells can lead to increased tumor progression and shortened survival in patients receiving ESAs. While obviously a concern if true, a recent NCI workshop concluded that, despite extensive investigation, there is a lack of appropriately controlled preclinical or clinical data to support or refute this hypothesis. The study by Henke et al (2006) in particular has both methodological and technical issues and does not provide strong evidence for this hypothesis. Amgen and J&JPRD, in addition to ongoing research efforts, have proposed unrestricted funding to support independent translational studies through NCI-NIH to address these important questions.
  - Decreased efficacy of local radiotherapy at higher hemoglobin targets:

    Paradoxically, tumor hypoxia (a known predictor of poor responsiveness to radiation) may be worsened at high hemoglobin concentrations through increased “viscous resistance.”

Risk Management and Risk Minimization Action Plan

- Amgen and J&JPRD have accelerated the timely provision of all available data to FDA that were still outstanding at the time of the May 2007 ODAC.
- An important postmarketing commitment study is ongoing, but delayed (EPO-ANE-3010). Challenges in enrollment were anticipated at the outset and were discussed at ODAC 2007. Recent amendments to the study, in consultation with FDA, should facilitate recruitment.
- The companies have worked toward agreement with FDA on the design of a new large, definitive, placebo-controlled clinical study (6186 subjects) to evaluate overall survival and tumor progression in subjects receiving ESAs in the labeled CIA indication.
- Amgen, J&JPRD, and Roche, under the guidance of an international steering committee, and with input from FDA, are working with the Cochrane Collaboration to facilitate an independent patient-level analysis of all data from appropriately designed and conducted controlled clinical studies in patients with cancer receiving ESAs.
- Various risk minimization activities by Amgen and J&JPRD, including safety-related updates to the ESA labeling and healthcare professional communications and education, have had an impact on appropriate prescribing of ESAs:
    - Driven by these risk minimization activities and changes to reimbursement, the number of patients receiving Aranesp® for CIA declined by 48% from Q4 2006 to November 2007 (based on US clinic claims data). Similar data have been reported for PROCRIT®. An increase in transfusion utilization has also been noted, suggesting that a careful balance between minimizing risk and maximizing the benefit of ESAs must be considered.
- Amgen and J&JPRD are working with FDA on the development of a Medication Guide in accordance with FDA regulations to further inform patients and enhance physician-patient discussions concerning the benefit:risk of ESAs. In addition, the companies are assessing the effectiveness of risk communication to patients and healthcare professionals.

- A formal program for further risk minimization (Risk Minimization Action Plan or RiskMAP) will include physician education, cancer patient/patient advocacy group communications, implementation of a Medication Guide per FDA regulation, tracking of risk communication to patients, and additional labeling changes focusing on appropriate initiation of ESAs in CIA. The effectiveness of these activities will be formally evaluated and reported to FDA.
    - Amgen and J&JPRD have involved several stakeholders in designing the RiskMAP for ESAs and now seek the ODAC's guidance regarding the appropriateness of the proposed plan.
- The use of ESAs in oncology settings facilitates structured communication of risk, as ESA use in the CIA indication is largely protocol driven and administered by healthcare professionals with expertise in benefit:risk decisions for potentially toxic therapies.

Conclusions

- ESAs continue to provide significant benefits to anemic patients with cancer receiving myelosuppressive chemotherapy through the reduction of transfusions, which are largely given to improve anemia-related symptoms.
- The weight of evidence has not indicated a clear effect of ESAs on mortality or tumor progression within the labeled indication of CIA. However, signals in individual studies conducted outside of the recommendations in the product labeling have raised real concerns. Amgen and J&JPRD are committed to addressing the safety of ESAs in CIA through further research and aggressive risk communication to patients and healthcare professionals.
- Amgen and J&JPRD believe that risk communication, through product labeling and a formal education and communication program, will minimize risk as the necessary data are acquired from both ongoing studies and the new, large, definitive study specifically designed to address the unanswered questions. The companies believe that the key to risk management of ESAs, given the current uncertainties of risk assessment in the labeled setting, is a fully-informed benefit:risk discussion between the patient and their physician.

- Amgen and J&JPRD are committed to taking appropriate measures to ensure that the risk minimization and marketing activities address the safety concerns and promote appropriate use.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition/Explanation
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
CI	confidence interval
CIA	chemotherapy-induced anemia
CRDAC	Cardiovascular and Renal Drugs Advisory Committee
DHCP	Dear Healthcare Professional
DMC	Data Monitoring Committee
DRSM	Drug Safety and Risk Management
EORTC	European Organisation for Research and Treatment of Cancer
EPO	erythropoietin
EPO-R	erythropoietin receptor
ESA	erythropoiesis-stimulating agent
FACT-Fatigue	Functional Assessment of Cancer Therapy - Fatigue
FDA	Food & Drug Administration
J&JPRD	Johnson & Johnson Pharmaceutical Research & Development, LLC
ODAC	Oncologic Drugs Advisory Committee
NCCN	National Comprehensive Cancer Network
NCD	National Coverage Determination
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
PFS	progression-free survival
RBC	red blood cell
SCLC	small-cell lung cancer
SDI	Surveillance Data, Inc
US	United States
VTE	vascular thrombotic event

STUDY KEY

Published Study	Study Number or Alias	Treatment Setting	Tumor Type	Number of Subjects
Aapro et al, 2008	BRAVE	CIA	Breast	463
Blohmer et al, 2004	AGO/NOGGO EPO-GER-8	CIA	Cervical	250
Cazzola et al, 1995	MF4313	CIA	Multiple myeloma or non-Hodgkin's lymphoma	146
Chang et al, 2005	EPO-CAN-17	CIA	Breast	354
Dammacco et al, 2001	EPO-INT-2	CIA	Multiple myeloma	145
Delarue et al, 2006	FR-2003-3005 FR-2007-0001 LNH03-6B (GELA)	CIA	Diffuse large B-cell lymphoma	458/660 planned
Del Mastro et al, 1997	Not Available	CIA	Breast	62
Engert et al, 2007	HD-15	CIA	Hodgkin's lymphoma	688/1500 planned
Grote et al, 2005	N93-004	CIA	SCLC	224
Hedenus et al, 2003	20000161	CIA	Hematological	344
Henke et al, 2003	ENHANCE	Radiotherapy	Head and Neck	351
Leyland-Jones et al, 2005	EPO-INT-76 (BEST)	CIA	Breast	939
Littlewood et al, 2001; Fallowfield et al, 2002; Fairclough et al, 2003; Patrick et al, 2003; Cella et al, 2003	EPO-INT-10	CIA	Solid or nonmyeloid malignancy	375
Machtay et al, 2007	RTOG-99-03 PR99-03-046	Radiotherapy	Head and Neck	148
Milroy et al, 2003	EPO-INT-49	CIA	NSCLC	424
Möbus et al, 2007	EPO-GER-7	CIA	Breast	643
O'Shaughnessy et al, 2005	PR00-27-005	CIA	Breast	100
Österborg et al, 1996	MF4250	CIA	Hematological	121
Österborg et al, 2005	MF4467	CIA	Hematological	349
Overgaard et al, 2007	SE-2002-9001 (DAHANCA-10)	Radiotherapy	Head and Neck	522

CIA = chemotherapy-induced anemia, AoC = anemia of cancer, SCLC = small-cell lung cancer, NSCLC = non-small cell lung cancer

STUDY KEY (continued)

Published Study	Study Number or Alias	Treatment Setting	Tumor Type	Number of Subjects
Pangalis et al, 1995	P-174	CIA	B-chronic lymphocytic leukemia	45
Pirker et al, 2007	20010145	CIA	SCLC	600
Pronzato et al, 2002	EPO-INT-47	CIA	Breast	220
Rose et al, 1994	J89-040	CIA	Chronic lymphocytic leukemia	221
Savonije et al, 2005	EPO-NED-17	CIA	Solid tumors	316
Smith et al, 2008	20010103	AoC	Nonmyeloid malignancy	989
Taylor et al, 2005	20030232	CIA	Nonmyeloid malignancy	391
Thatcher et al, 1999	CC2574-P-169	CIA	SCLC	130
Thomas et al, 2007	GOG-191	CIA, Radiotherapy	Cervical	114
Vadhan-Raj et al, 2004	PR00-03-006	CIA	Gastric and rectal	59
Vansteenkiste et al, 2002	980297	CIA	SCLC and NSCLC	314
Wilkinson et al, 2006	EPO-INT-45	CIA	Ovarian	182
Witzig et al, 2005	PR98-27-008	CIA	Mixed	344
Wright et al, 2007	EPO-CAN-20	AoC	NSCLC	70
Unpublished	DE-2001-0033 (PREPARE)	CIA	Breast	733
Unpublished	EPO-GBR-7	Radiotherapy	Head and Neck	301
Unpublished	EPO-GER-22	CIA	NSCLC	385
Unpublished	EPO-CAN-15	CIA	SCLC	104
Unpublished	EPO-INT-49	CIA	NSCLC	424
Unpublished	DE-2002-0015 ARA 03/ARA PLUS (WSG)	CIA	Breast	1090/1234 planned
Unpublished	EPO-ANE-3010	CIA	Breast	236/1000 planned

CIA = chemotherapy-induced anemia, AoC = anemia of cancer, SCLC = small-cell lung cancer, NSCLC = non-small cell lung cancer

1. EXECUTIVE SUMMARY

Amgen and Johnson & Johnson Pharmaceutical Research & Development (J&JPRD) are committed to robust risk management activities to optimize the safety of our erythropoiesis stimulating agent (ESA) products. This briefing document outlines the companies' ongoing and proposed plans to minimize risk by facilitating appropriate use of ESAs and promoting informed benefit:risk discussions and decisions between patients and their physicians.

ESAs are recombinant proteins that are nearly identical to human erythropoietin, both in structure and in biological activity. ESAs were first introduced in the US in 1989, and have over 11 million person-years of postmarketing experience in the treatment of anemia associated with cancer chemotherapy, chronic renal failure, human immunodeficiency virus treatment, and in anemic patients scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions.

ESAs have the established clinical benefit in chemotherapy-induced anemia (CIA) of reducing the need for red blood cell (RBC) transfusions, thus minimizing risks and burdens that may accompany transfusions while conserving this critical resource for emergency use. The benefits of transfusion reduction with ESAs are multiple, measurable, and vital to the health and welfare not only of patients with CIA, but also to the broader population who may require urgent and potentially life-saving transfusion for trauma, acute bleeding, or surgery.

ESAs exert their biological effect by binding to the erythropoietin (EPO) cell surface receptor (EPO-R) on RBCs, with resultant phosphorylation of associated Jak2 kinase and activation of downstream signaling. EPO-R are found on RBC precursors, and these are the only cells in which functional EPO-R has been convincingly demonstrated, as they are essential for adult red cell generation but not for non-erythroid cell types. Nonetheless, an important and unresolved question is whether there could be functional EPO-R on tumor cells that might promote their growth. Detailed reviews and a recent National Cancer Institute (NCI) workshop have attempted to clarify this important issue, but to date no conclusions are widely accepted, in part because this research has been severely hampered by the lack of reliable reagents for the measurement of functional

EPO-R. No evidence indicates that EPO-R functions as an oncogene. However, the theoretical possibility that ESAs could potentially act as growth factors for tumors is reflected in labeling for all products in this class.

Results of recent clinical studies in patients with cancer have raised questions about the relationship between ESA treatment and the potential risk of increased mortality or tumor progression. The safety signals that have been observed have arisen in settings that are not part of the approved labeling, but require a thorough risk assessment to define appropriate risk management within the currently labeled indication. FDA has convened 3 prior advisory panels to assess ESA safety (4 May 2004 Oncologic Drugs Advisory Committee [ODAC], 10 May 2007 ODAC, and 11 September joint Cardiovascular and Renal Drugs/Drug Safety and Risk Management Advisory Committee [CRDAC/DSRM]). Since the ODAC 2007 meeting, additional clinical results have become available, including data from studies included in the Amgen and J&JPRD ESA pharmacovigilance programs. Two of these studies (PREPARE and GOG-191) recently reported higher mortality and/or shorter time to tumor progression in the ESA group than in the control group. The results of the PREPARE study are from an unplanned interim analysis of incomplete data with ongoing follow-up, and the GOG-191 study had previously been terminated because of an unexpected increase in vascular thrombotic events (VTE). The data from the GOG-191 study are from a relatively small number of subjects (n = 114 of 460 planned), and the treatment differences observed in both PREPARE and GOG-191 were not statistically significant. These data were promptly communicated to FDA and the public, and have been incorporated into proposed labeling. Additional healthcare professional and patient communication of the updated labeling is also in progress. Amgen and J&JPRD have provided FDA with all data from studies addressing survival and tumor outcomes in patients treated with epoetin alfa or darbepoetin alfa as they have become available since the May 2007 ODAC.

In light of the seriousness of these safety concerns, the companies have repeatedly and thoroughly reviewed the results of the individual studies of concern, with the aid of external experts in the field, in addition to all ESA studies in subjects with cancer, to gain as robust an understanding of the potential risks as possible. These reviews have included all studies raising safety signals, as well as CIA studies similar in design to those identified in ESA warnings. Overall, these signals have not been consistently observed across studies, and meta-analyses (most recently including over

8000 subjects) do not indicate a clear effect of ESAs on mortality or tumor progression. By contrast, the well-recognized risk of VTE has been seen in individual randomized studies in this patient population and is readily detected in meta-analyses. Amgen and J&JPRD believe that the results of meta-analyses must be considered in light of the significant safety signals that were observed in the individual studies noted. However, the meta-analyses are helpful in demonstrating the lack of a clear effect of ESAs on the risk of mortality or tumor progression in the overall population of patients with CIA. To fully exclude this possibility will require double-blind, placebo-controlled studies in the CIA setting, which Amgen and J&JPRD have designed in collaboration with FDA. In addition, the assessment of risk continues to be informed by results of independent investigator-sponsored studies as they become available.

When safety concerns have been identified, they have arisen in investigational settings, for example, clinical studies designed to test the hypothesis that increasing hemoglobin concentrations beyond the labeled indication of 12 g/dL (ie, “beyond correction of anemia”) would improve therapeutic outcome by decreasing tumor hypoxia. These investigational approaches are no longer being pursued, and product labeling appropriately warns against these off-label uses. Overall, the weight of available evidence does not support a clear, generalized tumor promotion signal or decreased survival when ESAs are used in CIA. However, since these potential risks have not been completely excluded by placebo-controlled studies that have been specifically designed to rule out these effects in populations treated according to the labeling, Amgen and J&JPRD are committed to conducting such studies to address these concerns.

Amgen and J&JPRD continue to focus substantial effort on ongoing pharmacovigilance programs to answer these questions. All available data from pharmacovigilance studies from the 2004 ODAC meeting have been submitted to FDA, and an update on the status of these studies is provided in this document. The companies also have held 5 key meetings with FDA since the May 2007 ODAC to discuss the following:

- Actions and deliverables from the May 2007 ODAC meeting, including updates to labeling and additional data required by FDA
- Ongoing and new pharmacovigilance study designs
- Clinical experience with ESAs in myelodysplastic syndrome

- EPO-R biology, potential mechanisms for tumor progression, and methodologic limitations for detecting expression
- Details of a new large, placebo-controlled study in the labeled treatment setting

With respect to new and ongoing studies, the completion of further large, placebo-controlled studies to exclude small effect sizes presents significant challenges (as previously noted by ODAC). The companies and FDA have agreed on the design of a new large, definitive clinical study to evaluate overall survival and tumor progression in subjects with solid tumors receiving ESAs in accordance with the labeling. An additional potential study in multiple myeloma or lymphoid disease is also under discussion with FDA. Protocols will be submitted after guidance has been obtained from ODAC, with the intent of initiating these studies immediately.

Amgen and J&JPRD are committed to robust risk management activities to optimize the safety of ESAs. In particular, the companies have worked closely with FDA to address the potential risk of increased mortality and tumor progression through multiple revisions to the labeling and have communicated this information to healthcare professionals and patients. Additional risk management activities include educational efforts to ensure appropriate ESA use in accordance with the current labeling, specifically, using the lowest dose to avoid transfusions, not exceeding a hemoglobin level of 12 g/dL, and not administering ESAs outside of the CIA indication. Further proposed risk minimization activities include the following:

- physician, patient, and patient advocacy group initiatives designed to ensure awareness of the risks of ESA use
- formal ascertainment of the distribution of the Medication Guide and its receipt by patients
- potential additional labeling changes (eg, guidance on initiation hemoglobin level)
- formal assessment of appropriateness of ESA use
- formal monitoring of these activities, with regular reporting to FDA

ESAs remain an important therapeutic option in the management of CIA. The available evidence continues to support a favorable benefit:risk profile for ESAs for the treatment of CIA when used at the lowest dose necessary to avoid transfusions and at hemoglobin levels not to exceed 12 g/dL, in conjunction with appropriate risk minimization activities.

2. BACKGROUND AND REGULATORY HISTORY

2.1 Key Points

- Erythropoietin is a glycoprotein hormone that is the key regulator of RBC production and exerts its biological effect by binding to its cell surface receptor (EPO-R).
  - Although the presence of EPO-R has also been reported on non-erythroid precursors, functionality of the putative EPO-R outside of erythroid precursors has not been clearly demonstrated.
- Amgen is the innovator and US license holder for the ESAs epoetin alfa and darbepoetin alfa, which are approved for the treatment of CIA.
  - Epoetin alfa is marketed under the trade names Epogen® by Amgen and PROCRIT® by Ortho Biotech Products, LP in the US.
  - Darbepoetin alfa is marketed under the trade name Aranesp® by Amgen.
  - Amgen is responsible to the FDA for ensuring compliance with epoetin alfa licensing conditions, including postmarketing commitments. Under agreement between the companies, Ortho is responsible for providing all its relevant safety information to Amgen for timely submission to FDA.
- The safety of ESAs has been reviewed at 2 previous ODAC meetings in 2004 and 2007 and at a joint CRDAC/DSRM meeting in 2007.
  - The 2004 ODAC led to revised product labeling and the establishment of epoetin alfa and darbepoetin alfa pharmacovigilance programs that were acknowledged as FDA post-marketing commitments, including 5 ongoing studies with darbepoetin alfa and the initiation of an epoetin alfa postmarketing study, designed in conjunction with FDA and ODAC, to address tumor progression within the labeled treatment setting (EPO-ANE-3010).
  - Amgen and J&JPRD have worked to address the ongoing safety concerns through product labeling, communication with healthcare professionals and patients, execution of ongoing pharmacovigilance and postmarketing studies, and accelerated submission of data from all available studies to regulators.
  - Amgen and J&JPRD are also working closely with the FDA on the development of a Medication Guide to further inform patients and enhance physician-patient discussions concerning the benefit:risk of ESAs.
  - Amgen and J&JPRD are working closely with FDA to design and conduct additional pharmacovigilance studies to address the benefit:risk of ESAs when used according to the labeling.

- Amgen, J&JPRD, and Roche, along with independent investigators, have provided data to the Cochrane Collaboration to facilitate an independent patient-level analysis of all data from appropriately designed and conducted controlled clinical studies.
- Amgen and J&JPRD are committed to supporting efforts by NCI and FDA to develop the additional translational science necessary to determine whether potential mechanisms exist for the promotion of tumor progression by ESAs.

2.2 Erythropoietin Biology, Physiology, and Pharmacology

Erythropoietin is a glycoprotein hormone produced primarily by the kidney in response to hypoxia and is the key regulator of RBC production. EPO-R are found on RBC precursors, and these are the only cells in which functional EPO-R has been convincingly demonstrated, as they are essential for adult red cell generation but not for non-erythroid cell types (Wu et al, 1995; Suzuki et al, 2002). Although the presence of EPO-R has also been reported on non-erythroid precursors, including malignancies of epithelial and non-epithelial origin, functionality of the putative EPO-R outside of erythroid precursors has not been clearly demonstrated (as noted at the NCI Workshop in December 2007). This inability to definitively evaluate EPO-R is exacerbated by the lack of reliable reagents for detection of EPO-R.

2.3 Overview of Licensed ESAs

FDA-approved ESAs for oncology include epoetin alfa and darbepoetin alfa. Amgen is the manufacturer, patent owner, and FDA license holder for epoetin alfa. Ortho Biotech Products, LP is a distributor of epoetin alfa under Amgen's FDA license. Under the parties' agreements, epoetin alfa is marketed and distributed by Amgen as Epogen, and by Ortho as PROCRIT®. Amgen markets Epogen for use by patients with chronic renal disease on dialysis. Under a license from Amgen, Ortho markets PROCRIT® for all other approved indications for epoetin alfa. Over the years, Amgen and Ortho (including J&JPRD) each have exercised operational responsibility for certain postmarketing clinical development studies of epoetin alfa. However, as the FDA license holder, Amgen is responsible to the FDA for ensuring compliance with epoetin alfa licensing conditions, including post-marketing commitments. Under agreement between the companies, Ortho is responsible for providing all its relevant safety information to Amgen for timely submission to FDA. Epoetin alfa is also manufactured by an affiliate of J&JPRD for distribution outside the US (eg, EPREX®). Amgen created, developed, and is the license holder for darbepoetin alfa (Aranesp®).

Epoetin beta (NeoRecormon®/ Recormon® Hoffmann-La Roche), which is only approved for sale outside of the US, has the same amino acid sequence as epoetin alfa. Methoxy polyethylene glycol-epoetin beta (Mircera®; Hoffmann-La Roche) is an ESA approved for the treatment of anemia associated with chronic renal failure (not marketed in the US).

2.4 Response to Emerging Safety Issues

In response to concerns regarding increased mortality and tumor progression raised by certain clinical studies, safety data for ESAs in oncology were reviewed at two previous ODAC meetings in 2004 and 2007. Amgen and J&JPRD also participated in a joint CRDAC/DSRM meeting in September 2007 to assess the safety of ESAs in the chronic kidney disease indication.

The May 2004 ODAC was held in response to safety signals that first began to emerge in late 2002, with survival signals from two studies (BEST and ENHANCE, further discussed in Section 4.2) being of greatest concern. Both of these studies were designed to evaluate the hypothesis, which had been suggested by preclinical studies, that targeting higher hemoglobin levels would lead to improved tumor outcomes through amelioration of tumor hypoxia. After an Independent Data Monitoring Committee recommended discontinuation of the BEST study because of an unexpected increase in early mortality among subjects in the epoetin alfa-treated group, J&JPRD immediately notified investigators, the FDA, and other health authorities (April 2002), and initiated a review of all previously conducted oncology studies. J&JPRD also initiated a global re-evaluation of all ongoing epoetin alfa oncology clinical studies in non-anemic patient populations in response to concerns about elevated vascular thrombotic event (VTE) frequency in epoetin alfa-treated patients. This led to the premature termination of several studies evaluating hemoglobin correction beyond 12 g/dL (including EPO-CAN-20, GOG-191, and RTOG-9903). No evidence for increased tumor progression was seen at the time these primary analyses were done. J&JPRD subsequently discontinued all investigation of hemoglobin correction with epoetin alfa beyond the treatment of anemia in the oncology setting.

After the 2004 ODAC, the global product labeling for ESAs was revised to fully describe the potential risks of tumor progression and mortality. Dear Healthcare Professional (DHCP) Letters were distributed in the US and globally. In line with the ODAC's recommendations, both Amgen and J&JPRD developed and have since implemented

standardized approaches to data collection and/or analysis for VTEs, which have been used to evaluate adverse events in all studies (including combined analyses).

Amgen and J&JPRD also committed to additional pharmacovigilance studies to investigate the safety signals observed. These studies later became formal postmarketing commitments (Table 1). The companies have worked diligently to meet these postmarketing commitments. Difficulties in accrual to one of these studies (EPO-ANE-3010) were anticipated from the outset and discussed at the May 2007 ODAC. This ongoing study was recently amended in consultation with FDA to improve recruitment. All other postmarketing commitments have been met or are on track for completion. Data reporting for additional ongoing, randomized, single-tumor studies identified since the May 2007 ODAC as being potentially informative by FDA has been accelerated. An update on these studies is provided in Section 6.2.

Table 1. Pharmacovigilance Study Postmarketing Commitments

Study	Postmarketing Commitment (PMC) Date
N93-004	21 May 2004 (PMC fulfilled)
EPO-ANE-3010	21 May 2004
20010145	23 March 2006
DE-2001-0033 (PREPARE)	23 March 2006
SE-2002-9001 (DAHANCA 10)	23 March 2006
FR-2003-3005 (GELA)	23 March 2006
DE-2002-0015 (ARA 03/ARA PLUS)	23 March 2006

After the 2007 ODAC meeting, further actions were taken by Amgen and J&JPRD in response to recommendations of FDA and the committee, including the following:

- US labeling was revised in November 2007 to update the BOXED WARNING, INDICATIONS AND USAGE, CLINICAL EXPERIENCE, DOSAGE AND ADMINISTRATION, and WARNINGS sections (see Appendix 1)
- Further labeling revisions are currently under review at FDA to update the BOXED WARNING (provided below) and WARNINGS section with information from clinical studies in breast and cervical cancers:

WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR and THROMBOEMBOLIC EVENTS, and TUMOR PROGRESSION

Renal failure: **Patients experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemoglobin levels (13.5 vs. 11.3 g/dL; 14 vs. 10 g/dL) in two clinical studies. Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL.**

Cancer:

- **ESAs shortened overall survival and/or time-to-tumor progression in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers when dosed to target a hemoglobin of ≥ 12 g/dL.**
- **The risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to target a hemoglobin of < 12 g/dL.**
- **To minimize these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusions.**
- **Use only for treatment of anemia due to concomitant myelosuppressive chemotherapy.**
- **Discontinue following the completion of a chemotherapy course.**

(See WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events, WARNINGS: Increased Mortality and/or Tumor Progression, and DOSAGE AND ADMINISTRATION.)

Amgen and J&JPRD have taken a conservative approach in including these studies in the BOXED WARNING.

- DHCP letters to communicate these labeling changes
- Medication Guide and Patient Instructions for Use (currently under review by FDA) to further inform patients and enhance physician-patient discussion concerning the benefit:risk decision (submitted in October 2007; details are provided in Section 6.5)
- Proposed further revisions to the product labeling (submitted to FDA in December 2007) for epoetin alfa and darbepoetin alfa that addresses questions raised by FDA and ODAC 2007 regarding hemoglobin initiation, hemoglobin ceiling, discontinuation of ESA therapy after chemotherapy, and data from additional clinical studies
- Further exploration of EPO-R biology and methodologies, including working closely with NCI and FDA to develop the translational science necessary to evaluate ESA therapy in cancer

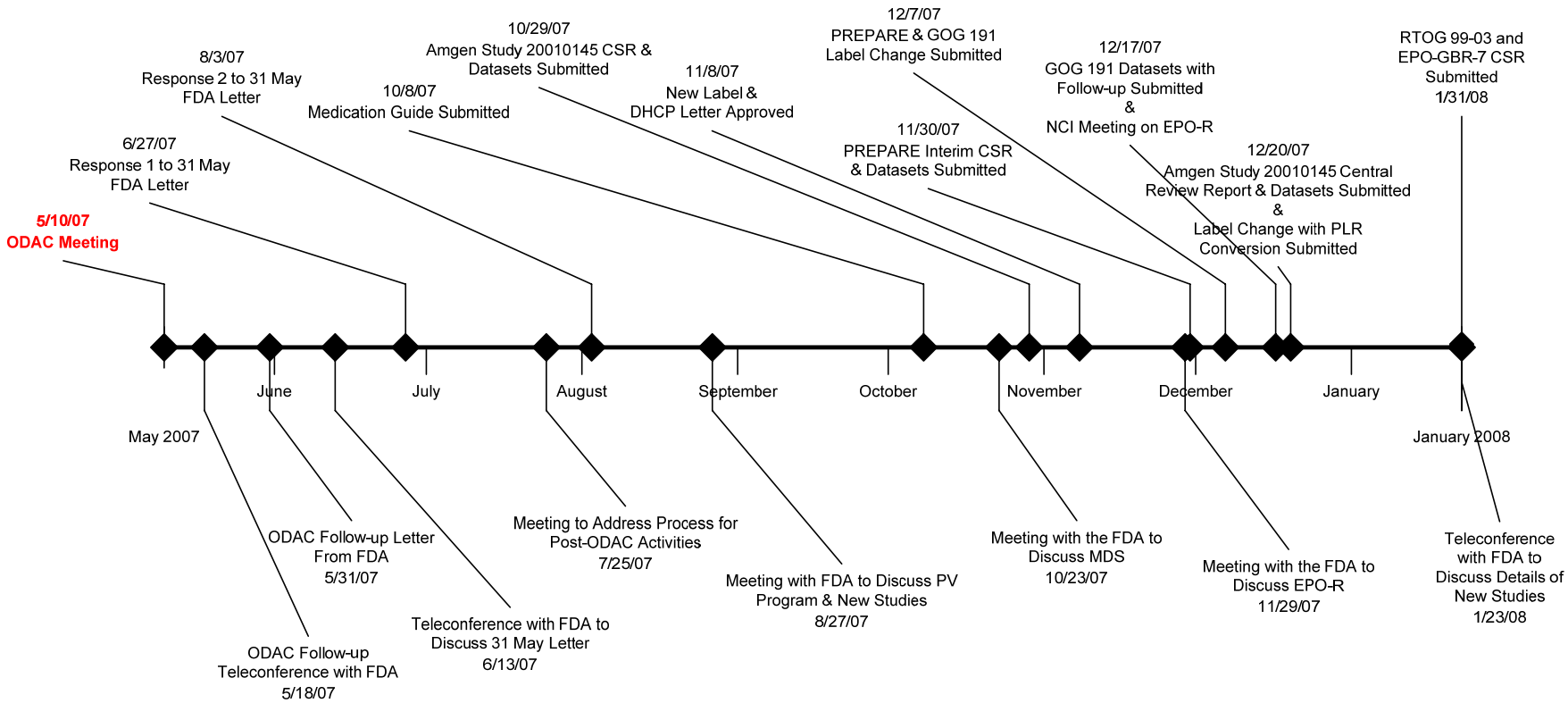
- Design of a large, definitive, placebo-controlled study in subjects with solid tumors to evaluate mortality and tumor progression when ESAs are used according to the labeling (details are provided in Section 6.3); an additional potential study in multiple myeloma or other lymphoid disease is also under discussion with FDA
- Engagement with the Cochrane Collaboration (along with Roche) to perform a patient-level combined analysis of all available controlled studies with ESAs in oncology patients (details are provided in Section 6.4)

The companies also have held 5 key meetings with FDA since the May 2007 ODAC to discuss the following:

- Actions and deliverables from the May 2007 ODAC meeting, including updates to labeling and additional data required by FDA
- Ongoing and new pharmacovigilance study designs
- Clinical experience with ESAs in myelodysplastic syndrome
- EPO-R biology, potential mechanisms for tumor progression, and methodologic limitations for detecting expression
- Details of a new large, placebo-controlled study in the labeled treatment setting

A timeline of key regulatory activities since ODAC 2007 is provided in Figure 1. Risk management and minimization activities are further discussed in Section 6.

Figure 1. Key Regulatory Submissions and Interactions Since the May 2007 ODAC Meeting (through January 2008)



CSR = clinical study report, PV = pharmacovigilance, MDS = myelodysplastic syndrome, EPO-R = erythropoietin receptor, DHCP = Dear Healthcare Professional, NCI = National Cancer Institute

3. BENEFITS OF ERYTHROPOIESIS STIMULATING AGENTS IN CHEMOTHERAPY-INDUCED ANEMIA

3.1 Key Points

- ESAs offer the only alternative to RBC transfusions in patients with CIA.
- RBC transfusions, which are primarily administered to treat symptomatic anemia, are associated with significant inherent risks and increase the burden on the US blood supply.
- ESAs have been proven to reduce RBC transfusions in patients with CIA in well-controlled clinical studies, supported by comprehensive meta-analyses.
- An extensive published literature of placebo-controlled studies supports the benefits of ESAs in improving anemia symptoms such as fatigue, which is recognized in practice guidelines and product labeling outside the US. Although these data do not meet FDA's current guidance for the registration of patient-reported outcome (PRO) endpoints, they are consistent with the expected clinical benefit of correcting anemia.

3.2 Clinical Need

Anemia is a common complication of myelosuppressive chemotherapy, with the frequency of occurrence depending on the underlying malignancy and the regimen and intensity of chemotherapy utilized (Groopman and Itri, 1999; Mercadante et al, 2000). Symptoms of anemia in patients with cancer who are receiving chemotherapy include fatigue and diminished patient-reported health status, although the causes of fatigue are multifactorial (Cella, 1997; Cella, 1998). Palliation of symptoms is a major goal in the management of patients with cancer, and the impact of fatigue is significant (Vogelzang et al, 1997; Curt et al, 2000). Anemia in older patients with underlying cardiovascular, renal, or pulmonary disease can result in serious complications (Balducci et al, 2006).

ESAs provide the only alternative to blood transfusions for patients with CIA, and avoidance of blood transfusion remains an important clinical benefit of these agents. The use of blood transfusions to relieve symptoms of anemia carries several types of risk for patients with cancer and the public as a whole, which have been well documented (Spiess, 2007). Furthermore, although at present the blood supply is

considered to be safe, there is always the potential for new, as yet unrecognized, infectious diseases transmissible via transfusion to emerge. For example, before they were recognized, both Hepatitis C and human immunodeficiency viruses were unknowingly transmitted to thousands of individuals via transfusion. To minimize the potential for future similar tragedies, transfusions should always be used cautiously, particularly when the goal of therapy is symptomatic relief and an alternative is available. Notably, many of these infectious agents can be transmitted through close family contact (eg, sexual contact). Thus, the benefits of transfusions should be weighed against the composite risk that the patient and healthy family contacts may be exposed to blood borne infection. FDA has explicitly recognized the desirability of alternatives to transfusion because of the associated risks (FDA Guidance for Industry: An Acceptable Circular of Information for the Use of Human Blood and Blood Components, December 2003).

Transfusions are disruptive for patients, caregivers, and physicians and divert substantial resources that would otherwise be available for patient care. For example, an entire day can be required to administer a blood transfusion; thus, many physicians will not have the capability to transfuse patients or may prefer to admit patients to a hospital or treatment facility. Consequently, the overall impact of transfusion can be substantial, both for practices and patient, and most patients prefer to avoid transfusion entirely if possible (Cantor et al, 1998; Cremieux et al, 2000; Demetri et al, 2001).

Finally, the nation's blood supply is a limited resource, and there is an imperative to preserve it for patients with acute need (eg, hemorrhage, surgery and trauma) and for times of severe shortages. The limited surplus in the blood supply has led to periodic shortages. Based on the 2005 Nationwide Blood Collection and Utilization Survey Report, 8.5% of surveyed hospitals reported postponement of elective surgeries on 1 or more days in 2004 because of blood inventory shortages (mean 3.39 days a year; range: 1 to 39 days a year) (Whitaker et al, 2007). Sixteen percent of hospitals reported not being able to meet their nonsurgical blood needs on at least 1 day (Whitaker et al, 2007).

3.3 Clinical Benefits of ESA Treatment

3.3.1 Transfusion Reduction

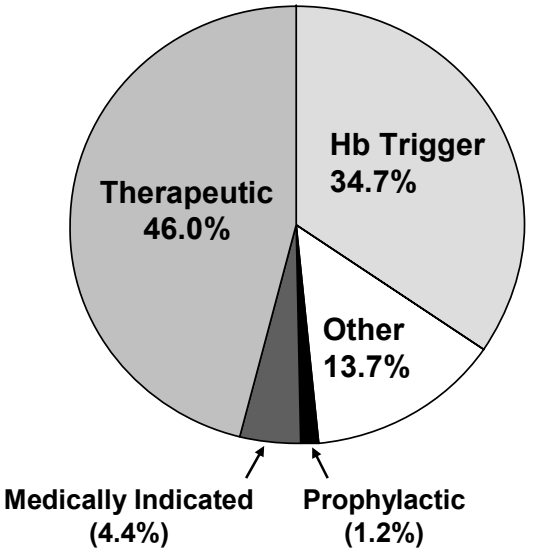
Well-controlled clinical studies have demonstrated the benefit of ESAs in reducing the need for RBC transfusions (Abels et al, 1992; Vansteenkiste et al, 2002; Hedenus et al, 2003; Witzig et al, 2004; Pirker et al, 2007). A recent independent meta-analysis of all randomized controlled studies comparing ESA versus no ESA for prophylaxis or treatment of anemia in cancer patients (42 studies with 6,510 subjects) demonstrated that patients treated with epoetin alfa or darbepoetin alfa had a 36% lower risk of transfusion than control patients (relative risk 0.64 [95% CI: 0.60 to 0.68]; percentage of total patients transfused 31% ESA vs 48% no ESA) (Bohlius et al, 2006).

3.3.2 Impact of ESAs on Symptoms of Anemia

Symptoms caused by anemia, including fatigue, are a substantial burden for patients undergoing cancer chemotherapy. Although the decision to transfuse a patient with cancer and anemia involves physician assessment of a range of clinical features, reducing the burden of suffering resulting from symptomatic anemia is a key consideration (Figure 2). As transfusions reduce the symptoms of anemia, and ESAs have been demonstrated to decrease the need for transfusions, it can be logically inferred that ESAs reduce symptoms of anemia as well.

Figure 2. Reasons Given For Transfusion at Time of Transfusion Data From 5 Phase 3 Darbepoetin alfa Studies (n = 2286)

(n = 2227 Case Report Form Responses)



Across all studies, recommendation for transfusion was Hb <8 g/dL (or signs & symptoms of anemia)

Several studies have suggested a relationship between treatment of anemia with ESAs and corresponding improvements in anemia-related symptoms and fatigue/energy (Appendix 2). These data provide support for the conclusion that ESAs alleviate symptomatic anemia and reduce fatigue in patients receiving cancer chemotherapy, although the studies do not meet FDA's current standards for the registration of PRO endpoints. The treatment benefit of ESAs in reducing cancer-related fatigue has recently been summarized in a Cochrane Collaboration review, which was based upon a search of the Cochrane Central Register of Controlled Trials (First Quarter 2007), MEDLINE (1966 to March 2007) and a selection of cancer journals (Minton et al, 2008). Studies were included in the review if they assessed drug therapy for the management of cancer-related fatigue compared to placebo, usual care, or a non-pharmacological intervention in randomized controlled studies of adult patients with a clinical diagnosis of cancer. The review included published and unpublished data from 9 studies (Hedenus et al, 2003; Kotasek et al, 2003; Littlewood et al, 2001; O'Shaughnessy et al, 2005; Osterborg et al, 2002; Smith et al, 2003; Vansteenkiste et al, 2002; Witzig et al, 2005; and Wright et al, 2007). The random-effects model resulted in an overall Z score of 5.08 ($p < 0.001$) with a standardized mean difference of -0.23 points (95% CI: -0.32 to -0.14) (Figure 3). The combined studies using the Functional Assessment of Cancer Therapy-Fatigue (FACT-Fatigue) resulted in a weighted mean difference of 3.75 (Minton et al, 2008). A 3-point increase in the FACT-F subscale score is generally considered an important change (Cella et al, 2002). The review concludes that "overall these studies may provide a clinically significant reduction in fatigue."

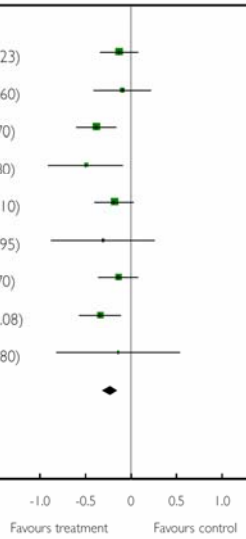
Figure 3. Cochrane Collaboration Review of Cancer-related Fatigue

Analysis 06.01. Comparison 06 Haemopoetic growth factors versus no intervention, Outcome 01 Erythropoetin or darbopoetin versus no treatment

Review: Drug therapy for the management of cancer related fatigue
Comparison: 06 Haemopoetic growth factors versus no intervention
Outcome: 01 Erythropoetin or darbopoetin versus no treatment

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
01 Placebo controlled trials							
Hedenus 2003	176	-3.33 (17.38)	173	-1.10 (17.23)		17.8	-0.13 [-0.34, 0.08]
Kotasek 2003	189	-3.40 (12.60)	50	-2.30 (11.60)		8.1	-0.09 [-0.40, 0.22]
Littlewood 2001	251	-3.30 (13.20)	124	1.60 (12.70)		16.7	-0.38 [-0.59, -0.16]
O'Shaughnessy 2005	47	3.00 (11.90)	47	9.40 (13.80)		4.6	-0.49 [-0.90, -0.08]
Osterborg 2002	170	-5.20 (12.20)	173	-3.00 (12.10)		17.4	-0.18 [-0.39, 0.03]
Smith 2003	46	-4.15 (12.35)	16	-0.25 (13.95)		2.4	-0.30 [-0.87, 0.27]
Vansteenkiste 2002	156	-0.80 (10.00)	158	0.60 (10.70)		16.0	-0.13 [-0.36, 0.09]
Witzig 2005	154	3.00 (23.22)	151	10.60 (22.08)		15.3	-0.33 [-0.56, -0.11]
Wright 2007	14	-4.50 (14.80)	20	-2.55 (13.80)		1.7	-0.13 [-0.82, 0.55]
Total (95% CI)	1203		912			100.0	-0.23 [-0.32, -0.14]

Test for heterogeneity chi-square=6.85 df=8 p=0.55 I^2 =0.0%
Test for overall effect z=5.08 p<0.00001



Improvement in fatigue and anemia symptoms with ESAs in cancer is also supported by a systematic review of the literature by the Agency for Healthcare Research and Quality (Seidenfeld et al, 2006). The evidence in support of ESAs is also recognized in treatment guidelines (National Comprehensive Cancer Network [NCCN], Canadian Cancer and Anemia Guidelines Development Group, and the European Organization for Research and Treatment of Cancer [EORTC]) and is incorporated into the product labeling in other regions (eg, European Summary of Product Characteristics, provided in Appendix 3).

3.4 Conclusion

Anemia is an important medical problem that is increased in patients receiving cancer chemotherapy. ESAs provide the only therapeutic alternative to transfusions, which are associated with well-documented risks and burden the limited US blood supply. ESAs have well-established benefits in reducing the need for transfusions, and clinical guidelines continue to recommend appropriate use of ESAs to relieve symptomatic anemia in patients receiving chemotherapy.

4. SAFETY CONCERNS IN PATIENTS WITH CANCER RECEIVING ERYTHROPOIESIS STIMULATING AGENTS

4.1 Key Points

- Over 50 randomized, controlled studies have reported data for mortality and/or tumor progression in patients with cancer.
- Data from 8 individual studies that have become available over the last 5 years have suggested a potential negative effect of ESAs on survival and/or tumor progression in patients with cancer. Two of these studies (PREPARE and GOG-191) were recently included in proposed labeling after the data became available in November 2007. All 8 studies were conducted in treatment settings not approved for ESAs; however, legitimate concerns remain that these risks have not been adequately excluded in the labeled setting.
- Other controlled studies of ESAs also performed outside of the labeled indication, but considered to be informative with respect to mortality and/or tumor progression, have not suggested an increased risk of these events.
- Meta-analyses in over 8000 subjects do not indicate a clear effect of ESAs on mortality or tumor progression. This is in contrast to the well-documented risk of vascular thrombotic events (VTE), which has consistently been detected in individual studies and meta-analyses.
- Amgen and J&JPRD believe that the results of meta-analyses must be considered in light of the significant safety signals that were observed in the individual studies noted. However, the lack of a consistent effect of ESAs on the risk of mortality or tumor progression in CIA across individual studies indicates that further research in the labeled indication is needed.
- Amgen and J&JPRD are working closely with FDA to design additional large, well-controlled, definitive studies to specifically explore the effect of ESAs on mortality and tumor progression when administered in accordance with approved labeling.

- The companies continue to proactively evaluate and accelerate the communication of all studies (including those for which Amgen and J&JPRD are not the sponsor) that could contribute useful information to the assessment of ESA safety in CIA.
- The observed risks in individual studies are prominently communicated in the BOXED WARNING and WARNINGS AND PRECAUTIONS sections of the current product labeling for epoetin alfa and darbepoetin alfa.

Over 50 randomized, controlled studies have reported results for mortality and/or tumor progression in patients with cancer (including those receiving chemotherapy, those receiving radiation alone, and those not receiving chemotherapy or radiotherapy). This section reviews the results of individual studies as well as meta-analyses of all relevant randomized controlled studies, as both provide important information on the potential risks of ESAs. For the purposes of this review, data for the following are discussed:

- 8 studies raising safety concerns (reported in the currently proposed labeling for epoetin alfa and darbepoetin alfa)
- 11 additional studies considered "potentially informative" by FDA at the May 2007 ODAC
- additional studies that have been published or submitted to FDA since the May 2007 ODAC
- meta-analyses including all relevant, randomized, controlled studies based on the Cochrane Collaboration report (Bohlius et al, 2006), updated with data available since the original report

4.2 Studies Raising Safety Concerns

At the time of the May 2007 ODAC meeting, 6 studies had suggested a negative effect of ESAs on mortality and/or tumor progression (BEST, ENHANCE, EPO-CAN-20, DAHANCA 10, Amgen Study 20010103, and Amgen Study 20000161) (Table 2). These data were communicated to the healthcare community in DHCP letters in January 2005 and January and March 2007, and have been described in detail previously (Oncologic Drugs Advisory Committee Briefing Information, 04 May 2004 and 10 May 2007).

Since the May 2007 ODAC, results from a number of other controlled, clinical studies have become available. Of these, 2 studies (PREPARE, GOG-191) have raised concerns. Key results from these studies are listed in Table 2, and more detailed summaries are provided in this section. Data from these studies were reviewed by FDA as they became available and have been included the proposed product labeling and a DHCP letter.

Although it is acknowledged that given the timing of the meeting, FDA may not have an opportunity to review all of these data thoroughly, all updated data from Amgen and J&JPRD for these studies have been provided to FDA and are included here for completeness.

All 8 studies were designed to explore the use of ESAs to target hemoglobin levels > 12 g/dL and/or in other off-label populations such as patients with anemia not receiving chemotherapy. Worldwide product labeling now appropriately and prominently warns against targeting hemoglobin levels > 12 g/dL and using ESAs in patients with cancer not treated with chemotherapy. However, concerns remain that the risk of tumor progression or decreased survival in patients receiving ESAs for CIA in accordance with the product labeling has not been rigorously excluded by dedicated studies.

Table 2. Safety Data of Concern

Study Designation(s) (Sponsor)	Study Population (n)	Study Design	Hemoglobin Target	Published Results for Survival and/or Disease Progression	Most Recent Results Provided to FDA for Review	Data reported to the FDA
Studies Added to the Labeling Since ODAC 2007						
PREPARE (AGO/GBG) (Part of Amgen's pharmacovigilance program)	Breast cancer receiving neoadjuvant chemotherapy (n = 733)	Randomized, open-label	12.5 g/dL to 13 g/dL	N/A	No significant difference in pathologic complete remission between groups (final data) Lower 3-year survival in ESA group (interim data) (86% vs 90%; HR 1.42, 95% CI: 0.93, 2.18) Lower 3-year PFS in ESA group (interim data) (73% vs 79%, HR 1.33, 95% CI: 0.99, 1.79)	Interim report and datasets 11/07
GOG-191 Thomas et al, 2007 (GOG)	Cervical cancer receiving chemotherapy (n = 114)[a,b]	Randomized, open-label	13 to 14 g/dL	Lower 3-year PFS in ESA group (58% vs 66%) Lower 3-year overall survival in ESA group (60% vs 74%)	At median follow-up of 30 months, ESA and control groups had similar 3-year PFS (KM estimates) (59% vs 62%) HR 1.056; 95% CI: 0.584, 1.909; p = 0.8561 and 3-year overall survival (KM estimates) (61% vs 71%) HR 1.284; 95% CI: 0.682, 2.419; p = 0.4372	Report and datasets 2/08

[a] Data were also presented at ODAC 2004.
[b] Study terminated early with approximately 25% of planned accrual (114 of 460 subjects) due to an unexpected increase in VTEs in the ESA group; 113 subjects received investigational product and were included in the analysis.
[c] Study terminated early due to increase in VTEs in the ESA group.

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Table 2. Safety Data of Concern

Study Designation(s) (Sponsor)	Study Population (n)	Study Design	Hemoglobin Target	Published Results for Survival and/or Disease Progression	Most Recent Results Provided to FDA for Review	Data reported to the FDA
Studies Presented at ODAC 2007						
BEST (EPO-INT-76) Leyland-Jones et al, 2005 (J&JPRD)[a]	Metastatic breast cancer receiving chemotherapy (n = 939)	Randomized, (double-blind treatment phase), placebo-controlled	12 to 14 g/dL	Higher 12-month mortality in ESA group: HR 1.37 (p = 0.01) 12-month PFS similar between ESA and control: HR 1.00 (p = 0.98)	Long-term follow-up (LTFU) for overall survival similar between ESA and control: HR 1.04; 95% CI: 0.90, 1.20; p = 0.6	1-year report and datasets 2002 LTFU report and datasets 12/07
ENHANCE Henke et al, 2003[a]	Head and neck receiving radiation alone (n = 351)	Randomized, double-blind, placebo-controlled	14 g/dL (women) 15 g/dL (men)	Higher mortality at ~ 60 months in ESA group: RR 1.39; 95% CI: 1.05, 1.84 Locoregional PFS poorer in ESA group: RR 1.62; 95% CI: 1.22, 2.14	N/A	N/A
EPO-CAN-20 Wright et al, 2007 (J&JPRD)[a]	Advanced NSCLC, no chemotherapy (n = 70)[c]	Randomized, double-blind, placebo-controlled	12 to 14 g/dL	More deaths in ESA group: 97% ESA vs 92% control Percentage of deaths due to disease progression: 88% ESA, 91% control	Median overall survival was shorter in the ESA group (2.23 vs 4.24 months; p = 0.0841) HR 1.57; 95% CI: 0.95, 2.58; p=0.0777 (based on a Cox proportional hazard model with treatment and stratification as factors).	Report and datasets 02/08

[a] Data were also presented at ODAC 2004.
[b] Study terminated early with approximately 25% of planned accrual (114 of 460 subjects) due to an unexpected increase in VTEs in the ESA group; 113 subjects received investigational product and were included in the analysis.
[c] Study terminated early due to increase in VTEs in the ESA group.

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Table 2. Safety Data of Concern

Study Designation(s) (Sponsor)	Study Population (n)	Study Design	Hemoglobin Target	Published Results for Survival and/or Disease Progression	Most Recent Results Provided to FDA for Review	Data reported to the FDA
Studies Presented at ODAC 2007 (continued)						
DAHANCA 10 Overgaard et al, 2007 (DAHANCA) Postmarketing commitment	Head and neck receiving radiation alone (n = 522)	Randomized, open-label	14 to 15.5 g/dL	Higher 5-year mortality in ESA group: RR 1.28 (95% CI: 0.98, 1.68) 5-year locoregional control poorer in ESA group: RR 1.44 (95% CI: 1.06, 1.96)	N/A	Publication online 11/2006 Abstract submitted to FDA 7/07
20000161 Hedenus et al, 2003; ODAC Briefing Materials, 2007 (Amgen)	Hematologic malignancy receiving chemotherapy (n = 344)	Randomized, double-blind, placebo-controlled	13 to 14 g/dL (women) 13 to 15 g/dL (men)	Higher mortality in ESA group: HR 1.36 (95% CI: 1.02, 1.82) PFS similar between ESA and placebo: HR 1.01 (95% CI: 0.79, 1.29)	N/A	Report and datasets 4/05 Long-term follow-up report and datasets 4/07
20010103 Smith et al, 2008 (Amgen)	Nonmyeloid malignancy, no chemotherapy or radiotherapy (n = 989)	Randomized, double-blind, placebo-controlled	12 to 13 g/dL	Higher mortality in ESA group: HR 1.22 (95% CI: 1.03, 1.45)	N/A	Report and datasets 4/07

[a] Data were also presented at ODAC 2004.

Page 3 of 3

[b] Study terminated early with approximately 25% of planned accrual (114 of 460 subjects) due to an unexpected increase in VTEs in the ESA group; 113 subjects received investigational product and were included in the analysis.

[c] Study terminated early due to increase in VTEs in the ESA group.

4.2.1 PREPARE

The PREPARE study (also known as DE-2001-0033) is one of Amgen's pharmacovigilance studies and was conducted by the German Gynecological Oncology (AGO) Study Group. This study was an open-label, randomized, multicenter, phase 3 study designed to evaluate the effects of neoadjuvant chemotherapy in subjects with breast cancer using a sequential dose-dense and dose-intensified regimen of epirubicin, paclitaxel, cyclophosphamide, 5-fluorouracil, and methotrexate compared with preoperative sequential administration of epirubicin and cyclophosphamide followed by paclitaxel, with or without darbepoetin alfa. Darbepoetin alfa was initially administered at a dose of 4.5 μg/kg Q2W to maintain hemoglobin concentrations between 12.5 g/dL and 13 g/dL. Accrual to this study is complete and follow-up continues.

The primary endpoint of this study is a comparison of disease-free survival for the two randomized chemotherapy treatments. However, as follow up is not complete, the interim analysis described below was for evaluation of the histopathologic endpoints and did not include a formal statistical analysis of overall survival or progression-free survival (PFS). The study is ongoing.

In November 2007, the final data for the secondary efficacy endpoint of pathologic complete remission was formally analyzed in a prespecified interim analysis of 733 subjects completing the 24-week treatment period. No evidence of a statistically significant increase in pathologic complete remission was observed in subjects receiving darbepoetin alfa compared with a control group that did not receive darbepoetin alfa. No formal statistical analyses were prespecified or conducted for the interim evaluation of relapse-free survival and overall survival, as data collection was incomplete for 20% of subjects. An unplanned interim analysis performed after a median follow-up of approximately 3 years indicated that the survival rate was lower (86% vs 90%, HR 1.42, 95% CI: 0.93, 2.18) and PFS rate was lower (73% vs 79%, HR 1.33, 95% CI: 0.99, 1.79) in the darbepoetin alfa-treated arm compared to the control arm.

Data collection/cleaning and long-term follow-up for the study continue, and the study investigator is expected to present the latest information from this study at the ODAC meeting.

4.2.2 GOG-191

This was an open-label, randomized, multicenter, investigator-sponsored study in subjects with cervical cancer receiving concurrent radiation and cisplatin. The study was

intended to determine whether epoetin alfa treatment to maintain higher hemoglobin levels could prolong PFS (primary clinical endpoint). Secondary clinical endpoints included overall survival and local tumor control. Planned recruitment was 460 subjects. Subjects were randomized 1:1 to receive epoetin alfa 40,000 IU SC once weekly or standard of care. Eligible subjects had hemoglobin concentrations < 14 g/dL at entry. Dosing was interrupted if hemoglobin exceeded 14 g/dL for 2 weeks or more, and then was restarted at the same dose when hemoglobin fell to < 13 g/dL.

The study enrolled 114 of a planned 460 cervical cancer patients receiving chemotherapy and radiotherapy. Of these, 113 received study medication and are included in the analysis. The study was terminated prematurely due to an increase in thromboembolic events in epoetin alfa-treated patients compared to control (17% vs 9%), based on data cutoff as of January 2004. These data were presented in briefing materials for the 2004 and 2007 ODAC meetings, and showed that after approximately 26 months of follow up, no differences in survival or PFS were noted between the groups. With the additional follow-up data as of April 2006, these analyses were repeated using the intent-to-treat population (114 randomized subjects). The incidence of TVEs remained numerically higher in epoetin alfa-treated patients compared to control (19% vs 9%, respectively). After a median duration of follow-up of 30 months, a total of 44 out of 114 subjects in the intent-to-treat population had a reappearance of disease, or progression for existing disease, or death (21 in the non-epoetin alfa group and 23 in the epoetin alfa group). The 3-year PFS rate was similar in the epoetin alfa and control groups (59% vs 62%, respectively). There was no statistically significant difference between the treatment groups using the log-rank test ($p = 0.8561$). The hazard ratio was 1.056 (95% CI: 0.584, 1.909) from a univariate Cox model. With respect to overall survival, there were 39 total deaths among the 114 subjects (17 in the non-epoetin alfa group and 22 in the epoetin alfa group). The 3-year overall survival rate was numerically higher in the non-epoetin alfa group than in the epoetin alfa group (71% vs 61%, respectively), but the difference was not statistically significant (log-rank $p = 0.4372$). The hazard ratio was 1.284 (95% CI: 0.682, 2.419) from a univariate Cox model.

4.3 Other Informative Controlled Studies

A review was conducted of all other controlled studies in the oncology setting with available data that have been considered informative by FDA (Oncologic Drugs Advisory Committee Meeting, 2007). Key published data from these studies are provided in Table 3. The timeline for providing these important data was presented at the

May 2007 ODAC, and all of these studies have been completed in accordance with (or in some cases, ahead of) this proposal. The companies continue to proactively evaluate and accelerate completion of all studies that could contribute useful information to the assessment of ESA safety in the CIA indication. Although it is acknowledged that FDA may not have an opportunity to review all of these data thoroughly given the timing of the ODAC meeting, all available results provided to FDA for review are included in Table 3 for completeness. These results have not changed significantly from the previously available data discussed at ODAC 2004 and 2007. These studies have not suggested an increased risk of mortality or tumor progression with ESAs, and contribute to the totality of data that should be considered in the assessment of the benefit:risk of these agents.

Data from additional large, controlled studies of interest that have been reported (HD-15, BRAVE) or submitted to FDA since ODAC 2007 are also provided in Table 4.

Table 3. Other Informative Controlled Clinical Studies

Study Designation(s) (Sponsor)	Tumor type (n)	Study Design	Hemoglobin Target	Published Results for Survival and/or Disease Progression	Most Recent Results Provided to FDA for Review	Data Reported to FDA
20010145 Pirker et al, 2007 (Amgen) Postmarketing commitment	Extensive stage SCLC receiving chemotherapy (n = 600)	Randomized, double-blind, placebo-controlled	13 g/dL	At median follow-up of 2.5 years, ESA and placebo had similar PFS: HR 1.02; 95% CI: 0.86, 1.21 and overall survival: HR 0.93; 95% CI: 0.78, 1.11	PFS based on blinded central review similar between ESA and placebo: HR: 0.97; 95% CI: 0.82, 1.16	Report and datasets 10/07
FR-2003-3005 LNH03-6B Delarue et al, 2006; ODAC Briefing Materials, 2007 (GELA) Postmarketing commitment	Diffuse Large B-cell Lymphoma receiving chemotherapy (n = 458/660 planned)	Randomized, controlled open-label	13 to 15 g/dL initially 11 to 13 g/dL in protocol amendment	At 1 year, ESA and control groups had similar overall survival (78% vs 70%) RR 0.75; 95% CI: 0.44, 1.76 and event-free survival (73% vs 64%) RR 0.75; 95% CI: 0.44, 1.26	N/A	N/A (study ongoing)
980297 Vansteenkiste et al, 2002; ODAC Briefing Materials, 2007 (Amgen)	SCLC and NSCLC receiving chemotherapy (n = 314)	Randomized, double-blind, placebo-controlled	13 to 14 g/dL (women) 13 to 15 g/dL (men)	After median follow-up of ~8 months, ESA and control had similar overall survival: HR 0.77 (95% CI: 0.59, 1.01) and PFS HR 0.79 (95% CI: 0.62, 1.00)	N/A	Report and datasets 4/05 Long-term follow-up datasets 3/07
20030232 Taylor et al, 2005 (Amgen)	Nonmyeloid malignancy, receiving chemotherapy (n = 391)	Randomized, double-blind, placebo-controlled	11 to 13 g/dL	ESA and placebo groups had similar incidence of on-study death (9% ESA, 10% placebo)	N/A	Report 8/06 Datasets 3/07

[a] Study terminated early

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Table 3. Other Informative Controlled Clinical Studies

Study Designation(s) (Sponsor)	Tumor type (n)	Study Design	Hemoglobin Target	Published Results for Survival and/or Disease Progression	Most Recent Results Provided to FDA for Review	Data reported to FDA
EPO-GER-7 Möbus et al, 2007 (AGO)	Breast cancer receiving adjuvant chemotherapy (n = 643)	Randomized, controlled, open-label	12.5 to 13 g/dL	At median follow-up of 62 months, ESA and control groups had similar disease-free survival (72% vs 71%; p = 0.86) and overall survival (81% vs 83%; p = 0.89)	At median follow-up of 56 months, ESA patients and control patients had similar disease-free survival (70.7% vs 72%; p = 0.97) and overall survival (82% in both groups; p = 0.94)	Report and datasets 2/08
EPO-GBR-7 (J&JPRD)	Head and neck cancer receiving radiation alone (n = 301)[a]	Randomized, controlled, open-label	12 g/dL withheld > 15 g/dL and restarted at < 14.5 g/dL at 50% of dose	N/A	Median local disease-free survival was similar for ESA and control groups (31 vs 35 months, respectively): HR 1.04, 95% CI: 0.77, 1.41; p = 0.791	Report 1/08 Datasets 2/08
N93-004 Grote et al, 2005 (J&JPRD) Postmarketing commitment	SCLC receiving chemotherapy (n = 224)	Randomized, double-blind, placebo-controlled	14 to 16 g/dL	3-year mortality similar between ESA and placebo: (91.7% ESA, 87.8% placebo) 3-year overall tumor response similar between groups: (60% ESA, 56% placebo)	3-year mortality similar between ESA and placebo: (91.7% ESA, 87.8% placebo) Median duration of survival was 10.5 vs 10.4 months for ESA-treated and placebo respectively Tumor response rates (72% ESA, 67% placebo)	Report and datasets 10/02
EPO-CAN-17 Chang et al, 2005 (J&JPRD)	Breast cancer receiving chemotherapy (n = 354)	Randomized, controlled, open-label	12 to 14 g/dL	2-year disease progression similar between ESA and control (41% ESA, 43% control) Deaths similar between ESA and control (27 deaths ESA, 28 deaths control)	Deaths similar between ESA and control (27 deaths ESA, 28 deaths control). Kaplan-Meier estimates of the survival curves were similar (log rank test, p = 0.82)	Report and datasets 2/08

[a] Study terminated early

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Table 3. Other Informative Controlled Clinical Studies

Study Designation(s) (Sponsor)	Tumor type (n)	Study Design	Hemoglobin Target	Published Results for Survival and/or Disease Progression	Most Recent Results Provided to FDA for Review	Data reported to FDA
RTOG-99-03 Machtay et al, 2007 (J&JPRD)	Head and neck, radiation alone (n = 148)[a]	Randomized, controlled, open-label	13.5 to 16 g/dL (men) 12 to 14 g/dL (women)	3-year mortality similar between ESA and placebo (56% ESA, 57% control) 3-year locoregional PFS similar between ESA and placebo (47% ESA, 52% control)	Similar results for ESA and placebo for 3-year mortality (56% vs 57%) HR 1.17; 95% CI: 0.72, 1.89; p = 0.53 and 3-year locoregional failure (44% vs 36%) HR 1.20; 95% CI: 0.72, 2.02; p = 0.56 and 3-year locoregional PFS (47% vs 52) HR = 1.19; 95% CI 0.76, 1.86; p = 0.46	Report 1/08 Datasets 2/08
EPO-GER-22 (J&JPRD)	Inoperable Stage III NSCLC receiving chemotherapy (n = 385)[a]	Randomized, controlled open-label	13 g/dL initially <12 g/dL (withhold at > 13 g/dL, resume at < 12 g/dL) in amendment	N/A	Median survival time was similar for ESA (359 days) and control (355 days): HR 0.807; 95% CI: 0.644, 1.012; p = 0.0623 Based on 9/07 database (observations ongoing)	Report 2/08 Datasets 2/08
EPO-GER-8/ AGO-NOGGO Blohmer et al, 2004 (AGO)	High risk cervical cancer receiving chemotherapy (n = 250)	Randomized, controlled, open-label	13 to 14 g/dL	Relapse or death events: 19 ESA vs 31 control Deaths: 16 ESA vs 23 control	Recurrence-free survival HR 0.67; 95% CI: 0.38, 1.17; p = 0.159 KM analysis: 21 events (17%) ESA, 32 events (25%) control; p = 0.0831 suggesting a slight trend favoring ESA group	Report and datasets 02/08

[a] Study terminated early

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Table 4. Additional Controlled Studies

Study Designation(s) (Sponsor)	Tumor type (n)	Study Design	Hemoglobin Target	Results for Survival and/or Disease Progression	Data reported to FDA
HD-15 Engert, 2007 (GHSG)	Advanced Hodgkin's lymphoma receiving chemotherapy (n = 688/1500 planned)	Randomized, double-blind, placebo-controlled	During chemotherapy period: 12 to 14 g/dL initially (13 g/dL in protocol amendment) After chemotherapy: ≤12 g/dL	Interim data from 688 subjects: 30-month overall survival similar (ESA vs control): OR 1.21; 95% CI: 0.32, 4.55 30-month freedom-from-treatment failure similar between ESA and control	N/A (study ongoing)
BRAVE Aapro et al, 2008 (Hoffman La Roche)	Metastatic breast cancer receiving chemotherapy (n = 463)	Randomized, controlled, open-label	ESA withheld at ≥ 15 g/dL and reinstated at < 13 g/dL	After 18 months, ESA and control groups had similar overall survival HR 1.07; 95% CI 0.87,1.33; p = 0.522 and PFS HR=1.07; 95% CI 0.89, 1.30; p = 0.448.	N/A
EPO-CAN-15 (J&JPRD)	Limited disease SCLC receiving chemotherapy (n = 104)	Randomized, double-blind, placebo-controlled	ESA treated patients 12 to 14 g/dL	Median time to progression was 15.8 months in the ESA group and 16.5 months in the control group (p = 0.633)	Report and datasets 02/08

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Table 4. Additional Controlled Studies

Study Designation(s) (Sponsor)	Tumor type (n)	Study Design	Hemoglobin Target	Results for Survival and/or Disease Progression	Data reported to FDA
EPO-INT-45 Wilkinson et al, 2006 (J&JPRD)	Ovarian cancer receiving chemotherapy (n= 182)	Randomized, controlled, open-label	12 to 14 g/dL	At the end of treatment, investigator assessed tumor evaluation in the 2 groups was similar for complete response, partial response, or no response. More patients had progressive disease in the ESA group versus control (11.4% versus 1.7%, respectively), but the difference was not statistically significant p=0.425). Three patients (in the ESA group) died during the study.	Study summary and datasets projected 3/08
EPO-INT-47 Pronzato et al, 2002 (J&JPRD)	Breast cancer receiving chemotherapy (n = 220)	Randomized, controlled	12 g/dL to 14 g/dL	No differences between ESA and control groups in tumor response, ECOG performance, or overall survival	Study summary and datasets projected 3/08
EPO-INT-49 Milroy et al, 2003 (J&JPRD)	NSCLC (stage IIIb, IV) receiving chemotherapy (n = 424)	Randomized, controlled	≤ 15 g/dL (men) ≤ 14 g/dL (women)	Deaths were similar between ESA and control groups (64% vs 60%). The Kaplan-Meier estimate for median survival was 254 and 265 days in the ESA and control group, respectively: HR 1.125; 95% CI: 0.883, 1.434	Study summary and datasets projected 3/08

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4.4 Updated Overall Assessment of Risk

To provide a thorough assessment of the risk of mortality and tumor progression in patients with cancer receiving ESAs, including the new data available since ODAC 2007, the companies have performed a comprehensive review of relevant clinical study data and published literature in this setting to date. The Cochrane Collaboration report (specifically, Analysis 05.05) was used as the basis for an updated meta-analysis of published trial results for mortality (Bohlius et al, 2006). All available data on mortality from relevant studies that have become available since the Cochrane Collaborative report was generated were added to this analysis, including all randomized, controlled trials comparing an ESA plus RBC transfusion with RBC transfusion alone for prophylaxis or treatment of anemia in cancer patients with or without concurrent antineoplastic therapy. This meta-analysis was based on prespecified criteria and included only studies that used randomized assignment of patients to treatment arms. Small studies (≤ 10 subjects per study arm) were excluded.

While Amgen and J&JPRD have conducted these meta-analyses to further evaluate the nature and consistency of the safety signals that have been observed, the companies acknowledge that neutral results in meta-analyses should not minimize the safety concerns raised by individual studies. These analyses are, however, useful for evaluating these safety concerns within the context of the overall available data. The ongoing independent meta-analysis by the Cochrane Collaboration will also provide important information in this regard (see Section 6.4).

The value of meta-analyses for identifying safety signals in the absence of definitive studies has been widely recognized and has been a basis for decision-making by several recent FDA Advisory Committees (eg, reviews of rofecoxib, rosiglitazone). Meta-analysis results are also the basis for safety labeling for SSRIs and anti-epileptics. Findings from meta-analyses have also provided the basis for well-recognized treatment guidelines (eg, Oxford review of adjuvant breast cancer treatment).

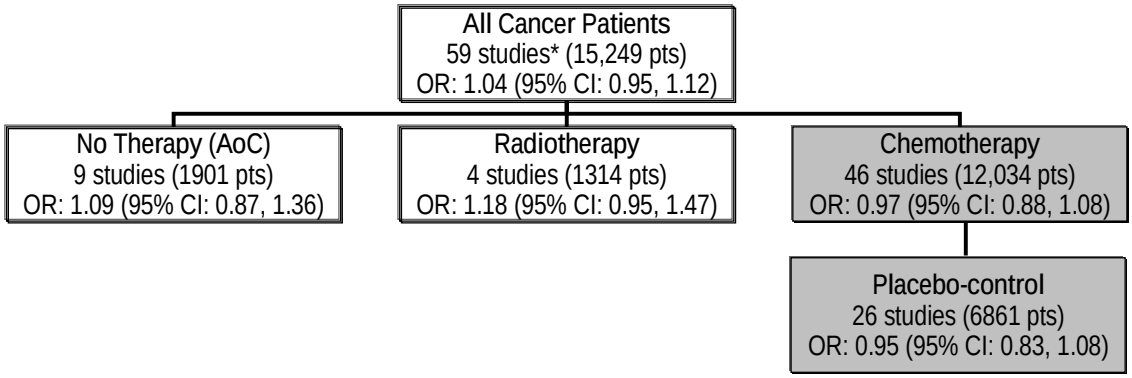
4.4.1 Overall Survival

A total of 59 controlled clinical studies have reported data for deaths on study or during long-term follow up (Figure 4). As noted in Section 4.2, 8 of these 59 studies have reported that subjects receiving ESAs had decreased overall survival and/or tumor progression compared with the control group. All 8 studies of concern are described in the WARNINGS AND PRECAUTIONS section of the proposed product labeling for ESAs. As previously noted, all of these studies were conducted in settings inconsistent with currently labeled product guidance (Section 4.2, Table 2).

The safety signals observed in these studies are inconsistent in that some studies reported potential negative effects during the treatment period (as early as 4 months in the BEST study), while others only reported differences in mortality after multiple years of follow-up (Study 20000161, GOG-191, and PREPARE).

In a comprehensive study-level analysis conducted by Amgen, a difference in the risk of mortality with ESAs was observed by treatment setting (ie, CIA, radiotherapy, or anemia of cancer), with the greatest negative signal occurring in subjects with head and neck cancer receiving radiotherapy alone who were treated beyond the correction of anemia (Figure 4). The results of radiotherapy studies in head and neck cancer are further discussed in Section 4.4.4.

Figure 4. Comprehensive Study-level Meta-Analysis of Death in All Available Studies

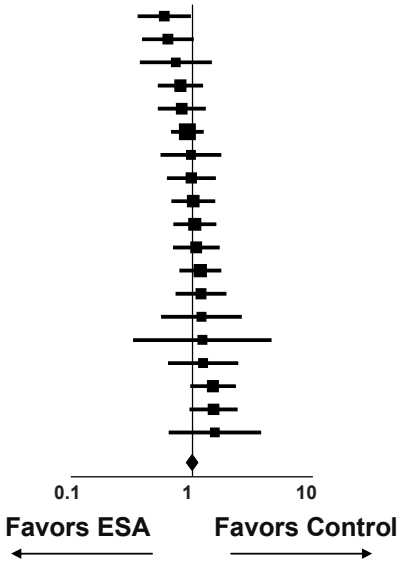


*Placebo or non ESA-controlled studies
If Leyland-Jones (BEST) 1-year data were used, then Overall OR=1.05 (0.97, 1.15), Chemotherapy OR = 1.02 (0.92, 1.13), and Placebo-controlled CIA OR = 1.01 (0.87, 1.17).
4 placebo-controlled CIA studies had no deaths in both arms.
Note: Odds ratios (OR) based on random-effects model; MDS not included, inclusion does not impact results.

Of the studies in the CIA setting (gray boxes in Figure 4), 19 have reported long-term survival (≥ 1 year of follow up). None of these studies specified a maximum hemoglobin of 12 g/dL during the treatment period per the current product labeling. As hazard ratios were not available for all studies, Amgen calculated odds ratios (ESA versus control) for each study. This analysis includes long-term follow-up data for all studies, including the BEST study, which indicated a negative effect of ESA use on survival (but not disease progression) at 12 months, but not during long-term follow-up (see Section 4.2). When the data from all 19 studies were meta-analyzed, there was an overall neutral survival risk for ESA use, with an odds ratio (ESA versus control) of 1.00 (95% CI: 0.89, 1.12) (Figure 5).

**Figure 5. Study-level Meta-analysis for Overall Death
19 Studies in CIA (Including 3 Chemotherapy/Radiotherapy*)
with Long-term Follow Up
(n = 8071; 4149 ESA, 3922 Control)**

Study name	Odds ratio	95% CI Lower limit	95% CI Upper limit
* EPO-GER-022	0.58	0.35	0.96
Vansteenkiste (AMG 980297)	0.62	0.38	1.01
* Blohmer (AGO-NOGGO)	0.73	0.37	1.44
Pirker(AMG 20010145)	0.79	0.52	1.21
Littlewood	0.81	0.52	1.28
Leyland-Jones (BEST ITT updt)	0.91	0.67	1.23
Chang 2005 (EPO-CAN-17)	0.97	0.55	1.73
Witzig 2005	0.98	0.62	1.55
Aapro 2006 (BRAVE)	1.02	0.67	1.53
Mobus	1.05	0.70	1.57
Osterborg 2005	1.08	0.69	1.67
Milroy (INT-49)	1.16	0.79	1.72
Savonije 2005	1.18	0.73	1.90
* Thomas (GOG-0191)	1.19	0.55	2.56
Engert 2007 (HD 15 IA)	1.21	0.32	4.55
Prozanto (INT-47)	1.23	0.63	2.39
Hedenus 2003 (AMG 20000161)	1.48	0.97	2.27
PREPARE	1.50	0.96	2.36
Grote 2005 (N93-004)	1.54	0.64	3.72
Random Effects Model	**1.00**	**0.89**	**1.12**



Overall I^2 = 12.3%; Fixed Effects Model =1.00(0.89, 1.11)
If 1-year BEST data are used, the Overall I^2 = 27.5%; Random Effects Model =1.04(0.92, 1.19)
with Fixed Effectx Model = 1.06 (0.95, 1.18)
Meta Analysis Using OR
* = Radiochemotherapy study

Note: The BEST study reported higher 12-month mortality (primary endpoint) in ESA group:
HR 1.37 (95% CI: 1.07, 1.74); estimated OR 1.42 (95% CI: 1.07, 1.90)

In summary, safety concerns have been noted in 8 studies, which have led to labeling changes to appropriately communicate this risk. Overall, these signals have not been consistently observed in individual studies, and meta-analyses in over 8000 subjects do not indicate a clear effect of ESAs on mortality in the CIA population. Thus, further research is needed to answer this question. Ongoing and planned studies to evaluate the risk of mortality with ESAs are discussed in Section 6.3.

4.4.2 Disease Progression

Twenty-four clinical studies examining ESA use in cancer patients in the settings of CIA, anemia of cancer, and radiotherapy have included a measure of disease progression. These measures have included outcomes such as PFS, tumor response, tumor control, and disease progression. However, the quality of the tumor assessments in the available studies is variable.

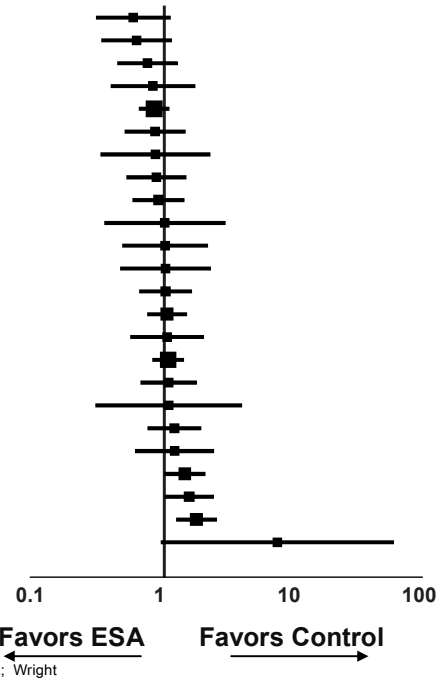
In general, studies to date have not rigorously assessed the endpoint of tumor progression to the same standard that would be required to demonstrate the efficacy of a therapeutic agent. This limitation can result in potentially conflicting results. For example, in the BEST study case report form, there was a "check box" option for recording disease progression as the cause of death. Thus, when checked as the cause of death, "disease progression" reflected the investigators' overall assessment of the course of the disease and not a specific, objective measure of tumor mass. As a result, although more deaths were attributed to disease progression in the ESA group, other more objective measures of tumor outcome (eg, response rate and time to progression) did not differ between treatment groups in this large, randomized, double-blind study.

Of the 24 studies with available data, only 1 has rigorously assessed tumor progression radiographically with blinded centralized review (Study 20010145, Pirker et al, 2007); this study did not show an increased risk of tumor progression in subjects receiving ESAs. Amgen study 20010145 was especially comprehensive in that the blinded central review of tumor response was done in a study population of subjects with a homogenous tumor type (small cell lung cancer [SCLC]) who were receiving the same chemotherapy regimen. In the postmarketing commitment study N93-004 (Grote et al, 2005), a double-blind study in subjects with SCLC receiving the same chemotherapy regimen, tumor response (the primary endpoint) was assessed radiographically at the completion of the third chemotherapy cycle, but did not include central review. In the remaining studies, tumor progression was evaluated by the investigator (21 studies) or by histopathology in the case of the PREPARE study (a randomized, controlled independent study by the German Gynecological Oncology Study Group in which darbepoetin alfa was administered to breast cancer patients receiving neo-adjuvant chemotherapy). The PREPARE study, as noted in Section 4.2.1, showed no difference in the pathologically assessed endpoint of pathologic complete remission, but an interim analysis of incomplete data showed a trend towards increased risk of disease progression in the ESA group.

To comprehensively examine the disease progression outcomes for all 24 studies, and to standardize the variable outcome measures used to evaluate disease progression, Amgen calculated odds ratios (ESA versus control) for each study (Figure 6).

Figure 6. Study-level Summary of Progression-related Endpoints: 24 Studies (n = 9197, 4640 ESA, 4557 Control)

Study name	Odds ratio	95% CI Lower limit	95% CI Upper limit
Vansteenkiste (AMG-980297)	0.58	0.30	1.11
Blohmer revised	0.61	0.33	1.13
* Osterborg 2005	0.74	0.44	1.25
* Chang 2005 (EPO-CAN-17)	0.82	0.39	1.72
Leyland-Jones (BEST)	0.84	0.64	1.08
* Grote 2005 (N93-004)	0.85	0.50	1.44
Engert (HD 15 IA)	0.86	0.33	2.24
Pirker (AMG145 w/cntl read)	0.87	0.52	1.46
* Milroy (INT-49)	0.90	0.57	1.41
* Vadhan-Raj	1.01	0.35	2.94
Thomas (GOG-0191)	1.02	0.48	2.15
* Prozanto (INT-47)	1.02	0.46	2.26
EPO-GBR-7	1.02	0.65	1.62
Mobus	1.05	0.75	1.48
Machtay (RTOG 99-03)	1.05	0.55	2.00
Aapro 2008 (est from HR)	1.07	0.82	1.40
Hedenus 2003 (AMG-20000161)	1.08	0.66	1.76
Wright 2007 (EPO-CAN-20)	1.08	0.30	3.95
* Witzig 2005	1.20	0.75	1.91
* Osterborg 96 Roche	1.20	0.60	2.40
PREPARE	1.44	1.01	2.05
Henke 2003 (ENHANCE)	1.56	1.01	2.39
Overgaard (DAHANCA 10 IA)	1.77	1.25	2.52
* Wilkinson 2006 (INT-45)	7.47	0.95	58.54



Pirker (AMG 145) is listed using data from the RadPharm central review
Note: Thomas (GOG-0191), Blohmer and Vadhan-Raj are RTx CTx;
Overgaard (DAHANCA), Henke 2003 (ENHANCE), Machtay (RTOG 99-03), and EPO-GBR 7 are RTx; Wright 2007 is AOC
All other studies are CIA
* denotes studies where disease progression was evaluated only as part of tumor assessment

In this analysis, ESA treatment was associated with both favorable and unfavorable disease progression outcomes, with most studies showing a neutral effect of ESAs on these endpoints. The 2 studies with a statistically significant increase in disease progression in the ESA group were performed in the radiotherapy setting (ENHANCE and DAHANCA 10) targeting higher hemoglobin levels. These results are further discussed in Section 4.4.4.

The updated Cochrane Collaboration analysis (described in Section 6.4) and the planned, large, definitive study (described in Section 6.3) will provide further insight into this important question.

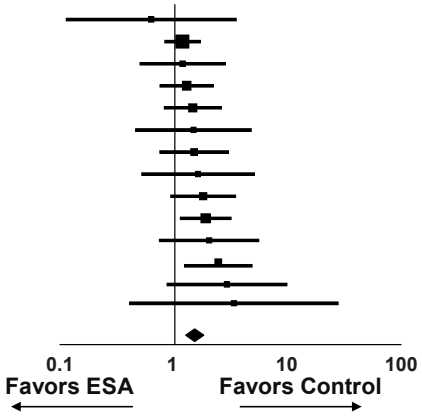
4.4.3 Risk of Vascular Thrombotic Events (VTEs)

In contrast to the inconsistent results observed for survival and tumor progression, meta-analysis for the known risk of VTEs reveals a clear signal in the majority of studies, with a hazard ratio of 1.67 (95% CI: 1.35, 2.06) in the published Cochrane Collaboration report (Bohlius et al, 2006). These risks have been observed during the on-study period

and have been seen in both individual randomized studies and in meta-analyses of the same CIA studies used for evaluating survival (where VTEs were reported): OR 1.49 (95% CI: 1.24, 1.79) (Figure 7). Thus, these results indicate that such analytic methods are sensitive to small absolute increases in risk for relatively rare events. The risk of VTE is documented in the product labeling of approved ESAs.

Figure 7. Study Level Meta-analysis of Reported VTE: CIA Studies With Long-term Follow-up (n = 5899; 2990 ESA, 2909 Control)

Study name	Odds ratio	95% CI Lower limit	95% CI Upper limit
Blohmer revised	0.62	0.11	3.45
Leyland-Jones (BEST)	1.17	0.81	1.67
Grote 2005 (N93-004)	1.17	0.49	2.77
Chang 2005 (EPO-CAN-17)	1.27	0.74	2.17
EPO-GER-022	1.44	0.81	2.56
Vansteenkiste (AMG-980297)	1.46	0.45	4.69
Engert (HD 15 IA)	1.48	0.74	2.96
Witzig 2005	1.60	0.51	5.00
Pirker (AMG-145)	1.77	0.92	3.42
Mobus	1.86	1.12	3.11
Hedenus 2003 (AMG-2000161)	2.00	0.73	5.46
Aapro 2008	2.41	1.22	4.76
Thomas (GOG-0191)	2.87	0.85	9.66
Savonije 2005	3.53	0.43	29.11
Random Effects Model	**1.49**	**1.24**	**1.79**



I^2 = 0%;Fixed Effects Model = Random Effects Model
Meta Analysis Using OR

4.4.4 ESA Safety in Specific Cancers

Clinical studies raising safety concerns regarding ESA use were conducted in subjects with breast cancer, lung cancer, lymphoid malignancies, cervical cancer, and head and neck cancer. As the inconsistent results for survival and tumor progression noted above could be related to a tumor-specific phenomenon, similar analyses were performed looking at individual tumor types for any consistent patterns. As hazard ratios were not available for all studies, Amgen calculated odds ratios (ESA versus control) for each study. All available data (including long-term follow-up) have been included for all studies.

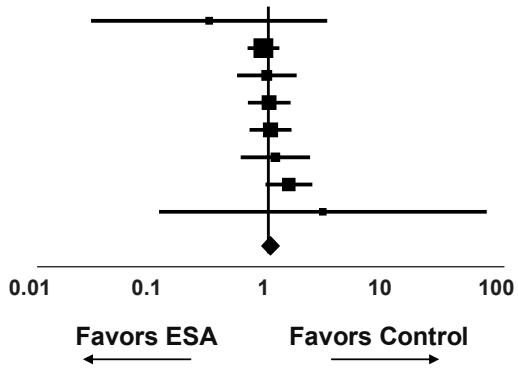
Breast Cancer

In the setting of breast cancer, 8 studies have reported data for overall survival or deaths on study (Figure 8). Of these 8 studies, 2 have raised safety concerns. When

measured at the 12-month timepoint (the primary endpoint of the study), data from the BEST study (Leyland-Jones et al, 2005) indicated a negative effect of ESA use on survival (but not disease progression); however, this signal was not seen in long-term follow-up (see Section 4.2). An unplanned interim analysis of incomplete data from the PREPARE study did not indicate a statistically significant effect of ESAs on survival or disease progression; however, a safety signal for both endpoints was seen during long-term follow-up (but not during the 6-month study period) (see Section 4.2.1). Data collection and long-term follow-up for this study continues.

Figure 8. Study-level Meta-analysis of Overall Death
8 Breast Cancer Studies
(n = 3517; 1748 ESA, 1769 control)

Study name	Odds ratio	95% CI Lower limit	95% CI Upper limit
Del Mastro	0.31	0.03	3.17
Leyland-Jones (BEST ITT updt)	0.91	0.67	1.23
Chang 2005 (EPO-CAN-17)	0.97	0.55	1.73
Aapro 2006 (BRAVE)	1.02	0.67	1.53
Mobus	1.05	0.70	1.57
Prozanto (INT-47)	1.15	0.59	2.26
PREPARE	1.50	0.96	2.36
O'Shaughnessy 2005	2.94	0.12	73.93
Random Effects Model	**1.04**	**0.88**	**1.24**



I^2 = 0%;Fixed Effects Model = Random Effects Model
If BEST 1-year data are used, I^2 = 0%;Fixed Effects Model = Random Effects Model = 1.22 (1.03, 1.45)
Meta Analysis Using OR

Note: The BEST study reported higher 12-month mortality (primary endpoint) in ESA group: HR 1.37 (95% CI: 1.07, 1.74); estimated OR 1.42 (95% CI: 1.07, 1.90)

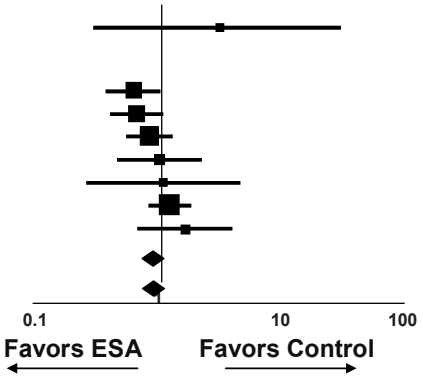
Note: O'Shaughnessy et al, 2005 reported only 1 death

Lung Cancer

In the setting of lung cancer, 8 studies have reported data for overall survival or deaths on study (Figure 9). One of these 8 studies indicated a negative effect of ESAs on overall survival (EPO-CAN-20). EPO-CAN-20 was conducted in subjects with NSCLC who were not receiving chemotherapy, which is not an approved indication for ESAs, and was halted after only 70 subjects were enrolled due to an increase in VTEs in the ESA group (Wright et al, 2007). Results in studies of subjects receiving chemotherapy consistently demonstrated neutral survival outcomes.

Figure 9. Study-level Meta-analysis of Overall Death
8 Lung Cancer Studies
(n = 2247; 1143 ESA, 1104 Control)

Tx Type	Study name	Odds ratio	95% CI Lower limit	95% CI Upper limit
AOC				
	Wright 2007 (EPO-CAN-20)	2.82	0.28	28.56
CIA				
	*EPO-GER-022	0.58	0.35	0.96
	Vansteenkiste (AMG 980297)	0.62	0.38	1.01
	Pirker(AMG 20010145)	0.79	0.52	1.21
	*EPO-CAN-15	0.93	0.43	2.00
	Thatcher combined	1.03	0.24	4.31
	Milroy (INT-49)	1.16	0.79	1.72
	Grote 2005 (N93-004)	1.54	0.64	3.72
Random Effects Model: CIA		**0.85**	**0.66**	**1.10**
Random Effects Model: Overall		**0.86**	**0.67**	**1.11**



Overall I^2 = 25.5%; Fixed Effects Model = 0.85 (0.70, 1.05); CIA I2 = 28.3%; Fixed Effects Model = 0.85 (0.69, 1.04)
Meta Analysis Using OR
* = Radiochemotherapy study

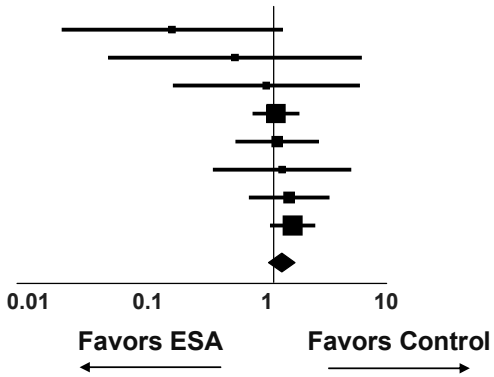
Lymphoid Malignancy

In the setting of lymphoid malignancy, 8 studies have reported data for overall survival or deaths on study (Figure 10). Only 1 study (Amgen Study 20000161) indicated a negative effect of ESAs on overall survival. This effect was not observed in the other studies of patients with lymphoid malignancies, even those with a similar design to Study 20000161 (eg, Österborg et al, 2005).

Four of these studies, including Amgen Study 20000161, had a tumor progression endpoint (Study 20000161; Österborg et al, 1996; Österborg et al, 2005; and HD-15), and none indicated an increased risk of tumor progression in subjects receiving ESAs.

Figure 10. Study-level Meta-analysis of Overall Death
8 Lymphoid Malignancy Studies
(n = 2142; 1205 ESA, 937 Control)

Study name	Odds ratio	95% CI Lower limit	95% CI Upper limit
Dammacco (INT-2)	0.14	0.02	1.21
Cazzola (Roche)	0.49	0.04	5.56
Pangalis (P-174)	0.89	0.15	5.36
Osterborg 2005	1.08	0.69	1.67
Osterborg 1996 (Roche)	1.10	0.50	2.44
Engert 2007 (HD 15 IA)	1.21	0.32	4.55
Rose	1.39	0.64	2.98
Hedenus 2003 (AMG 20000161	1.48	0.97	2.27
Random Effects Model	**1.20**	**0.93**	**1.55**



I^2 = 0.0%; Fixed Effects Model = Random Effects Model
Meta Analysis Using OR
1 study (Hedenus AMG 990114; not plotted) had no deaths in either group

Cervical Cancer

In the setting of cervical cancer, 2 studies have reported data (both long-term) for overall survival (Table 5). One of these studies showed a trend towards a negative effect of ESAs on overall survival (p = 0.45; GOG-191), while the other (AGO/NOGGO) suggested potential benefit. As noted in Section 4.2.2, the GOG-191 study was a randomized, controlled study that closed early after < 25% accrual due to increased VTEs in the ESA group and indicated that subjects who received ESAs showed a trend toward decreased overall survival compared with the control group (Thomas et al, 2007). The AGO/NOGGO study (Blohmer et al, 2004) study was a randomized, controlled study in which subjects receiving ESAs had numerically improved overall survival compared to the control group.

Table 5. Summary of Cervical Cancer Studies Evaluating Overall Survival

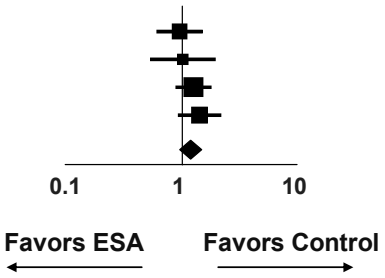
Study Designation	Tumor Type	Overall Survival	Progression Endpoints	Follow-up
Study with negative signal				
GOG-191	Stage IIB, IIIB, and IVA cervical cancer (n=114)	ESA: 61% alive Control: 71% alive	PFS ESA: 59% Control: 62%	3 years
Study with neutral signal				
AGO/NOGGO	High-risk cervical cancer (n=250)	Deaths ESA: 14% Control: 18%	Relapse events ESA: 17% Control: 25%	4 years

Head and Neck Cancer

Two studies have reported a statistically significant negative effect of ESAs on local-regional control in patients with head and neck cancer receiving radiation and chemotherapy (ENHANCE, DAHANCA 10) (Figure 11). These studies were designed to test the hypothesis that increasing hemoglobin concentrations beyond correction of anemia would enhance the effect of radiation by improving tumor oxygenation, which is not a labeled use of ESAs nor one that is currently under investigation. Of two additional studies exploring a similar hypothesis, one (RTOG-9903 [Machtay et al, 2007]) showed a similar trend that did not reach statistical significance, and the other (J&JPRD Study EPO-GBR-7) did not indicate an adverse effect in ESA-treated patients. Product labeling now clearly states that ESAs should not be used in patients receiving radiotherapy alone and that hemoglobin concentrations should not exceed 12 g/dL.

Figure 11. Study-level Meta-analysis of Overall Death
4 Head and Neck Cancer Studies
(n = 1314; 663 ESA, 651 Control)

Study name	Odds ratio	95% CI Lower limit	95% CI Upper limit
EPO-GBR-7	0.95	0.60	1.49
Machtay (RTOG 99-03)	1.01	0.53	1.93
Overgaard (DAHANCA-10, IA)	1.25	0.88	1.78
Henke 2003 (ENHANCE)	1.41	0.93	2.16
Random Effects Model	**1.18**	**0.95**	**1.47**



I^2 = 0%;Fixed Effects Model = Random Effects Model
Meta Analysis Using OR
All studies were radiotherapy studies

In both ENHANCE and DAHANCA 10, tumor growth was limited to progression within the primary radiation treatment field. Importantly, and still unexplained, is the finding that this local failure was not accompanied by any other signs of tumor stimulation (eg, development of new metastases or growth of existing tumors outside of the radiation field), which might be expected if ESA therapy was stimulating tumor cell proliferation. Thus, other biologically plausible explanations for the clinical findings in these head and neck cancer studies warrant consideration.

One alternative hypothesis that has been advanced is that ESAs can decrease the effectiveness of local radiation when hemoglobin is pushed too high. Paradoxically, tumor hypoxia (a known predictor of poor responsiveness to radiation) may be worsened at high hemoglobin concentrations (Vaupel and Mayer, 2004). Proposed mechanisms for this effect include decreased capillary blood flow as a result of increased blood viscosity at higher hemoglobin concentrations. As VTE is a well documented adverse effect of both ESA therapy and cancer, this explanation represents a plausible alternative to the hypothesis of ESA-mediated tumor promotion, since both ENHANCE and DAHANCA 10 were designed to elevate hemoglobin well beyond the labeled hemoglobin ceiling of 12 g/dL, a known risk factor for excess VTE. Notably, radiation failure has not been seen when hemoglobin is kept within more modest targets. It should also be possible to test the hypothesis that excessive elevation of hemoglobin

adversely impacts the therapeutic benefit of radiation in carefully designed animal studies. Amgen and J&JPRD have proposed unrestricted funding to support independent translational studies through NCI-NIH to address these important questions.

4.5 Conclusion

Safety concerns regarding increased mortality or tumor progression have been noted in 8 studies, which have led to changes in the BOXED WARNING and WARNINGS AND PRECAUTIONS sections of the labeling to communicate this risk. The studies raising concerns were conducted in off-label settings such as ESA administration beyond the correction of anemia or in the absence of chemotherapy.

Safety signals have not been observed in other informative, controlled studies in CIA, and meta-analyses in over 8000 subjects do not indicate a clear effect of ESAs on mortality or tumor progression. In contrast, the well-recognized risk of VTEs in this patient population treated with ESAs is detected in meta-analysis of these same studies, even though it is an uncommon event (6% of patients) with an absolute increase in risk of ~3%. Studies conducted to date, including those in which ESAs were associated with increased mortality, do not show definitive evidence of tumor promotion.

The strongest evidence of increased risk with ESA treatment was observed in settings where ESAs were administered beyond the correction of anemia. ESAs are not approved for this use, and the product labeling for ESAs states that they are not to be administered at hemoglobin levels above 12 g/dL.

Amgen and J&JPRD believe that the results of meta-analyses must be considered in light of the significant safety signals that were observed in the individual studies noted. However, the lack of a consistent effect of ESAs on the risk of mortality or tumor progression in CIA across individual studies indicates that further research in the labeled indication is needed. The companies are committed to further evaluation and risk management of these serious safety concerns, as well as to the ongoing pharmacovigilance program and proposed new studies (discussed in Section 6).

5. POTENTIAL MECHANISMS FOR INCREASED RISK OF MORTALITY

5.1 Key Points

- Hypotheses for a true biologic effect of ESAs on survival include the following:
  - Increased risk of cardiovascular and thromboembolic events with ESAs:

    VTEs are common in cancer patients, and certain chemotherapy regimens increase this risk. VTEs are also a recognized complication of ESA treatment. It is known that VTEs are underdiagnosed as a proximate cause of death in cancer patients. Thus, it is plausible that VTE could represent a mechanism for increased mortality with ESAs in cancer patients.

  - Increased risk of tumor promotion and/or angiogenesis through the EPO-R:

    A logical and theoretically testable hypothesis is that the expression of EPO-R on cancer cells can lead to increased tumor progression and shortened survival in patients receiving ESAs. While obviously a concern if true, a recent NCI workshop concluded that, despite extensive investigation, there is a lack of appropriately controlled preclinical or clinical data to support or refute this hypothesis. The study by Henke et al (2006) in particular has both methodological and technical issues and does not provide strong evidence for this hypothesis. Amgen and J&JPRD, in addition to ongoing research efforts, have proposed unrestricted funding to support independent translational studies through NCI-NIH to address these important questions.

  - Decreased efficacy of local radiotherapy at higher hemoglobin targets:

    Paradoxically, tumor hypoxia (a known predictor of poor responsiveness to radiation) may be worsened at high hemoglobin concentrations through increased “viscous resistance.”

5.2 Cardiovascular/Thromboembolic Events

The relationship between thrombosis and cancer is well established, and a number of investigators have demonstrated that patients with cancer are at a higher risk for thrombotic events relative to individuals without cancer (Heit et al, 2000; Blom et al, 2005). Chemotherapy and radiotherapy (in particular to the pelvic region) also increase the risk of thrombosis. Additionally, data from numerous clinical studies indicate that ESAs are associated with an increased risk of cardiovascular/thromboembolic events. This risk has been quantified in multiple placebo-controlled studies, has remained stable over time, and is documented in the product labeling for ESAs. The current product labeling of approved ESAs states that (1) ESAs increased the risk for serious cardiovascular/ thromboembolic events in

controlled clinical studies when administered to target hemoglobin of greater than the upper limit of 12 g/dL, and (2) a rate of hemoglobin rise of greater than 1 g/dL over a 2-week period may contribute to these risks. To reduce these risks, healthcare professionals are advised to use the lowest dose of ESAs that will gradually increase the hemoglobin concentration to a level that will avoid the need for transfusions. Therefore, the hemoglobin concentration should not be allowed to exceed the upper safety limit of 12 g/dL, and the rate of increase in hemoglobin should be no higher than 1 g/dL in a 2-week period.

The effect of ESAs on the risk of cardiovascular/thromboembolic events in oncology patients has been determined in study-level and patient-level meta-analyses. As noted in Section 4.4.3, a meta-analysis by the Cochrane Collaboration (Bohlius et al, 2006) of the use of ESAs versus no ESA treatment in a total of 9353 oncology patients from 57 randomized controlled studies confirmed the increased risk of thromboembolic events in patients treated with ESAs (relative risk = 1.67, 95% CI: 1.35 to 2.06; 35 studies and 6769 patients) (Bohlius et al, 2006). The authors of that study noted that the potential harmfulness of ESAs depends on the underlying risk for thromboembolic complications in the patient population.

In several of the studies raising safety concerns, the incidence of clinically relevant VTEs was higher in the ESA group than in the control group (20000161, BEST, GOG-191). However, VTE as a cause of death in patients with cancer may be difficult to document, as the cause of death is not usually confirmed by autopsy. In the BEST study, the difference in survival rates between the 2 groups occurred early (near maximal by 4 months on study) (Leyland-Jones et al, 2005). These early differences are consistent with an increased risk of death due to VTE, as the frequency of these events would be expected to be greatest early on while most patients are still receiving ESA treatment. However, if the early mortality signal seen in BEST was due to accelerated tumor progression, this would suggest a potent ESA effect on tumor cell growth that would be readily measurable and consistently observed across multiple studies. Additionally, since ESA treatment in BEST was continued after chemotherapy ended, any effect of ESA on tumor cell growth would be expected to result in continued divergence of the survival curves over time. Several additional lines of evidence from BEST support the suggestion that the survival signal was due to fatal VTE occurrence, and not due to accelerated tumor growth:

- Time-to-progression curves showed no difference between the ESA group and control.
- The incidence of clinically relevant VTEs was higher in the ESA group than in the control group.
- Excess mortality associated with epoetin alfa was predominantly observed in patients with baseline hemoglobin concentrations greater than 12 g/dL. High hemoglobin is a known risk factor for VTE occurrence.

These observations suggest that if the excess mortality in BEST did not arise by chance, an increase in fatal VTEs may be a plausible alternative explanation to ESA-mediated tumor progression. Given the higher risks for VTEs observed with ESA use in several studies with non-anemic patients and/or high target hemoglobin concentrations (such as BEST), J&JPRD discontinued all such studies in 2003.

In summary, the increased risk of VTEs in oncology patients receiving ESAs provides one possible explanation for increases in mortality associated with ESA use. This signal for increased VTEs with ESAs has been detected and confirmed using meta-analytic techniques. Increases in VTE have been particularly problematic at high target hemoglobin concentrations, a setting where survival signals have also been observed.

5.3 The EPO-R Hypothesis

The potential for ESAs to cause tumor proliferation through an EPO-R mediated mechanism is a hypothesis that warrants evaluation through appropriately designed studies. However, although numerous papers have been published on this topic, the data remain inconclusive. Therefore, Amgen and J&JPRD have proposed funding for translational studies through NCI-NIH to address these important questions.

Rigorous testing of the EPO/EPO-R hypothesis has been limited to date by a lack of validated reagents for detection of EPO-R on tumor cells or in clinical specimens. A detailed summary of the preclinical data related to the role of erythropoietin and EPO-R in tumor proliferation has previously been provided (Oncologic Drugs Advisory Committee Briefing Materials, 2007). Commercially available reagents such as the Santa Cruz C-20 antibody used by Henke et al (2006) appear to recognize both EPO-R and non-EPO-R proteins including HSP-70 that may be prognostic indicators, but not predictive of an ESA-mediated mechanism (Elliott et al, 2006a,b; Brown et al, 2007; Della Ragione et al, 2007; Kirkeby et al, 2007; Laugsch et al, 2008).

Although many translational clinical studies have been performed with the intent of assessing biopsy specimens for presence of EPO-R, only one randomized study (ENHANCE [Henke et al, 2003 and 2006]) has attempted to evaluate the interaction of the effect of ESAs and expression of the EPO-R in tumor tissue, which is the relevant treatment question. The authors concluded that "EPO-R is variably expressed on head and neck cancer cells and is associated with a detrimental effect of epoetin beta administration."

Numerous reviews and editorials have outlined the limitations of the ENHANCE study on which the exploratory analysis by Henke et al is based (Blumberg and Heal, 2004; Freidlin and Korn, 2004; Haddad and Posner, 2004; Kaanders and van der Kogel, 2004). For example, there were clinically significant baseline imbalances between the 2 arms of the study that favored placebo, the adverse outcome appeared to be limited to patients with hypopharyngeal tumors, and the adverse effect appeared to diminish in patients who received treatment according to the study protocol (Oncologic Drugs Advisory Committee Briefing Materials, Roche, 2004).

The conclusions by Henke et al are also limited by technical issues. It has been demonstrated that the C-20 antibody detects HSP-70 in addition to other non-EPO-R proteins (Brown et al., 2007; Della Ragione et al, 2007; Elliott et al, 2006a,b; Kirkeby et al, 2007; Laugsch et al, 2008). There were also technical concerns with the immunohistochemistry assays themselves (Taylor et al, 2006). For example, there appeared to be no consistent approach to sample handling, collection, or storage to ensure antigen preservation. There was an absence of appropriate positive and negative controls: the "positive" control was fetal kidney tissue and no EPO-R-negative cell type was used to demonstrate antibody specificity. While fetal kidney is a potentially appropriate control for endogenous EPO production, there is little evidence to support it is an appropriate control for EPO-R.

As noted in Section 4.4.4, a plausible alternative hypothesis for the adverse outcomes seen in ENHANCE (assuming these were not due to biases in the study design) is that escalation of hemoglobin above the recommended ceiling of 12 g/dL led to paradoxical tumor hypoxia, a known predictor for failure of locoregional radiation. Since there was no evidence for tumor growth outside of the radiation field, a generalized tumor promotion effect is not strongly suggested by the ENHANCE data.

It is extremely important that future studies be designed to more rigorously test the hypothesis that the interaction of ESA with EPO-R leads to adverse tumor outcomes (Agarwal et al, 2007; Della Ragione et al, 2007; Jelkmann and Laugsch, 2007; Sturiale et al, 2007). These studies should use a validated detection method for EPO-R, standardized methods for tissue collection and storage, and include cell lines that are known to overexpress EPO-R and do not express EPO-R as positive and negative controls, respectively.

Detailed reviews and a recent NCI workshop have attempted to clarify this important issue, but to date no conclusions are widely accepted as this area of research has been severely hampered by the lack of reliable reagents. Amgen and J&JPRD continue efforts to identify a more specific antibody to EPO-R. Paraffin-embedded tumor blocks have been collected from consenting subjects in study EPO-GBR-7, which evaluated a population similar to that in the ENHANCE study. Tumor blocks are also being collected prospectively from consenting subjects for a variety of analyses in other ongoing studies and could potentially be used to evaluate the interaction of ESAs with EPO-R should a suitable antibody methodology be identified. Amgen and J&JPRD have proposed funding to advance independent preclinical research into this question.

6. RISK MANAGEMENT AND RISK MINIMIZATION ACTION PLAN

6.1 Key Points

- Amgen and J&JPRD have accelerated the timely provision of all available data to FDA that were still outstanding at the time of the May 2007 ODAC.
- An important postmarketing commitment study is ongoing, but delayed (EPO-ANE-3010). Challenges in enrollment were anticipated at the outset and were discussed at ODAC 2007. Recent amendments to the study, in consultation with FDA, should facilitate recruitment.
- The companies have worked toward agreement with FDA on the design of a new large, definitive, placebo-controlled clinical study (6186 subjects) to evaluate overall survival and tumor progression in subjects receiving ESAs in the labeled CIA indication.
- Amgen, J&JPRD, and Roche, under the guidance of an international steering committee, and with input from FDA, are working with the Cochrane Collaboration to facilitate an independent patient-level analysis of all data from appropriately designed and conducted controlled clinical studies in patients with cancer receiving ESAs.
- Various risk minimization activities by Amgen and J&JPRD, including safety-related updates to the ESA labeling and healthcare professional communications and education, have had an impact on appropriate prescribing of ESAs:
    - Driven by these risk minimization activities and changes to reimbursement, the number of patients receiving Aranesp® for CIA declined by 48% from Q4 2006 to November 2007 (based on US clinic claims data). Similar data have been reported for PROCRIT®. An increase in transfusion utilization has also been noted, suggesting that a careful balance between minimizing risk and maximizing the benefit of ESAs must be considered.
- Amgen and J&JPRD are working with FDA on the development of a Medication Guide in accordance with FDA regulations to further inform patients and enhance physician-patient discussions concerning the benefit:risk of ESAs. In addition, the companies are assessing the effectiveness of risk communication to patients and healthcare professionals.

- A formal program for further risk minimization (Risk Minimization Action Plan or RiskMAP) will include physician education, cancer patient/patient advocacy group communications, implementation of a Medication Guide per FDA regulation, tracking of risk communication to patients, and additional labeling changes focusing on appropriate initiation of ESAs in CIA. The effectiveness of these activities will be formally evaluated and reported to FDA.
    - Amgen and J&JPRD have involved several stakeholders in designing the RiskMAP for ESAs and now seek the ODAC's guidance regarding the appropriateness of the proposed plan.
- The use of ESAs in oncology settings facilitates structured communication of risk, as ESA use in the CIA indication is largely protocol driven and administered by healthcare professionals with expertise in benefit:risk decisions for potentially toxic therapies.

As noted in Section 2.4, Amgen and J&JPRD have taken several actions to address the risks of mortality and tumor progression with ESAs, including changes to the product labeling, communication to healthcare professionals and patients, and discussions with FDA to define appropriate investigation of these risks going forward.

In addition to these actions, the companies are continuing to report and communicate data from ongoing pharmacovigilance and postmarketing commitment studies and to work with FDA to design new studies to evaluate the safety of ESAs when administered in accordance with the product labeling. Additional risk management activities include educational efforts to ensure appropriate ESA use in accordance with the current labeling, including using the lowest dose to avoid transfusions and not exceeding a hemoglobin level of 12 g/dL. These are proposed in the format of a RiskMAP. The companies also propose gathering information to measure the effectiveness of these programs.

Further information on the Amgen and J&JPRD RiskMAP is presented in this section.

6.2 Pharmacovigilance Program and Postmarketing Commitments

The current ESA oncology pharmacovigilance program for Amgen and J&JPRD comprises 6 randomized clinical studies that include survival as a prespecified endpoint. These clinical studies, along with an additional completed study (J&JPRD-sponsored N93-004), are formal postmarketing commitments. Summaries of the status of these studies are provided in Table 6.

Table 6. ESA Postmarketing Commitment Studies

Study (Sponsor)	Tumor Type	Study Title	Study Status	Interim Data	Final Data
20010145 (Amgen)	SCLC	A randomized, double blind, placebo-controlled study of subjects with previously untreated extensive-stage small-cell lung cancer (SCLC) treated with platinum plus etoposide chemotherapy with or without darbepoetin alfa	Event-driven analysis complete; follow-up continuing (all subjects followed until death)	CSR 10/29/07 Datasets 10/29/07	Projected 2008
DE-2001-0033 PREPARE (AGO/GBG)	Breast	Randomized comparison of a preoperative, dose-intensified, interval-shortened sequential chemotherapy with epirubicin, paclitaxel and CMF ± darbepoetin alfa versus a preoperative, sequential chemotherapy with epirubicin and cyclophosphamide followed by paclitaxel in standard dosage ± darbepoetin alfa in patients with primary breast cancer	Treatment period complete; follow-up continuing	CSR 11/30/07 Datasets 11/30/07	Projected 2009
SE-2002-9001 DAHANCA 10 (DAHANCA)	Head and Neck	Study of the importance of novel erythropoiesis stimulating protein (Aranesp®) for the effect of radiotherapy in patients with primary squamous cell carcinoma of the head and neck	Study halted; data collection continuing	Abstract ECCO (2007)	Projected 2008
FR-2003-3005 LNH03-6B (GELA)	Diffuse Large B-cell Lymphoma	Randomized study of intensified CHOP plus rituximab given every 14 days (R-CHOP 14) versus CHOP plus rituximab given every 21 days (R-CHOP 21) and randomized study of frontline/prophylactic darbepoetin alfa treatment versus usual symptomatic treatment of anemia in non previously treated patients aged from 60 to 80 years, with CD20+ diffuse large B-cell lymphoma	Ongoing (Accrual 440/660 subjects) DSMC recommended continuation of the study unchanged in Q4 2007	N/A	Projected 2010
DE-2002-0015 ARA 03/ARA PLUS (WSG)	Breast	Adjuvant therapy for breast cancer: Impact of erythropoiesis-stimulating factors on survival in high-risk breast cancer treatment. Prospective randomized comparison of CEF/TAC chemotherapy ± darbepoetin alfa (Aranesp®) for patients with positive lymph nodes	Ongoing (Accrual 1090/1234 subjects)	N/A	Projected 2011
N93-004 (J&JPRD)	SCLC	The effect of r-HuEPO in patients with small cell lung cancer (SCLC): A randomized, double-blind, placebo-controlled trial	Complete	N/A	CSR and datasets 10/2002
EPO-ANE-3010 (J&JPRD)	Breast	A randomized, open-label, multicenter, phase 3 study of epoetin alfa plus standard supportive care versus standard supportive care in anemic patients with metastatic breast cancer receiving first-line standard chemotherapy	Ongoing (Accrual 236/1000)	N/A	Projected 2013

Study N93-004 was a double-blind, placebo-controlled study that planned to enroll 400 subjects with newly-diagnosed, limited or extensive stage SCLC who were to be treated with etoposide and cisplatin. This study was conducted in predominantly non-anemic cancer patients. Survival was similar in the 2 treatment groups. Although the results of Study N93-004 did not suggest any substantive effect of epoetin alfa on tumor treatment response or disease progression in SCLC, and the 95% confidence intervals excluded an impairment of response rate of 6% or higher, the study was terminated for poor accrual in agreement with FDA after 224 subjects had been enrolled. As a consequence, the FDA viewed the study to be non-definitive and requested a new commitment study.

Study EPO-ANE-3010 is considered by FDA to be of adequate design for assessing tumor outcomes within the currently labeled ESA indication. The study was further refined with the objective of enhancing feasibility of timely completion after feedback from an expert external global Advisory Board in July 2004. The revised protocol was submitted to FDA in December 2004. Additional protocol amendments to facilitate timely recruitment were discussed with FDA in August 2007, and a revised protocol has been submitted.

All other postmarketing commitment studies have been completed or are on track for completion by the commitment date. All available data have been submitted to FDA, including regular safety updates for potentially informative studies that were requested at the time of the May 2004 ODAC.

At the time of ODAC 2007, the limitations of current studies to definitively answer questions on the risk of mortality and tumor progression with ESAs were discussed with FDA and the committee. These limitations included lack of systematic radiographic assessments of disease progression, lack of systematic VTE assessments, hemoglobin targets not consistent with the current labeling information, and off-label doses and dose adjustments. The companies are in agreement that, while the ongoing studies will provide relevant information on the safety concerns that have been raised, further research is required to address these issues.

6.3 New Studies

In response to the recommendations of the 10 May 2007 ODAC, Amgen and J&JPRD have carefully considered potential new study designs and have consulted with FDA on plans to further evaluate the risk of mortality and tumor progression with ESAs within the

labeled indication of CIA. The major area of concern is insufficient data regarding the effect of ESAs on these risks in a setting consistent with the current product labeling (ie, hemoglobin not to exceed 12 g/dL in CIA) in a placebo-controlled study specifically designed to measure overall survival and tumor progression.

Substantial efforts have been made with advisors from the oncology clinical community worldwide to address the design and feasibility of large, controlled studies evaluating survival and tumor progression. Feedback from international advisory boards on these study concepts was obtained, which were discussed with FDA in a meeting in August 2007 and most recently in January 2008. Based on this input, Amgen has been working with FDA to design a large, adequate and well-controlled study comparing the safety of ESAs administered to a maximum hemoglobin level of 12 g/dL (per the product labeling) versus placebo in 3 major tumor types (advanced NSCLC, advanced breast cancer, and advanced colorectal cancer). The companies and FDA have agreed on the design, and a protocol will be submitted after guidance has been obtained from ODAC, with the intent of initiating these studies immediately.

Because of the size of the planned study and the global use of ESAs, the resulting study will be conducted in multiple countries. As such, the study will need to be acceptable to investigators and ethics committees/institutional review boards worldwide, and will need to be agreed upon with multiple regulatory agencies.

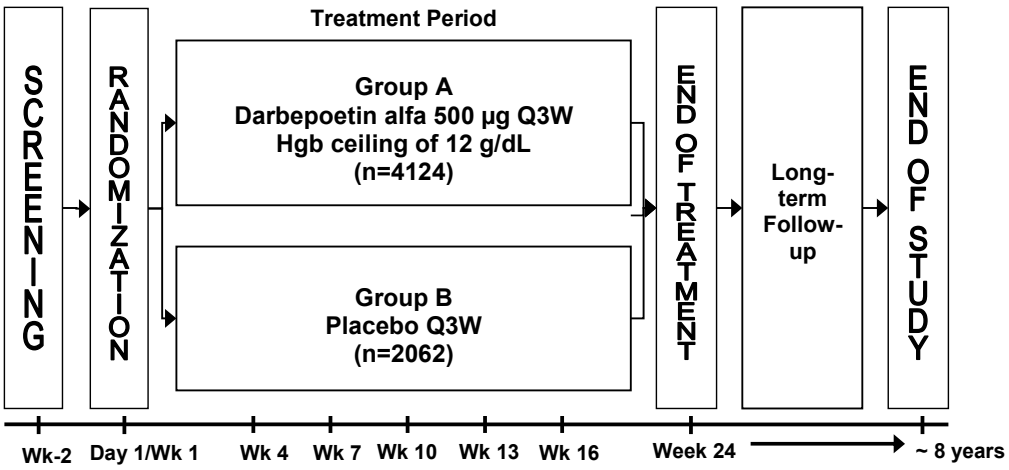
Proposed Study 20070782: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Long-term Safety and Efficacy of Darbepoetin Alfa 500 µg Once Every Three Weeks (Q3W) Administered to a Hemoglobin Ceiling of 12.0 g/dL in Anemic Subjects with Advanced Stage Cancer Receiving Multi-cycle Chemotherapy

The study is designed as a phase 3, randomized, double-blind, placebo-controlled study in subjects with CIA receiving multicycle chemotherapy for the treatment of advanced stage or metastatic cancer. Three independent studies of 3 distinct tumor types will be conducted under a single umbrella protocol. A total of 6186 subjects with either metastatic breast cancer on or about to receive first- or second-line chemotherapy (n = 2247), metastatic or advanced stage (with malignant pleural effusion) NSCLC on or about to receive first-line chemotherapy (n = 1857), or metastatic colorectal cancer on or about to receive first-line chemotherapy (n = 2082), will be randomized in a 2:1 allocation to 2 treatment groups:

- darbepoetin alfa 500 µg Q3W with a hemoglobin ceiling of 12.0 g/dL
- placebo Q3W

Within each tumor-specific study, randomization will be stratified by disease-specific prognostic factors. Subjects will receive ESAs for a maximum of 8 weeks after completion of a chemotherapy course for hemoglobin concentrations < 12.0 g/dL. Subjects will be followed for survival until death, or until approximately 1808 deaths for that tumor-specific study have occurred. A study schema is provided in Figure 12.

Figure 12. New Proposed Study Schema



Note: Centrally read radiographic studies will be performed at screening, weeks 8, 16, and 24, then once-every-3-months during long-term follow-up.
Note: The end of treatment visit will be performed at week 24 or 30 days after the last dose of IP for subjects that withdraw early. IP can be continued for up to and no more than 8 weeks after completion of chemotherapy for Hgb < 12.0 g/dL
Note: Subjects will be followed for survival until death, or until 1808 deaths have occurred (End of Study) for that tumor specific study.

The primary endpoint of this study is overall survival, and the secondary endpoint is PFS. Other safety endpoints are the incidence of adverse events, including thromboembolic events and adverse events associated with RBC transfusions, the incidence of hemoglobin ≥ 12.0 g/dL, and the incidence of neutralizing antibody formation to darbepoetin alfa. Other efficacy endpoints include incidence of at least 1 RBC transfusion or hemoglobin level ≤ 8.0 g/dL from week 5 to end of treatment period, incidence of at least 1 RBC transfusion or hemoglobin level ≤ 8.0 g/dL from study day 1 to end of treatment period, and change in hemoglobin level from baseline to end of treatment period.

An independent Data Monitoring Committee (DMC) will assess safety for all 3 tumor types on a regular basis throughout the study. The DMC will convene approximately once every 6 months for the first 2 years and once per year thereafter during the course of the study, and the recommendations of the DMC will be reported to FDA and other regulatory authorities.

This adequate and well-controlled study will provide robust data to address the safety of ESAs when administered in accordance with the product labeling in two of the tumor types where adverse outcomes have been observed in unlabeled uses. This study will supplement the ongoing pharmacovigilance efforts relating to early stage breast cancer (ARA PLUS and PREPARE), metastatic breast cancer (EPO-ANE-3010), and lymphoid malignancies (GELA LNH03-6B and HD15).

Amgen and J&JPRD are working with FDA to optimize the ESA oncology pharmacovigilance program, and have gained agreement that existing proposals for the new large, definitive study and preclinical work will be key components of these efforts. The companies are in discussion with FDA as to whether any additional studies will be required, and will work with FDA to address remaining concerns in the setting of multiple myeloma or other lymphoid disease.

6.4 Updated Cochrane Analysis

In addition to ongoing and planned clinical studies, Amgen, J&JPRD, and Roche have provided individual patient-level data to the independent Cochrane Collaboration to support a patient-level combined analysis of all available controlled studies with ESAs in oncology patients.

This project will create a database of over 12,000 patients in controlled studies of ESAs in oncology. Such an approach will provide the ability to perform subgroup analyses (eg, by tumor type, baseline hemoglobin, risk factors for VTE) that have not previously been possible. These analyses should allow a rational assessment of areas that would benefit from further study and can be updated as results from the ongoing single-tumor studies become available. Furthermore, important additional data will be made available to the FDA from studies using ESAs not licensed in the US.

It is anticipated that the Cochrane Collaboration will have results from preliminary analyses available for presentation at the time of the March ODAC meeting.

6.5 Risk Minimization Activities

The overall objectives of the RiskMAP are to minimize serious adverse events and outcomes and facilitate correct and appropriate use of ESAs by emphasizing adherence to the FDA-approved product labeling. This section describes the actions that have been taken to date, assessment of the effects of these actions, and proposed future actions to minimize the risks of ESAs.

6.5.1 Activities to Date

Changes to the Product Labeling

The FDA-approved product labeling remains the cornerstone of risk management and communication efforts for ESAs in the US. The US labeling (Appendix 1) and Patient Package Insert (Appendix 4) for epoetin alfa and darbepoetin alfa were revised in March and November 2007 to further address the risk of mortality and tumor progression. Additional labeling revisions to further describe these risks are under review at FDA at the time of the submission of this briefing document. The labeling revisions, including the BOXED WARNING, were developed in collaboration with FDA to add clarity in describing the safety risks associated with ESA therapy, including risks associated with off-label use (eg, hemoglobin ceiling above 12 g/dL, patients not receiving chemotherapy). The revised class labeling also includes the following specific instructions on the appropriate use of ESAs to minimize their risks (for full product labeling, see Appendix 1):

- Use the lowest dose needed to avoid RBC transfusions in cancer patients
- Use only for treatment of anemia due to concomitant myelosuppressive chemotherapy
- Do not exceed the upper safety limit of 12 g/dL
- Discontinue following the completion of a chemotherapy course

Further revisions to the product labeling to provide additional guidance on the appropriate use of ESAs are under consideration (see Section 6.5.4).

Communication with Healthcare Professionals and Patients

The changes to the product labeling were communicated to the healthcare community through DHCP letters (in March and November 2007) and letters to investigators participating in clinical studies of ESAs. Updated Patient Package Inserts were made

available to patients. The companies have also updated informed consent documents to communicate these safety concerns to patients participating in ongoing ESA studies in all indications. In addition, the companies have provided relevant public communications to the healthcare community regarding safety issues associated with ESA use, including press releases and immediate postings on the companies' web sites. The results of the studies raising concerns have been presented at national and international conferences.

Amgen and J&JPRD are working closely with the FDA on the development of a Medication Guide and Patient Instructions for Use to further inform patients and enhance physician-patient discussion concerning the benefit:risk decision. A draft Medication Guide was submitted to FDA in October 2007 and is currently under review. Plans for the distribution and tracking of the Medication Guide are provided in Section 6.5.4.

Educational efforts have been undertaken to ensure that healthcare professionals, patients, professional medical organizations, and advocacy groups are well informed about the potential risks of ESAs and the appropriate use of these agents. Amgen's and J&JPRD's medical field forces, composed of regional medical liaisons, have provided timely communications on ESA safety to the healthcare community as new information has become available. The medical field force has also made available for healthcare professionals relevant published literature, epoetin alfa and darbepoetin alfa product labeling, DHCP letters on ESA safety issues, a document of FDA Frequently Asked Questions (FAQs) regarding ESA use, and FAQs on the NCD, ODAC outcomes, and ESA study results. Other efforts have included unrestricted educational support for independent Continuing Medical Education (CME) training, and proactive education of members of the companies' speakers bureaus. New and relevant data have been shared with appropriate professional medical societies as they have become available. Efforts have also included providing materials on ESA safety issues at scientific booths at major biomedical meetings.

Amgen and J&JPRD are also committed to the responsible marketing of epoetin alfa and darbepoetin alfa to patients and healthcare professionals. For several months after the initial BOXED WARNING was introduced in March 2007 through the May 2007 ODAC, Amgen's sales force concentrated their efforts on informing healthcare professionals of the changes to the FDA approved labeling and the observed safety signals in clinical studies. Both companies have used sales forces to provide tools to optimize the

appropriate use of ESAs to physicians. Ortho Biotech discontinued all direct-to-consumer broadcast advertising in 2005, and Amgen has never run direct-to-consumer broadcast advertising for its ESA products.

In addition to these formal communications, efforts were undertaken to highlight ESA safety issues as they arose to national advocacy groups and scientific organizations. Throughout 2007, there was an ongoing open dialog with key representatives and scientific advisors from multiple organizations, and data were shared with these groups as they became available.

6.5.2 Changes in ESA Utilization to Date

In discussing changes in ESA utilization, the effect of reimbursement changes cannot be independently assessed from those resulting from labeling changes and risk communication. Thus, for completeness, the changes in reimbursement that have occurred during the time period under discussion are also outlined here.

The Centers for Medicare & Medicaid Services (CMS) National Coverage Determination (NCD) was issued in July 2007 and stipulated that ESAs should be initiated when hemoglobin is < 10 g/dL, and that after 4 weeks of therapy, should be discontinued if hemoglobin is > 10 g/dL.

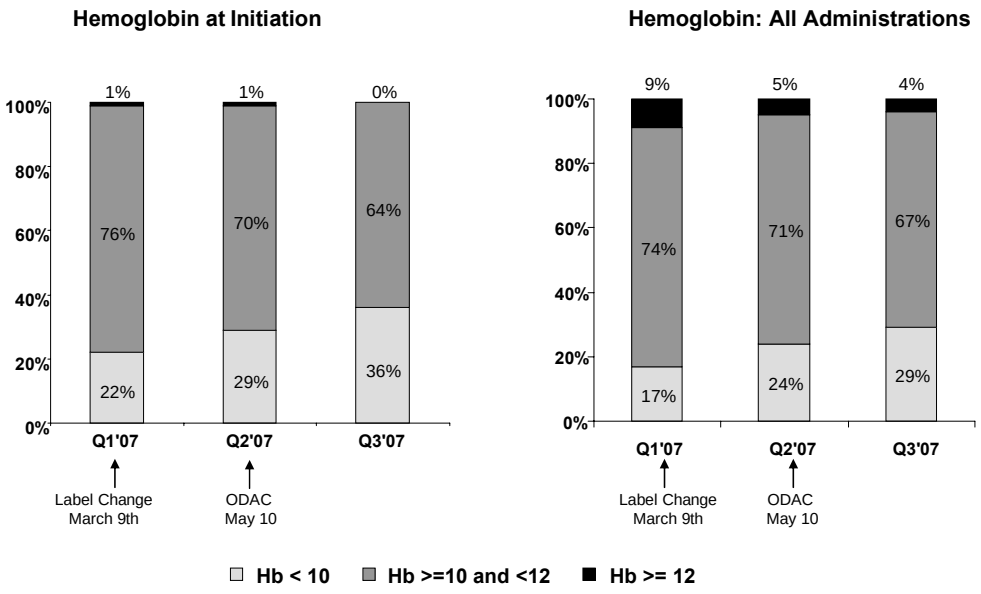
In addition, further information/approval requirements have been used by some private insurers to guide prescribing, dispensing, and use of ESAs to target appropriate patients. These systems link product access to laboratory testing or other documentation. For example, some private insurers as well as other plans have instituted “prior authorization procedures” before a patient can be treated with an ESA. At least one private insurer is formally capturing hemoglobin data during treatment. Some private insurers are also recertifying patients after four weeks of therapy to ensure they are still appropriate candidates.

Analysis of ESA Utilization by Claims and Electronic Medical Record (EMR) Data

Analyses of claims and EMR data suggest that the recent changes in ESA labeling and communication of this information to healthcare professionals have been associated with decreased use of ESAs in CIA, in the context of coincident reimbursement changes in a segment of the population. A snapshot of monthly ESA use in physician’s offices across the US was captured using Surveillance Data, Inc (SDI) clinic claims data (approximately 30% to 40% of all US claims). In this analysis, the number of patients receiving

Aranesp® for CIA declined by 48% from the fourth quarter of 2006 to November 2007, from approximately 50,000 to 28,000 patients. Additionally, an analysis of clinic-based SDI EMR data (n = 3000 Aranesp® patients, and 1500 PROCRIT® patients) found that of patients being treated for anemia, the duration of ESA therapy administered in late 2007 was shortened as compared to early 2007. The analysis also found that oncologists were initiating ESAs at lower hemoglobin levels and were stopping therapy sooner. As a result, the percentage of patients with hemoglobin levels < 10 g/dL at ESA initiation increased from 22% in the first quarter of 2007 to 36% in the third quarter of 2007 (Figure 13).

Figure 13. ESA Treatment by Hemoglobin Values



Source: SDI EMR (Varian)

Analysis of Transfusion Incidence

In some cases, decreased ESA utilization may have had the consequence of increasing the volume of RBC transfusions administered to cancer patients. Amgen recently performed an analysis of the Premier Perspective™ Comparative hospital claims database (98 continuously-reporting hospitals in 29 states with 312,000 to 372,000 Medicare cancer outpatient discharges per year), to evaluate the impact of reimbursement restrictions on transfusions. Among Medicare oncology patients, the number of patients receiving transfusions increased 13%, and the number of transfusion procedures increased 14% in the third quarter of 2007 compared with the third quarter of

2006 in the sample of 98 hospitals (the cancer patient population remained relatively constant over the time period and there was no shift in the site of care within the hospitals). Those cancer patients receiving chemotherapy had a greater increase in transfusions than those cancer patients who were not receiving chemotherapy.

Further support for these findings comes from an (independent) retrospective review in a single, large hematology/oncology practice (OBI, data on file). Inclusion criteria consisted of Medicare cancer chemotherapy patients receiving ≥ 2 ESA doses. Cohorts were defined as pre- or post-NCD based on the date of their initial ESA administration. Compared to the pre-NCD cohort, hemoglobin levels were significantly lower at each measured timepoint post-NCD (mean hemoglobin in g/dL, pre- vs post-NCD: baseline, 10.7 vs 9.7, $p < 0.0001$; week 4, 11.0 vs 10.1, $p < 0.0001$; week 8, 11.2 vs 10.3, $p = 0.0016$) and a greater proportion of patients required transfusion (pre-NCD 9.5% vs post-NCD 21.4%).

Summary

Risk management measures and changes in reimbursement have been associated with reduced ESA exposure, lower starting and achieved hemoglobin values, and a reduced duration of treatment, which indicates that oncologists are exercising conservative judgment in caring for their patients. However, there is some evidence that the more restrictive changes in reimbursement, as well as the changes in practice, are leading to increased use of transfusions. Thus, further risk management activity needs to strike a careful balance between minimizing risk and maximizing the benefit of ESAs, as further restrictions on the use of ESAs could negatively affect their beneficial effects on transfusion reduction. There is also a need to avoid disruption of patient care in other indications for which ESAs are prescribed.

6.5.3 Effects of Risk Communication on Awareness of ESA Safety Issues

During 2007, a number of surveys were conducted among practicing oncologists to evaluate their knowledge of ESA safety issues. A total of 100 oncologists across the US took part in these online surveys. For inclusion in the survey, the oncologists had to have been in clinical practice for at least 2 years and had to see at least 50 adult cancer patients per month.

Surveys conducted after key events throughout 2007, such as the distribution of the DHCP letter describing the results of the 20010103 study, the ESA labeling change on

09 March 2007, or the issuance of the NCD in July 2007 revealed that oncologists were aware of ESA safety issues. After updates to ESA product labeling in November 2007, 52% of the 100 oncologists surveyed were knowledgeable about the labeling changes and had high levels of concern regarding these changes. As a result of the labeling changes, more than half planned to decrease ESA use in their cancer patients over the following 3 months. In addition, one third planned to stop ESA therapy after the last dose of chemotherapy.

6.5.4 Risk Minimization Action Plan (RiskMAP)

Current activities have been successful in altering clinical practice to minimize the use of ESAs in inappropriate patient populations. Additional proposed actions are therefore directed at improving the dissemination of information, educating patients and clinicians on ESA safety issues, and importantly, monitoring the success of these measures.

The US labeling communicates the potential risks associated with use of ESAs at hemoglobin levels ≥ 12 g/dL. To further manage and address these safety concerns, Amgen and J&JPRD have formulated a Risk Minimization Action Plan (RiskMAP). The companies are actively monitoring the impact of these activities. Discussions with patient advocacy organizations, oncologists, and regulators contributed significantly to the design of the proposed RiskMAP.

Proposed Risk Minimization Action Plan (RiskMAP)

Goals and objectives:

The RiskMAP for ESAs was designed in accordance with FDA recommendations (Guidance for Industry, 2005), with the goal of minimizing risk by facilitating appropriate use of ESAs and promoting informed benefit:risk discussions and decisions between patients and their physicians (particularly, oncologists) regarding ESA use in CIA.

The specific objectives of the RiskMAP are based upon education of potential risks and appropriate use, as defined in the ESA labeling, including the following:

- use the lowest dose needed to avoid red blood cell transfusion
- use only for treatment of anemia due to concomitant myelosuppressive chemotherapy
- do not exceed a hemoglobin of 12 g/dL
- discontinue following the completion of a chemotherapy course

Use outside of these parameters is not recommended. An additional objective of the RiskMAP is to promote informed benefit:risk discussions and decisions regarding ESA use in oncology through the enhanced Medication Guide program (described below).

The risks of ESA therapy are addressed through the following tools: 1) further proposed revisions to the product labeling, 2) targeted education and outreach (including physician education initiatives and patient/patient advocacy group initiatives) and 3) Reminder Systems, such as an enhanced system for the distribution of the Medication Guide and an enhanced system to ascertain that the Medication Guide is distributed and received by the patient.

1. Further Revisions to the Product Labeling

Further updates and revisions to the product labeling have been submitted to FDA for consideration. These updates include a definition of a hemoglobin level for the initiation of ESA treatment. The data support an initiation hemoglobin level of ≤ 11 g/dL, based on efficacy in transfusion avoidance. However, to further minimize any potential risk, the companies propose consideration of a hemoglobin initiation level of ≤ 10 g/dL, which could be applicable to the majority of patients. In patients whose hemoglobin levels are dropping gradually and who are not at increased risk for complications of anemia (eg, those with significant comorbidities), an initiation level of ≤ 10 g/dL could also preserve substantial efficacy in terms of transfusion avoidance so long as appropriate flexibility is maintained for exercising clinical judgment, as is reflected in current treatment guidelines (American Society of Clinical Oncology/American Society of Hematology [ASCO/ASH] and EORTC).

2. Targeted Education and Outreach

The educational tools in this category employ specific, targeted education and outreach efforts regarding safety risks. Their main goal is to increase appropriate knowledge and risk-minimizing behaviors of key groups (health care practitioners and patients), to ensure appropriate product use. The educational efforts are based upon the US product labeling, the US Patient Package Insert, and the Medication Guide, which describe the risks associated with use of ESAs when not used as recommended, as well as the uncertainty in risk assessment in the labeled setting.

Health Care Professional Education Tools

Further planned initiatives to educate healthcare professionals on the risks of ESAs include the following:

- A revised DHCP letter distributed in February 2008 after FDA approval; this letter included additional information relating to dissemination of the Patient Package Insert and physician-patient discussions regarding the benefit:risk of ESAs (after FDA approval, the Medication Guide will replace the Patient Package Insert)
- Training programs for health care professionals, including physician education on any additional changes to the product labeling
- Continuing education (CE) for healthcare professionals, including product-focused programs developed by sponsor-supported accredited, independent CE programs
- Dissemination of safety information through sales force and regional medical liaisons (highlighting appropriate patient use or product risks)

Proposed Educational Programs

Amgen and J&J PRD will implement a variety of programs to educate healthcare professionals on the risks of ESAs for the treatment of CIA. Teams of healthcare professionals experienced in managing CIA patients treated with ESAs will lead each session. These will include case study presentations, with focused problem-solving exercises related to patient management issues.

- Medical education pilot program for targeted healthcare professionals:

  The program would be developed by healthcare professionals experienced in ESA therapy, with presentations by trained speakers for live programs, Self-directed On-line Learning programs, and CD-ROMs.

- Medical educational program evaluation:

  A knowledge assessment questionnaire will be administered before and after each program to quantitatively determine the program's performance against stated objectives and key learnings. These parameters measuring the effectiveness of the educational program will guide revisions to both format and content of future programs.

- On-line education for healthcare professionals

  All healthcare professionals who have an interest in ESAs but are unable to attend a live training session will be provided the same medical education via a web-based program. Regional medical liaisons will be available upon request to provide training to healthcare professionals as desired.

- Healthcare professional education through medical and scientific associations
- Medical education training materials:

  All program participants will receive a Professional Training Kit that will include the ESA US product labeling, the Patient Package Insert, Medication Guide (currently under review by FDA), copies of the program slides with speaker notes, key published papers, and appropriate responses to frequently asked questions.

Patient and Patient Advocacy Group Initiatives

Planned initiatives involving patients and patient advocacy groups include the following:

- Increased distribution and use of patient information such as the Patient Package Insert and the Medication Guide (currently under review at the FDA)
- Continued discussion with leading Patient Advocacy Organizations who are members of the Cancer Leadership Council and Oncology Nursing Society, in the design and implementation of educational programs for patients.
- Market research evaluating whether the patient has read the Medication Guide and discussed it with the physician

Patient Education Program

Amgen and J&JPRD will distribute detailed patient instruction materials to provide clear, straightforward information for CIA patients who are considering ESA therapy. These materials, prepared at the sixth grade reading level, will address both the appropriate use and potential risks of ESAs for CIA.

Patient Support Materials

- **ESAs Educational Brochure**. This brochure will closely follow the Medication Guide and is intended to assist patients, along with their physicians, in determining if they are appropriate candidates for ESA therapy (according to labeled indications) and provide them with information regarding potential safety risks that could occur in association with ESA therapy. Space will be provided for the patient to write out questions for their healthcare professional.
- **ESAs Educational Flip Chart.** This in-office piece will allow healthcare professionals to review general CIA disease management topics, along with benefits and safety risks of blood transfusion and of ESAs as treatment modalities for CIA, and educate the patient on ESAs safety issues.

3. Reminder Systems

The tools in the reminder system category are used in addition to the tools in the targeted education and outreach category, and their objective is to complement and provide a back-up strategy for targeted education and outreach tools to ensure that they are used and result in appropriate prescribing to minimize the identified risks.

Medication Guide Enhanced Distribution System

As noted in Section 6.5.1, the companies have developed a Medication Guide and Patient Instructions for Use that is currently under review by FDA. In addition to its risk communication and patient education function, the companies propose use of the Medication Guide in the context of a enhanced distribution system. While the Medication Guide is a very valuable tool for patient education and appropriate risk communication, its main limitation is the difficulty in tracking its receipt, review, and understanding by patients.

The inception and development of the Medication Guide Enhanced Distribution was based on the following:

- Compensating for a tool's limitation through enhancements
- As a mechanism to increase the utility and effectiveness of the Medication Guide
- Feedback from stakeholders (ie, oncologists) that this system enhancement would add value to the risk minimization program by enabling an informed decision process, bringing the patient at the center of risk minimization activities, enabling a risk-benefit discussion between patient and physician in the oncologist's office, while offering a "reality check" for feasibility of implementing and accepting the tool in the usual healthcare practice. The feasibility dialogue with the stakeholders included feed-back that this proposed risk minimization process is introduced in a manner that would be practical to implement without causing unacceptable disruption to the practice of oncology, preserving patient and physician autonomy, and avoiding the potential unintended consequences of limiting access to ESA benefits due to a "nuisance factor."
- To ensure the system is achieving the intended goal that patients are adequately informed, the companies will develop and implement a survey to determine whether physicians are discussing benefit:risk with patients before administration of ESAs and whether patients recall that discussion
- A pilot study will be implemented in selected practices to test this system and additional enhancements to the Medication Guide in real life

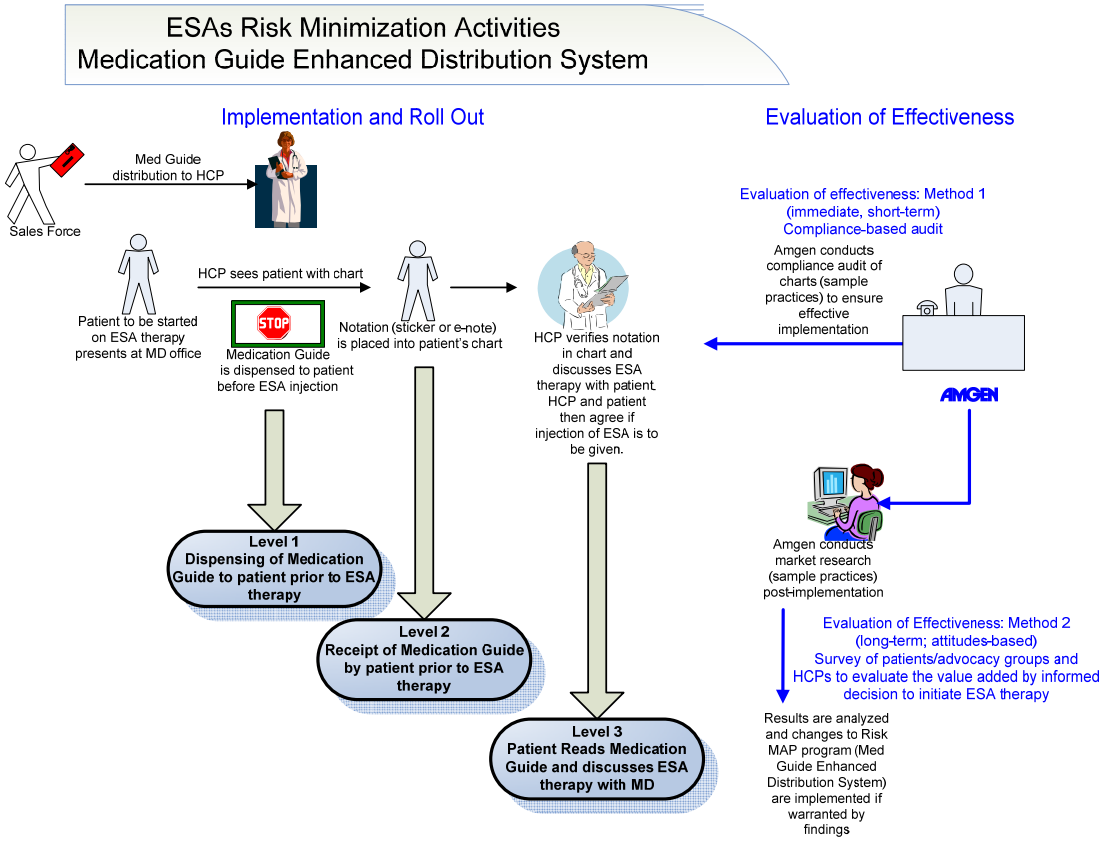
The companies propose to evaluate whether the Medication Guide is received by patients in oncology offices before initiation of ESA therapy through surveys and other tools that would allow for voluntary tracking of distribution and receipt by patients in the

oncologist's office (eg, a sticker on the Medication Guide that would be signed by the patient and added to their medical record).

Rather than using formal reminder system tools such as mandatory informed consent before authorization to dispense an agent – which exhibit some success in minimizing risk but may lead to disruptions in medical and pharmacy practice and unintended consequences, such as obstructing patient access to a product's benefits and inappropriate underutilization – this enhanced system for the Medication Guide provides all the required elements to enhance safe product use without the disadvantages associated with a formal informed consent process.

Based on the continued evaluation of RiskMAP effectiveness, and depending on the effectiveness of the Medication Guide program, Amgen and J&JPRD will determine next steps, which may include revising the RiskMAP to ensure effective risk mitigation strategies are in place. In addition to the other benefits, the enhanced use of the Medication Guide offers the advantage of preserving the relationship and interaction between patient and physician, encourages a dialogue around the benefit:risk profile of the ESAs, and facilitates an informed decision by the patient through this valuable exchange. The use of ESAs in oncology settings facilitates structured communication of risk, as ESA use in the CIA indication is largely protocol driven and administered by healthcare professionals with extensive expertise in benefit:risk decisions for potentially toxic therapy.

A proposed workflow for the Medication Guide Enhanced Distribution program is represented in the flowchart below. The compliance audits through chart review and surveys will have a critical role in the evaluation of the effectiveness of the Medication Guide Enhanced Distribution program.



Amgen and J&JPRD commit to the evaluation of the effectiveness of these activities through surveys and to periodic reporting to the FDA on the effectiveness of the RiskMAP.

6.5.5 Evaluation of the RiskMAP and Monitoring of Risk Minimization Activities

An evaluation of these tools will be conducted before implementation:

- A pilot study will be conducted in selected practices to evaluate the Medication Guide enhanced program.
- Focus groups will be conducted with patients and patient advocacy groups to evaluate the Medication Guide enhanced program and its value to patients.

Assessment of RiskMAP – RiskMAP Evaluation

The results of the RiskMAP for ESAs will be evaluated using a number of metrics: 1) Process Metrics to document the implementation of the RiskMAP, and 2) Outcome Metrics, where the effectiveness of the program will be assessed. Process metrics will include audits of selected practices through chart review to ensure the system is implemented and that patients are informed. Outcome metrics will include utilization

reviews to ensure that appropriate prescribing has occurred in the appropriate patient population. Sample surveys including patients, patient advocacy groups, and healthcare professionals (oncologists, nurses, pharmacists) will be conducted to evaluate stakeholders' attitudes towards the enhanced distribution system for the Medication Guide, and assess its value for promoting informed decisions in patients.

These measurements and assessment tools will allow the companies to determine if any of the risk minimization activities are not effective, and to implement strategies to correct the issue and ensure continued safe and appropriate use for the product. If the existing methodologies are not shown to be effective, additional strategies such as informed consent will be considered.

Periodic Reporting to the FDA on the Effectiveness of the RiskMAP

Amgen and J&JPRD propose to report semiannually on the overall program, with an option to reduce or expand use of particular tools. The Agency will be notified of any change through an amendment to the program. The companies propose that approximately 2 years after introduction of the RiskMAP, Amgen, J&JPRD and the Agency discuss the impact of this RiskMAP, modifications that might be made to the program, and the discontinuation of other aspects that, based on findings, do not appear to be adding value.

6.6 Postmarketing Surveillance

In compliance with current global regulatory policies, Amgen's and J&JPRD's pharmacovigilance units continually and systematically collect adverse events from multiple sources to conduct real-time and periodic medical assessments of single and aggregate cases to identify potential safety signals. Early detection of safety signals enables both companies to proactively develop and implement appropriate and timely risk management strategies. Both companies continue to closely monitor, assess and evaluate postmarketing surveillance reports for darbepoetin alfa and epoetin alfa.

The combined cumulative patient exposure for Aranesp®, Epogen®, PROCRIT®, and EPREX® for all marketed indications since first marketing approval is over 11 million person-years (2.1 million person-years for Aranesp®; 4 million person-years for Epogen®; 2.0 million person-years for PROCRIT®; and 3.0 million person-years for EPREX®), of which the estimated cumulative exposure for the oncology indication is over 1.6 million

person-years (636,660 person-years for Aranesp®; 914,936 person-years for PROCRIT®; and 238,272 person-years for EPREX®).

This represents substantial patient experience to date, in which safety is continuously monitored through spontaneous case reports of adverse reactions. Although post-marketing surveillance is an imprecise tool for detecting subtle safety signals, Amgen's and J&JPRD's ongoing post-marketing surveillance programs have not identified any new significant safety signals. VTEs are listed events across all approved indications in the product labeling. Overall, the frequency of the reports and observed reporting rate has remained stable, although the sensitivity of the reporting rate to changes and inaccuracies in the estimates of exposure must be emphasized. The frequency, nature, and severity of these reports are consistent with Amgen's and J&JPRD's prior experience and are adequately reflected in product labeling.

7. CONCLUSIONS

ESAs continue to provide significant benefits to anemic patients with cancer receiving chemotherapy, which include reduction of transfusions given to improve anemia-related symptoms. The benefit:risk profile of ESA therapy in patients with CIA is favorable with appropriate guidance to administer the lowest dose necessary to avoid transfusions and not exceed a hemoglobin of 12.0 g/dL.

Signals in individual studies conducted outside of the recommendations in the product labeling (eg, high hemoglobin targets or non-chemotherapy populations) have raised legitimate concerns that require appropriate risk management. These risks are prominently reflected in the class labeling for these products worldwide. The weight of evidence has not indicated a clear effect of ESAs on mortality or tumor progression within the labeled indication of CIA. However, real concerns remain that these risks have not been adequately excluded in the labeled setting.

Amgen and J&JPRD believe that risk communication, through product labeling and a formal education and communication program, will minimize risk as the necessary data are acquired from both ongoing studies and the new, large, definitive study specifically designed to address the unanswered questions. The companies believe that the key to risk management of ESAs, given the current uncertainties of risk assessment in the labeled treatment setting, is a fully informed benefit:risk discussion between the patient and their physician (particularly, oncologist).

Amgen and J&JPRD are committed to the responsible marketing of epoetin alfa and darbepoetin alfa to both patients and physicians. To this end, the companies are taking appropriate measures to ensure that the risk minimization and marketing activities address the safety concerns and promote appropriate use. We welcome the input of the ODAC members to help guide this overall process.

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Appendix 1. US Labeling

Aranesp®
(darbepoetin alfa)
For Injection

WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR and THROMBOEMBOLIC EVENTS, and TUMOR PROGRESSION

Renal failure: **Patients experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemoglobin levels (13.5 vs. 11.3 g/dL; 14 vs. 10 g/dL) in two clinical studies. Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL.**

Cancer:

- **ESAs shortened overall survival and/or time-to-tumor progression in clinical studies in patients with advanced breast, head and neck, lymphoid, and non-small cell lung malignancies when dosed to target a hemoglobin of ≥ 12 g/dL.**
- **The risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to target a hemoglobin of < 12 g/dL.**
- **To minimize these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusions.**
- **Use only for treatment of anemia due to concomitant myelosuppressive chemotherapy.**
- **Discontinue following the completion of a chemotherapy course.**

(See WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events, WARNINGS: Increased Mortality and/or Tumor Progression, 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 (IV) or subcutaneous (SC) administration.

Single-dose vials are available containing 25, 40, 60, 100, 150, 200, 300, or 500 mcg of Aranesp®.

Single-dose prefilled syringes and prefilled SureClick™ autoinjectors are available containing 25, 40, 60, 100, 150, 200, 300, or 500 mcg of Aranesp®. Each prefilled syringe is equipped with a needle guard that covers the needle during disposal.

Single-dose vials, prefilled syringes and autoinjectors are available in two formulations that contain excipients as follows:

Polysorbate solution Each 1 mL contains 0.05 mg polysorbate 80, and is formulated at pH 6.2 ± 0.2 with 2.12 mg sodium phosphate monobasic monohydrate, 0.66 mg sodium phosphate dibasic anhydrous, and 8.18 mg sodium chloride in Water for Injection, USP (to 1 mL).

Albumin solution Each 1 mL contains 2.5 mg albumin (human), and is formulated at pH 6.0 ± 0.3 with 2.23 mg sodium phosphate monobasic monohydrate, 0.53 mg sodium phosphate dibasic anhydrous, and 8.18 mg sodium chloride in Water for Injection, USP (to 1 mL).

CLINICAL PHARMACOLOGY

Mechanism of Action

Aranesp® stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. A primary growth factor for erythroid development, erythropoietin is produced in the kidney and released into the bloodstream in response to hypoxia. In responding to hypoxia, erythropoietin interacts with progenitor stem cells to increase red blood cell (RBC) production. Production of endogenous erythropoietin is impaired in patients with chronic renal failure (CRF), and erythropoietin deficiency is the primary cause of their anemia. Increased hemoglobin levels are not generally observed until 2 to 6 weeks after initiating treatment with Aranesp® (see **DOSAGE AND ADMINISTRATION**). In patients with cancer receiving concomitant chemotherapy, the etiology of anemia is multifactorial.

Pharmacokinetics

Adult Patients

The pharmacokinetics of Aranesp® were studied in patients with CRF and cancer patients receiving chemotherapy.

Following intravenous (IV) administration in CRF patients, Aranesp® serum concentration-time profiles were biphasic, with a distribution half-life of approximately 1.4 hours and a mean terminal half-life of 21 hours. The terminal half-life of Aranesp® was approximately 3-fold longer than that of Epoetin alfa when administered intravenously.

Following subcutaneous (SC) administration, absorption is slow and rate limiting. The observed half-life in CRF patients, which reflected the rate of absorption, was 49 hours (range: 27 to 89 hours). Peak concentrations occurred at 34 hours (range: 24 to 72 hours). The bioavailability of Aranesp® as measured in CRF patients after SC administration was 37% (range: 30% to 50%).

Following the first SC dose of 6.75 mcg/kg (equivalent to 500 mcg for a 74-kg patient) in patients with cancer, the mean terminal half-life was 74 hours (range: 24 to 144 hours). Peak concentrations were observed at 90 hours (range: 71 to 123 hours) after a dose of 2.25 mcg/kg, and 71 hours (range: 28 to 120 hours) after a dose of 6.75 mcg/kg. When administered on a once-every-3-week (Q3W) schedule, 48-hour post-dose Aranesp® levels after the fourth dose were similar to those after the first dose.

Over the dose range of 0.45 to 4.5 mcg/kg Aranesp® administered IV or SC on a once-weekly (QW) schedule and 4.5 to 15 mcg/kg administered SC on a Q3W schedule, systemic exposure was approximately proportional to dose. No evidence of accumulation was observed beyond an expected < 2-fold increase in blood levels when compared to the initial dose.

Pediatric Patients

Aranesp® pharmacokinetics were studied in 12 pediatric CRF patients (age 3-16 years) receiving or not receiving dialysis. Following a single IV or SC Aranesp® dose, Cmax and half-life were similar to those obtained in adult CRF patients. Following a single SC dose, the average bioavailability was 54% (range: 32% to 70%), which was higher than that obtained in adult CRF patients.

CLINICAL STUDIES

Throughout this section of the package insert, the Aranesp® study numbers associated with the nephrology and cancer clinical programs are designated with the letters "N" and "C", respectively.

Chronic Renal Failure Patients

The safety and effectiveness of Aranesp® have been assessed in a number of multicenter studies. Two studies evaluated the safety and efficacy of Aranesp® for the correction of anemia in adult patients with CRF, and three studies (2 in adults and 1 in pediatric patients) assessed the ability of Aranesp® to maintain hemoglobin concentrations in patients with CRF who had been receiving other recombinant erythropoietins.

De Novo Use of Aranesp®

In two open-label studies, Aranesp® or Epoetin alfa was administered for the correction of anemia in CRF patients who had not been receiving prior treatment with exogenous erythropoietin. Study N1 evaluated CRF patients receiving dialysis; Study N2 evaluated patients not requiring dialysis (predialysis patients). In both studies, the starting dose of Aranesp® was 0.45 mcg/kg administered once weekly. The starting dose of Epoetin alfa was 50 U/kg 3 times weekly in Study N1 and 50 U/kg twice weekly in Study N2. When necessary, dosage adjustments were instituted to maintain hemoglobin in the study target range of 11 to 13 g/dL. (Note: The recommended hemoglobin target is lower than the target range of these studies. See **DOSAGE AND ADMINISTRATION** for recommended clinical hemoglobin target.) The primary efficacy endpoint was the proportion of patients who experienced at least a 1.0 g/dL increase in hemoglobin concentration to a level of at least 11.0 g/dL by 20 weeks (Study N1) or 24 weeks (Study N2). The studies were designed to assess the safety and effectiveness of Aranesp® but not to support conclusions regarding comparisons between the two products.

In Study N1, the hemoglobin target was achieved by 72% (95% CI: 62%, 81%) of the 90 patients treated with Aranesp® and 84% (95% CI: 66%, 95%) of the 31 patients treated with Epoetin alfa. The mean increase in hemoglobin over the initial 4 weeks of Aranesp® treatment was 1.10 g/dL (95% CI: 0.82 g/dL, 1.37 g/dL).

In Study N2, the primary efficacy endpoint was achieved by 93% (95% CI: 87%, 97%) of the 129 patients treated with Aranesp® and 92% (95% CI: 78%, 98%) of the 37 patients treated with Epoetin alfa. The mean increase in hemoglobin from baseline through the initial 4 weeks of Aranesp® treatment was 1.38 g/dL (95% CI: 1.21 g/dL, 1.55 g/dL).

Conversion From Other Recombinant Erythropoietins

Two adult studies (N3 and N4) and one pediatric study (N5) were conducted in patients with CRF who had been receiving other recombinant erythropoietins. The studies compared the abilities of Aranesp® and other erythropoietins to maintain hemoglobin concentrations within a study target range of 9 to 13 g/dL in adults and 10 to 12.5 g/dL in pediatric patients. (Note: The recommended hemoglobin target is lower than the target range of these studies. See **DOSAGE AND ADMINISTRATION** for recommended clinical hemoglobin target.) CRF patients who had been receiving stable doses of other recombinant erythropoietins were randomized to Aranesp®, or to continue with their prior erythropoietin at the previous dose and schedule. For patients randomized to Aranesp®, the initial weekly dose was determined on the basis of the previous total weekly dose of recombinant erythropoietin.

Adult Patients

Study N3 was a double-blind study conducted in North America, in which 169 hemodialysis patients were randomized to treatment with Aranesp® and 338 patients continued on Epoetin alfa. Study N4 was an open-label study conducted in Europe and Australia in which 347 patients were randomized to treatment with Aranesp® and 175 patients were randomized to continue on Epoetin alfa or Epoetin beta. Of the 347 patients randomized to Aranesp®, 92% were receiving hemodialysis and 8% were receiving peritoneal dialysis.

In Study N3, a median weekly dose of 0.53 mcg/kg Aranesp® (25th, 75th percentiles: 0.30, 0.93 mcg/kg) was required to maintain hemoglobin in the study target range. In Study N4, a median weekly dose of 0.41 mcg/kg Aranesp® (25th, 75th percentiles: 0.26, 0.65 mcg/kg) was required to maintain hemoglobin in the study target range.

Pediatric Patients

Study N5 was an open-label, randomized study, conducted in the United States in pediatric patients from 1 to 18 years of age with CRF receiving or not receiving dialysis. Patients that were stable on Epoetin alfa were randomized to receive either darbepoetin alfa (n = 82) administered once weekly (SC or IV) or to continue receiving Epoetin alfa (n = 42) at the current dose, schedule, and route of administration. A median weekly dose of 0.41 mcg/kg Aranesp® (25th, 75th percentiles: 0.25, 0.82 mcg/kg) was required to maintain hemoglobin in the study target range.

Cancer Patients Receiving Chemotherapy

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

Once-Weekly (QW) Dosing

The safety and effectiveness of Aranesp® in reducing the requirement for RBC transfusions in patients undergoing chemotherapy was assessed in a randomized, placebo-controlled, double-blind, multinational study (C1). This study was conducted in anemic (Hgb ≤ 11 g/dL) patients with advanced, small cell or non-small cell lung cancer, who received a platinum-containing chemotherapy regimen. Patients were randomized to receive Aranesp® 2.25 mcg/kg (n = 156) or placebo (n = 158) administered as a single weekly SC injection for up to 12 weeks. The dose was escalated to 4.5 mcg/kg/week at week 6, in subjects with an inadequate response to treatment, defined as less than 1 g/dL hemoglobin increase. There were 67 patients in the Aranesp® arm who had their dose increased from 2.25 to 4.5 mcg/kg/week, at any time during the treatment period.

Efficacy was determined by a reduction in the proportion of patients who were transfused over the 12-week treatment period. A significantly lower proportion of patients in the Aranesp® arm, 26% (95% CI: 20%, 33%) required transfusion compared to 60% (95% CI: 52%, 68%) in the placebo arm (Kaplan-Meier estimate of proportion; $p < 0.001$ by Cochran–Mantel-Haenszel test). Of the 67 patients who received a dose increase, 28% had a 2 g/dL increase in hemoglobin over baseline, generally occurring between weeks 8 to 13. Of the 89 patients who did not receive a dose increase, 69% had a 2 g/dL increase in hemoglobin over baseline, generally occurring between weeks 6 to 13. On-study deaths occurred in 14% (22/156) of patients treated with Aranesp® and 12% (19/158) of the placebo-treated patients.

Once-Every-3-Week (Q3W) Dosing

The safety and effectiveness of Q3W Aranesp® therapy in reducing the requirement for red blood cell (RBC) transfusions in patients undergoing chemotherapy was assessed in a randomized, double-blind, multinational study (C2). This study was conducted in anemic (Hgb < 11 g/dL) patients with non-myeloid malignancies receiving multicycle chemotherapy. Patients were randomized to receive Aranesp® at 500 mcg Q3W (n = 353) or 2.25 mcg/kg (n = 352) administered weekly as a SC injection for up to 15 weeks. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 mcg in the Q3W group and 1.35 mcg/kg in the QW group) if hemoglobin increased by more than 1 g/dL in a 14-day period. Study drug was withheld if hemoglobin exceeded 13 g/dL. In the Q3W group, 254 patients (72%) required dose reductions (median time to first reduction at 6 weeks). In the QW group, 263 patients (75%) required dose reductions (median time to first reduction at 5 weeks).

Efficacy was determined by a comparison of the Kaplan-Meier estimates of the proportion of patients who received at least one RBC transfusion between day 29 and the end of treatment. Three hundred thirty-five patients in the Q3W group and 337 patients in the QW group remained on study through or beyond day 29 and were evaluated for efficacy. Twenty-seven percent (95% CI: 22%, 32%) of patients in the Q3W group and 34% (95% CI: 29%, 39%) in the weekly group required a RBC transfusion. The observed difference in the transfusion rates (Q3W-QW) was -6.7% (95% CI: -13.8%, 0.4%).

INDICATIONS AND USAGE

Aranesp® is indicated for the treatment of anemia:

- associated with chronic renal failure, including patients on dialysis and patients not on dialysis.
- in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. Aranesp® use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being. Aranesp® is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy.

CONTRAINDICATIONS

Aranesp® is contraindicated in patients with:

- uncontrolled hypertension
- known hypersensitivity to the active substance or any of the excipients

WARNINGS

Increased Mortality, Serious Cardiovascular and Thromboembolic Events

Patients with chronic renal failure experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemogloblin levels (13.5 vs. 11.3 g/dL; 14 vs. 10 g/dL) in two 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]

Increased risk for serious cardiovascular events was also reported from a randomized, prospective trial of 1265 hemodialysis patients with clinically evident cardiac disease (ischemic heart disease or congestive heart failure). In this trial, patients were assigned to Epoetin alfa treatment targeted to a maintenance hemoglobin of either 14 ± 1 g/dL or 10 ± 1 g/dL.[3] Higher mortality (35% vs. 29%) was observed in the 634 patients randomized to a target hemoglobin of 14 g/dL than in the 631 patients assigned a target hemoglobin of 10 g/dL. The reason for the increased mortality observed in this study is unknown; however, the incidence of nonfatal myocardial infarction, vascular access thrombosis, and other thrombotic events was also higher in the group randomized to a target hemoglobin of 14 g/dL.

An increased incidence of thrombotic events has also been observed in patients with cancer treated with erythropoietic agents. In patients with cancer who received Aranesp®, pulmonary emboli, thrombophlebitis, and thrombosis occurred more frequently than in placebo controls (see **ADVERSE REACTIONS: *Cancer Patients Receiving Chemotherapy*, Table 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 3 - 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 Tumor Progression

Erythropoiesis-stimulating agents, when administered to target a hemoglobin of > 12 g/dL, shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy [Cancer Studies 3 and 4 (DAHANCA 10) in Table 1]. ESAs also shortened survival in patients with metastatic breast cancer (Cancer Study 1) and in patients with lymphoid malignancy (Cancer Study 2) receiving chemotherapy when administered to target a hemoglobin of ≥ 12 g/dL. In addition, ESAs shortened survival in patients with non-small cell lung cancer and in a study enrolling patients with various malignancies who were not receiving chemotherapy or radiotherapy; in these two studies, ESAs were administered to target a hemoglobin of ≥ 12 g/dL (Cancer Studies 5 and 6 in Table 1). Although studies evaluated hemoglobin targets of ≥ 12 g/dL in these tumor types, the risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to target a hemoglobin of < 12 g/dL.

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 Lymphoid malignancy (n=344)	13-15 g/dL (M) 13-14 g/dL (F)	11.0 g/dL 9.8, 12.1 g/dL	Proportion of patients achieving a hemoglobin response	Decreased overall survival
Radiotherapy Alone				
Cancer Study 3 Head and neck cancer (n=351)	≥15 g/dL (M) ≥14 g/dL (F)	Not available	Locoregional progression-free survival	Decreased 5-year locoregional progression-free survival Decreased overall survival
Cancer Study 4 Head and neck cancer (n=522)	14-15.5 g/dL	Not available	Locoregional disease control	Decreased locoregional disease control
No Chemotherapy or Radiotherapy				
Cancer Study 5 Non-small cell lung cancer (n=70)	12-14 g/dL	Not available	Quality of life	Decreased overall survival
Cancer Study 6 Non-myeloid malignancy (n=989)	12-13 g/dL	10.6 g/dL 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 and Thromboembolic Events**). Mortality at 4 months (8.7% vs. 3.4%) was significantly higher in the Epoetin alfa arm. The most common investigator-attributed cause of death within the first 4 months was disease progression; 28 of 41 deaths in the Epoetin alfa arm and 13 of 16 deaths in the placebo arm were attributed to disease progression. Investigator assessed time to tumor progression was not different between the two groups. 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 5 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 6 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 locoregional progression-free survival and overall survival:

Cancer Study 3 (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 4 (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).

Hypertension

Patients with uncontrolled hypertension should not be treated with Aranesp®; blood pressure should be controlled adequately before initiation of therapy. Blood pressure may rise during treatment of anemia with Aranesp® or Epoetin alfa. In Aranesp® clinical trials, approximately 40% of patients with CRF required initiation or intensification of antihypertensive therapy during the early phase of treatment when the hemoglobin was increasing. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with Aranesp® or Epoetin alfa.

Special care should be taken to closely monitor and control blood pressure in patients treated with Aranesp®. During Aranesp® therapy, patients should be advised of the importance of compliance with antihypertensive therapy and dietary restrictions. If blood pressure is difficult to control by pharmacologic or dietary measures, the dose of Aranesp® should be reduced or withheld (see **DOSAGE AND ADMINISTRATION**). A clinically significant decrease in hemoglobin may not be observed for several weeks.

Seizures

Seizures have occurred in patients with CRF participating in clinical trials of Aranesp® and Epoetin alfa. During the first several months of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely. While the relationship between seizures and the rate of rise of hemoglobin is uncertain, it is recommended that the dose of Aranesp® be decreased if the hemoglobin increase exceeds 1 g/dL in any 2-week period.

Pure Red Cell Aplasia

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

Albumin (Human)

Aranesp® is supplied in two formulations with different excipients, one containing polysorbate 80 and another containing albumin (human), a derivative of human blood (see **DESCRIPTION**). Based on effective donor screening and product manufacturing processes, Aranesp® formulated with albumin carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS

General

The safety and efficacy of Aranesp® therapy have not been established in patients with underlying hematologic diseases (e.g., hemolytic anemia, sickle cell anemia, thalassemia, porphyria).

The needle cover of the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Lack or Loss of Response to Aranesp®

A lack of response or failure to maintain a hemoglobin response with Aranesp® doses within the recommended dosing range should prompt a search for causative factors. Deficiencies of folic acid, iron, or vitamin B_{12} should be excluded or corrected. Depending on the clinical setting, intercurrent infections, inflammatory or malignant processes, osteofibrosis cystica, occult blood loss, hemolysis, severe aluminum toxicity, and bone marrow fibrosis may compromise an erythropoietic response. In the absence of another etiology, the patient should be evaluated for evidence of PRCA and sera should be tested for the presence of antibodies to erythropoietin (see **WARNINGS: Pure Red Cell Aplasia**). 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 (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. <u>If a serious allergic or anaphylactic reaction occurs, Aranesp® should be immediately and permanently discontinued and appropriate therapy should be administered.</u>

Patients with CRF Not Requiring Dialysis

Patients with CRF not yet requiring dialysis may require lower maintenance doses of Aranesp® than patients receiving dialysis. Though predialysis patients generally receive less frequent monitoring of blood pressure and laboratory parameters than dialysis patients, predialysis patients may be more responsive to the effects of Aranesp®, and require judicious monitoring of blood pressure and hemoglobin. Renal function and fluid and electrolyte balance should also be closely monitored.

Dialysis Management

Therapy with Aranesp® results in an increase in RBCs and a decrease in plasma volume, which could reduce dialysis efficiency; patients who are marginally dialyzed may require adjustments in their dialysis prescription.

Laboratory Tests

After initiation of Aranesp® therapy, the hemoglobin should be determined weekly until it has stabilized and the maintenance dose has been established (see **DOSAGE AND ADMINISTRATION**). After a dose adjustment, the hemoglobin should be determined weekly for at least 4 weeks, until it has been determined that the hemoglobin has stabilized in response to the dose change. The hemoglobin should then be monitored at regular intervals.

In order to ensure effective erythropoiesis, iron status should be evaluated for all patients before and during treatment, as the majority of patients will eventually require supplemental iron therapy. Supplemental iron therapy is recommended for all patients whose serum ferritin is below 100 mcg/L or whose serum transferrin saturation is below 20%.

Information for Patients

Patients should be informed of the increased risks of mortality, serious cardiovascular events, thromboembolic events, and tumor progression when used in off-label dose regimens or populations (see

WARNINGS). Patients should be informed of the possible side effects of Aranesp® and be instructed to report them to the prescribing physician. Patients should be informed of the signs and symptoms of allergic drug reactions and be advised of appropriate actions. Patients should be counseled on the importance of compliance with their Aranesp® treatment, dietary and dialysis prescriptions, and the importance of judicious monitoring of blood pressure and hemoglobin concentration should be stressed.

In those rare cases where it is determined that a patient can safely and effectively administer Aranesp® at home, appropriate instruction on the proper use of Aranesp® should be provided for patients and their caregivers, including careful review of the accompanying "Information for Patients" insert. Patients and caregivers should also be cautioned against the reuse of needles, syringes, prefilled SureClick™ autoinjectors, or drug product, and be thoroughly instructed in their proper disposal. A puncture-resistant container for the disposal of used syringes, autoinjectors, and needles should be made available to the patient. Patients should be informed that the needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex), which should not be handled by persons sensitive to latex.

Drug Interactions

No formal drug interaction studies of Aranesp® have been performed.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenicity: The carcinogenic potential of Aranesp® has not been evaluated in long-term animal studies. Aranesp® did not alter the proliferative response of non-hematological cells in vitro or in vivo. In toxicity studies of approximately 6 months duration in rats and dogs, no tumorigenic or unexpected mitogenic responses were observed in any tissue type. Using a panel of human tissues, the in vitro tissue binding profile of Aranesp® was identical to Epoetin alfa. Neither molecule bound to human tissues other than those expressing the erythropoietin receptor.

Mutagenicity: Aranesp® was negative in the in vitro bacterial and CHO cell assays to detect mutagenicity and in the in vivo mouse micronucleus assay to detect clastogenicity.

Impairment of Fertility: When administered intravenously to male and female rats prior to and during mating, reproductive performance, fertility, and sperm assessment parameters were not affected at any doses evaluated (up to 10 mcg/kg/dose, administered 3 times weekly). An increase in post implantation fetal loss was seen at doses equal to or greater than 0.5 mcg/kg/dose, administered 3 times weekly.

Pregnancy Category C

When Aranesp® was administered intravenously to rats and rabbits during gestation, no evidence of a direct embryotoxic, fetotoxic, or teratogenic outcome was observed at doses up to 20 mcg/kg/day. The only adverse effect observed was a slight reduction in fetal weight, which occurred at doses causing exaggerated pharmacological effects in the dams (1 mcg/kg/day and higher). No deleterious effects on uterine implantation were seen in either species. No significant placental transfer of Aranesp® was observed in rats. An increase in post implantation fetal loss was observed in studies assessing fertility (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility: Impairment of Fertility**).

Intravenous injection of Aranesp® to female rats every other day from day 6 of gestation through day 23 of lactation at doses of 2.5 mcg/kg/dose and higher resulted in offspring (F1 generation) with decreased body weights, which correlated with a low incidence of deaths, as well as delayed eye opening and delayed preputial separation. No adverse effects were seen in the F2 offspring.

There are no adequate and well-controlled studies in pregnant women. Aranesp® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

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

Pediatric Use

Pediatric CRF Patients

A study of the conversion from Epoetin alfa to Aranesp® among pediatric CRF patients over 1 year of age showed similar safety and efficacy to the findings from adult conversion studies (see **CLINICAL PHARMACOLOGY** and **CLINICAL STUDIES**). Safety and efficacy in the initial treatment of anemic pediatric CRF patients or in the conversion from another erythropoietin to Aranesp® in pediatric CRF patients less than 1 year of age have not been established.

Pediatric Cancer Patients

The safety and efficacy of Aranesp® in pediatric cancer patients have not been established.

Geriatric Use

Of the 1598 CRF patients in clinical studies of Aranesp®, 42% were age 65 and over, while 15% were age 75 and over. Of the 873 cancer patients in clinical studies receiving Aranesp® and concomitant chemotherapy, 45% were age 65 and over, while 14% were age 75 and over. No overall differences in safety or efficacy were observed between older and younger patients.

ADVERSE REACTIONS

General

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of Aranesp® cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.

Immunogenicity

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

In clinical studies, the percentage of patients with antibodies to Aranesp® was examined using the BIAcore assay. Sera from 1501 CRF patients and 1159 cancer patients were tested. At baseline, prior to Aranesp® treatment, binding antibodies were detected in 59 (4%) of CRF patients and 36 (3%) of cancer patients. While receiving Aranesp® therapy (range 22-177 weeks), a follow-up sample was taken. One additional CRF patient and eight additional cancer patients developed antibodies capable of binding Aranesp®. None of the patients had antibodies capable of neutralizing the activity of Aranesp® or endogenous erythropoietin at baseline or at end of study. No clinical sequelae consistent with PRCA were associated with the presence of these antibodies.

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

Chronic Renal Failure Patients

Adult Patients

In all studies, the most frequently reported serious adverse reactions with Aranesp® were vascular access thrombosis, congestive heart failure, sepsis, and cardiac arrhythmia. The most commonly reported adverse reactions were infection, hypertension, hypotension, myalgia, headache, and diarrhea (see **WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events** and **Hypertension**). The most frequently reported adverse reactions resulting in clinical intervention (e.g.,

discontinuation of Aranesp®, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were hypotension, hypertension, fever, myalgia, nausea, and chest pain.

The data described below reflect exposure to Aranesp® in 1598 CRF patients, including 675 exposed for at least 6 months, of whom 185 were exposed for greater than 1 year. Aranesp® was evaluated in active-controlled (n = 823) and uncontrolled studies (n = 775).

The rates of adverse events and association with Aranesp® are best assessed in the results from studies in which Aranesp® was used to stimulate erythropoiesis in patients anemic at study baseline (n = 348), and, in particular, the subset of these patients in randomized controlled trials (n = 276). Because there were no substantive differences in the rates of adverse reactions between these subpopulations, or between these subpopulations and the entire population of patients treated with Aranesp®, data from all 1598 patients were pooled.

The population encompassed an age range from 18 to 91 years. Fifty-seven percent of the patients were male. The percentages of Caucasian, Black, Asian, and Hispanic patients were 83%, 11%, 3%, and 1%, respectively. The median weekly dose of Aranesp® was 0.45 mcg/kg (25th, 75th percentiles: 0.29, 0.66 mcg/kg).

Some of the adverse events reported are typically associated with CRF, or recognized complications of dialysis, and may not necessarily be attributable to Aranesp® therapy. No important differences in adverse event rates between treatment groups were observed in controlled studies in which patients received Aranesp® or other recombinant erythropoietins.

The data in Table 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 = 1598)
APPLICATION SITE	
Injection Site Pain	7%
BODY AS A WHOLE	
Peripheral Edema	11%
Fatigue	9%
Fever	9%
Death	7%
Chest Pain, Unspecified	6%
Fluid Overload	6%
Access Infection	6%
Influenza-like Symptoms	6%
Access Hemorrhage	6%
Asthenia	5%
CARDIOVASCULAR	
Hypertension	23%
Hypotension	22%
Cardiac Arrhythmias/Cardiac Arrest	10%
Angina Pectoris/Cardiac Chest Pain	8%
Thrombosis Vascular Access	8%
Congestive Heart Failure	6%
CNS/PNS	
Headache	16%
Dizziness	8%
GASTROINTESTINAL	
Diarrhea	16%
Vomiting	15%
Nausea	14%
Abdominal Pain	12%
Constipation	5%
MUSCULO-SKELETAL	
Myalgia	21%
Arthralgia	11%
Limb Pain	10%
Back Pain	8%

(Continued)

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

Event	Patients Treated with Aranesp® (n = 1598)
RESISTANCE MECHANISM	
Infection[a]	27%
RESPIRATORY	
Upper Respiratory Infection	14%
Dyspnea	12%
Cough	10%
Bronchitis	6%
SKIN AND APPENDAGES	
Pruritus	8%

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

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

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

Event	Patients Treated with Aranesp® (n = 1598)
Acute Myocardial Infarction	2%
Seizure	1%
Stroke	1%
Transient Ischemic Attack	1%

Pediatric Patients

In Study N5, Aranesp® was administered to 81 pediatric CRF patients who had stable hemoglobin concentrations while previously receiving Epoetin alfa (see **CLINICAL STUDIES**). In this study, the most frequently reported serious adverse reactions with Aranesp® were fever and dialysis access infection. The most commonly reported adverse reactions were fever, headache, upper respiratory infection, hypertension, hypotension, injection site pain, and cough. Aranesp® administration was discontinued because of injection site pain in two patients and moderate hypertension in a third patient.

Studies have not evaluated the effects of Aranesp® when administered to pediatric patients as the initial treatment for the anemia associated with CRF.

Thrombotic Events

Vascular access thrombosis in hemodialysis patients occurred in clinical trials at an annualized rate of 0.22 events per patient year of Aranesp® therapy. Rates of thrombotic events (e.g., vascular access thrombosis, venous thrombosis, and pulmonary emboli) with Aranesp® therapy were similar to those observed with other recombinant erythropoietins in these trials; the median duration of exposure was 12 weeks.

Cancer Patients Receiving Chemotherapy

The incidence data described below reflect the exposure to Aranesp® in 873 cancer patients including patients exposed to Aranesp® QW (547, 63%), Q2W (128, 16%), and Q3W (198, 23%). Aranesp® was evaluated in seven studies that were active-controlled and/or placebo-controlled studies of up to 6 months duration. The Aranesp®-treated patient demographics were as follows: median age of 63 years (range of

20 to 91 years); 40% male; 88% Caucasian, 5% Hispanic, 4% Black, and 3% Asian. Over 90% of patients had locally advanced or metastatic cancer, with the remainder having early stage disease. Patients with solid tumors (e.g., lung, breast, colon, ovarian cancers) and lymphoproliferative malignancies (e.g., lymphoma, multiple myeloma) were enrolled in the clinical studies. All of the 873 Aranesp®-treated subjects also received concomitant cyclic chemotherapy.

The most frequently reported serious adverse events included death (10%), fever (4%), pneumonia (3%), dehydration (3%), vomiting (2%), and dyspnea (2%). The most commonly reported adverse events were fatigue, edema, nausea, vomiting, diarrhea, fever, and dyspnea (see **Table 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 Q3W (n = 353) and Aranesp® 2.25 mcg/kg QW (n = 352), the incidences of all adverse events and of serious adverse events were similar between the two groups.

Thrombotic and Cardiovascular Events

Overall, the incidence of thrombotic events was 6.2% for Aranesp® and 4.1% for placebo. However, the following events were reported more frequently in Aranesp®-treated patients than in placebo controls: pulmonary embolism, thromboembolism, thrombosis, and thrombophlebitis (deep and/or superficial). In addition, edema of any type was more frequently reported in Aranesp®-treated patients (21%) than in patients who received placebo (10%).

OVERDOSAGE

The expected manifestations of Aranesp® overdosage include signs and symptoms associated with an excessive and/or rapid increase in hemoglobin concentration, including any of the cardiovascular events described in **WARNINGS** and listed in **ADVERSE REACTIONS**. Patients receiving an overdosage of Aranesp® should be monitored closely for cardiovascular events and hematologic abnormalities. Polycythemia should be managed acutely with phlebotomy, as clinically indicated. Following resolution of the effects due to Aranesp® overdosage, reintroduction of Aranesp® therapy should be accompanied by close monitoring for evidence of rapid increases in hemoglobin concentration (> 1 g/dL in any 2-week period). In patients with an excessive hematopoietic response, reduce the Aranesp® dose in accordance with the recommendations described in **DOSAGE AND ADMINISTRATION**.

DOSAGE AND ADMINISTRATION

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

Aranesp® is supplied in vials or in prefilled syringes with UltraSafe® Needle Guards*. Following administration of Aranesp® from the prefilled syringe, the UltraSafe® Needle Guard should be activated to prevent accidental needle sticks.

Aranesp® is also supplied in prefilled SureClick™ autoinjectors containing the same dosage strengths as the prefilled syringes. Because the autoinjectors are designed to deliver the full content, autoinjectors should only be used for patients who need the full dose. If the required dose is not available in an autoinjector, prefilled syringes, or vials should be used to administer the required dose. Autoinjectors are for subcutaneous administration only.

Chronic Renal Failure Patients

Aranesp® is administered either IV or SC as a single weekly injection. ***In patients on hemodialysis, the IV route is recommended.*** The dose should be started and slowly adjusted as described below based on hemoglobin levels. If a patient fails to respond or maintain a response, this should be evaluated (see **WARNINGS: Pure Red Cell Aplasia, PRECAUTIONS: Lack or Loss of Response to Aranesp®** and **PRECAUTIONS: Laboratory Tests**). When Aranesp® therapy is initiated or adjusted, the hemoglobin should be followed weekly until stabilized and monitored at least monthly thereafter. 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 recommended starting dose of Aranesp® for the correction of anemia in adult CRF patients is 0.45 mcg/kg body weight, administered as a single IV or SC injection once weekly. 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. Predialysis patients, in particular, may require lower maintenance doses. Some patients have been treated successfully with a SC dose of Aranesp® administered once every 2 weeks.

Dose Adjustment

The dose should be adjusted for each patient to achieve and maintain 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 < 1500 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 (IV or SC) 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

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

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

The recommended starting dose for Aranesp® administered once-every-3-weeks (Q3W) is 500 mcg as a SC injection.

For both dosing schedules, the dose should be adjusted for each patient to maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed the upper safety limit of 12 g/dL. 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 12 g/dL, 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® 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 bright light. After removing the vials, prefilled syringes, or autoinjectors from the cartons, keep them covered to protect from room light until administration. Vigorous shaking or exposure to light may denature Aranesp®, causing it to become biologically inactive. Always store vials, prefilled syringes, or autoinjectors of Aranesp® in their carton until use.

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

Do not dilute Aranesp®.

Do not administer Aranesp® in conjunction with other drug solutions.

Aranesp® contains no preservatives. Discard any unused portion. **Do not pool unused portions from the vials or prefilled syringes. Do not use the vial, prefilled syringe, or autoinjector more than one time.**

Following administration of Aranesp® from the prefilled syringe, activate the UltraSafe® Needle Guard. Place your hands behind the needle, grasp the guard with one hand, and slide the guard forward until the needle is completely covered and the guard clicks into place. NOTE: If an audible click is not heard, the needle guard may not be completely activated.

The prefilled SureClick™ autoinjector is designed to deliver the full dose. The completion of the injection is signaled by an audible click. Removal of the autoinjector from the injection site automatically extends a needle cover.

The autoinjectors, the syringes used with vials, and the entire prefilled syringe with activated needle guard should be disposed of in a puncture-proof container.

See the accompanying “Information for Patients” leaflet for complete instructions on the preparation and administration of Aranesp® for patients, including injection site selection.

HOW SUPPLIED

Aranesp® is available in single-dose vials in two solutions, an albumin solution and a polysorbate solution. The words “Albumin Free” appear on the polysorbate container labels and the package main panels as

well as other panels as space permits. Aranesp® single-dose prefilled syringes and prefilled SureClick™ autoinjectors are available in albumin and polysorbate solutions. Both prefilled syringes and autoinjectors are supplied with a 27-gauge, ½-inch needle.

Each prefilled syringe is equipped with an UltraSafe® Needle Guard that is manually activated to cover the needle during disposal. The needle cover of the prefilled syringe contains dry natural rubber (a derivative of latex). The autoinjector has a needle cover that automatically extends as the autoinjector is removed from the injection site after completion of the injection.

Aranesp® is available in the following packages:

Single-dose Vial, Polysorbate Solution

1 Vial/Pack, 4 Packs/Case	4 Vials/Pack, 4 Packs/Case	4 Vials/Pack, 10 Packs/Case
200 mcg/1 mL (NDC 55513-006-01)	200 mcg/1 mL (NDC 55513-006-04)	25 mcg/1 mL (NDC 55513-002-04)
300 mcg/1 mL (NDC 55513-110-01)	300 mcg/1 mL (NDC 55513-110-04)	40 mcg/1 mL (NDC 55513-003-04)
500 mcg/1 mL (NDC 55513-008-01)		60 mcg/1 mL (NDC 55513-004-04)
		100 mcg/1 mL (NDC 55513-005-04)
		150 mcg/0.75 mL (NDC 55513-053-04)

Single-dose Vial, Albumin Solution

1 Vial/Pack, 4 Packs/Case	4 Vials/Pack, 4 Packs/Case	4 Vials/Pack, 10 Packs/Case
200 mcg/1 mL (NDC 55513-014-01)	200 mcg/1 mL (NDC 55513-014-04)	25 mcg/1 mL (NDC 55513-010-04)
300 mcg/1 mL (NDC 55513-015-01)	300 mcg/1 mL (NDC 55513-015-04)	40 mcg/1 mL (NDC 55513-011-04)
500 mcg/1 mL (NDC 55513-016-01)		60 mcg/1 mL (NDC 55513-012-04)
		100 mcg/1 mL (NDC 55513-013-04)
		150 mcg/0.75 mL (NDC 55513-054-04)

Single-dose Prefilled Syringe (SingleJect®) with a 27-gauge, ½-inch needle with an UltraSafe® Needle Guard, Polysorbate Solution

1 Syringe/Pack, 4 Packs/Case	4 Syringes/Pack, 4 Packs/Case	4 Syringes/Pack, 10 Packs/Case
200 mcg/0.4 mL (NDC 55513-028-01)	200 mcg/0.4 mL (NDC 55513-028-04)	25 mcg/0.42 mL (NDC 55513-057-04)
300 mcg/0.6 mL (NDC 55513-111-01)	300 mcg/0.6 mL (NDC 55513-111-04)	40 mcg/0.4 mL (NDC 55513-021-04)
500 mcg/1 mL (NDC 55513-032-01)		60 mcg/0.3 mL (NDC 55513-023-04)
		100 mcg/0.5 mL (NDC 55513-025-04)
		150 mcg/0.3 mL (NDC 55513-027-04)

Single-dose Prefilled Syringe (SingleJect®) with a 27-gauge, ½-inch needle with an UltraSafe® Needle Guard, Albumin Solution

1 Syringe/Pack, 4 Packs/Case	4 Syringes/Pack, 4 Packs/Case	4 Syringes/Pack, 10 Packs/Case
200 mcg/0.4 mL (NDC 55513-044-01)	200 mcg/0.4 mL (NDC 55513-044-04)	25 mcg/0.42 mL (NDC 55513-058-04)
300 mcg/0.6 mL (NDC 55513-046-01)	300 mcg/0.6 mL (NDC 55513-046-04)	40 mcg/0.4 mL (NDC 55513-037-04)
500 mcg/1 mL (NDC 55513-048-01)		60 mcg/0.3 mL (NDC 55513-039-04)
		100 mcg/0.5 mL (NDC 55513-041-04)
		150 mcg/0.3 mL (NDC 55513-043-04)

Single-dose prefilled SureClick™ Autoinjector with a 27-gauge, ½-inch needle, Polysorbate Solution

1 Autoinjector/Pack

25 mcg/0.42 mL
(NDC 55513-090-01)

40 mcg/0.4 mL
(NDC 55513-091-01)

60 mcg/0.3 mL

(NDC 55513-092-01)

100 mcg/0.5 mL
(NDC 55513-093-01)

150 mcg/0.3 mL
(NDC 55513-094-01)

200 mcg/0.4 mL
(NDC 55513-095-01)

300 mcg/0.6 mL
(NDC 55513-096-01)

500 mcg/1 mL
(NDC 55513-097-01)

Single-dose prefilled SureClick™ Autoinjector with a 27-gauge, ½-inch needle, Albumin Solution

1 Autoinjector/Pack

25 mcg/0.42 mL
(NDC 55513-080-01)

40 mcg/0.4 mL
(NDC 55513-081-01)

60 mcg/0.3 mL
(NDC 55513-082-01)

100 mcg/0.5 mL
(NDC 55513-083-01)

150 mcg/0.3 mL
(NDC 55513-084-01)

200 mcg/0.4 mL
(NDC 55513-085-01)

300 mcg/0.6 mL
(NDC 55513-086-01)

500 mcg/1 mL
(NDC 55513-087-01)

Storage

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

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Rx only

This product, or its use, may be covered by one or more US Patents, including US Patent No. 5,618,698, in addition to others including patents pending.

AMGEN®

Manufactured by:

Amgen Manufacturing, Limited, a subsidiary of Amgen Inc.
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PROCRIT®

EPOETIN ALFA

Full Prescribing Information

Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1789

Distributed by:
Ortho Biotech Products, L.P.
Raritan, New Jersey 08869-0670

PROCRIT®
(Epoetin alfa)
FOR INJECTION

WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR and THROMBOEMBOLIC EVENTS, and TUMOR PROGRESSION

Renal failure: **Patients experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemoglobin levels (13.5 vs. 11.3 g/dL; 14 vs. 10 g/dL) in two clinical studies. Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL.**

Cancer:

- **ESAs shortened overall survival and/or time-to-tumor progression in clinical studies in patients with advanced breast, head and neck, lymphoid, and non-small cell lung malignancies when dosed to target a hemoglobin of > 12 g/dL.**
- **The risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to target a hemoglobin of < 12 g/dL.**
- **To minimize these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusions.**
- **Use only for treatment of anemia due to concomitant myelosuppressive chemotherapy.**
- **Discontinue following the completion of a chemotherapy course.**

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

(See WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events, WARNINGS: Increased Mortality and/or Tumor Progression, 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. PROCRIT® (Epoetin alfa), a 165 amino acid glycoprotein manufactured by recombinant DNA technology, has the same biological effects as endogenous erythropoietin.[1] It has a molecular weight of 30,400 daltons and is produced by mammalian cells into which the human erythropoietin gene has been introduced. The product contains the identical amino acid sequence of isolated natural erythropoietin.

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

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

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

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

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

CLINICAL PHARMACOLOGY

Chronic Renal Failure Patients

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

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

PROCRIT® has been shown to stimulate erythropoiesis in anemic patients with CRF, including both patients on dialysis and those who do not require regular dialysis.[4-12] The first evidence of a response to the three times weekly (TIW) administration of PROCRIT® is an increase in the reticulocyte count within 10 days, followed by increases in the red cell count, hemoglobin, and hematocrit, usually within 2 to 6 weeks.[4,5] Because of the length of time required for erythropoiesis — several days for erythroid progenitors to mature and be released into the circulation — a clinically significant increase in hematocrit is usually not observed in less than 2 weeks and may require up to 6 weeks in some patients. Once the hematocrit reaches the suggested target range (30% to 36%), that level can be sustained by PROCRIT® therapy in the absence of iron deficiency and concurrent illnesses.

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

Zidovudine-treated HIV-infected Patients

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

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

Cancer Patients on Chemotherapy

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

Pharmacokinetics

In adult and pediatric patients with CRF, the elimination half-life of plasma erythropoietin after intravenously administered PROCRIT® ranges from 4 to 13 hours.[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 PROCRIT® half-life among adult patients above or below 65 years of age.

The pharmacokinetic profile of PROCRIT® in children and adolescents appears to be similar to that of adults. Limited data are available in neonates.[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 PROCRIT® have not been studied in HIV-infected patients.

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

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

INDICATIONS AND USAGE

Treatment of Anemia of Chronic Renal Failure Patients

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

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

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

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

Treatment of Anemia in Zidovudine-treated HIV-infected Patients

PROCRIT® is indicated for the treatment of anemia related to therapy with zidovudine in HIV-infected patients. PROCRIT® is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients. PROCRIT® is not indicated for the treatment of anemia in HIV-infected patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding, which should be managed appropriately. PROCRIT® use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.

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

Treatment of Anemia in Cancer Patients on Chemotherapy

PROCRIT® is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. PROCRIT® is indicated to decrease the need for transfusions in patients who will be receiving concomitant chemotherapy for a minimum of 2 months. PROCRIT® is not indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding, which should be managed appropriately. PROCRIT® use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.

PROCRIT® is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy.

Reduction of Allogeneic Blood Transfusion in Surgery Patients

PROCRIT® 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] PROCRIT® is not indicated for anemic patients who are willing to donate autologous blood (see BOXED WARNINGS and DOSAGE AND ADMINISTRATION).

CLINICAL EXPERIENCE: RESPONSE TO PROCRIT®

Chronic Renal Failure Patients

When dosed with PROCRIT®, 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 PROCRIT® administered and individual patient variation. In clinical trials at starting doses of 50 to 150 Units/kg TIW, adult patients responded with an average rate of hematocrit rise of:

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

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 PROCRIT® or placebo. By the end of the study, average hemoglobin increased to approximately 11 g/dL in the PROCRIT®-treated patients and remained unchanged in patients receiving placebo. PROCRIT®-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 PROCRIT® therapy. In the three largest of these clinical trials, the median maintenance dose necessary to maintain the hematocrit between 30% to 36% was approximately 75 Units/kg TIW. In the US multicenter phase 3 study, approximately 65% of the patients required doses of 100 Units/kg TIW, or less, to maintain their hematocrit at approximately 35%. Almost 10% of patients required a dose of 25 Units/kg, or less, and approximately 10% required a dose of more than 200 Units/kg TIW to maintain their hematocrit at this level.

A multicenter unit dose study was also conducted in 119 patients receiving peritoneal dialysis who self-administered PROCRIT® subcutaneously for approximately 109 patient-years of experience. Patients responded to PROCRIT® administered SC in a manner similar to patients receiving IV administration.[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 PROCRIT®. The largest study was a placebo-controlled, randomized trial in 113 children with anemia (hematocrit ≤ 27%) undergoing peritoneal dialysis or hemodialysis. The initial dose of PROCRIT® was 50 Units/kg IV or SC TIW. The dose of study drug was titrated to achieve either a hematocrit of 30% to 36% or an absolute increase in hematocrit of 6 percentage points over baseline.

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

Patients With CRF Not Requiring Dialysis

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

PROCRIT® has been studied in four placebo-controlled trials enrolling 297 anemic (hematocrit < 30%) HIV-infected (AIDS) patients receiving concomitant therapy with zidovudine (all patients were treated with Epoetin alfa manufactured by Amgen Inc). In the subgroup of patients (89/125 PROCRIT® and 88/130 placebo) with prestudy endogenous serum erythropoietin levels ≤500 mUnits/mL, PROCRIT® reduced the mean cumulative number of units of blood transfused per patient by approximately 40% as compared to the placebo group.[24] Among those patients who required transfusions at baseline, 43% of patients treated with PROCRIT® versus 18% of placebo-treated patients were transfusion-independent during the second and third months of therapy. PROCRIT® therapy also resulted in significant increases in hematocrit in comparison to placebo. When examining the results according to the weekly dose of zidovudine received during month 3 of therapy, there was a statistically significant ($p < 0.003$) reduction in transfusion requirements in patients treated with PROCRIT® (n = 51) compared to placebo treated patients (n = 54) whose mean weekly zidovudine dose was ≤ 4200 mg/week.[23]

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

In a 6 month open-label PROCRIT® study, patients responded with decreased transfusion requirements and sustained increases in hematocrit and hemoglobin with doses of PROCRIT® up to 300 Units/kg TIW.[23-25]

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

Cancer Patients on Chemotherapy

Adult Patients

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

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

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

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

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

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

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

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

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

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

Weekly (QW) Dosing

PROCRIT® was also studied in a placebo-controlled, double-blind trial utilizing weekly dosing in a total of 344 anemic cancer patients. In this trial, 61 (35 placebo arm and 26 in the PROCRIT® arm) patients were treated with concomitant cisplatin containing regimens and 283 patients received concomitant chemotherapy regimens that did not contain cisplatinum. Patients were randomized to PROCRIT® 40,000 Units weekly (n = 174) or placebo (n = 170) SC for a planned treatment period of 16 weeks. If hemoglobin had not increased by > 1 g/dL after 4 weeks of therapy or the patient received RBC transfusion during the first 4 weeks of therapy, study drug was increased to 60,000 Units weekly. Forty-three percent of patients in the Epoetin alfa group required an increase in PROCRIT® dose to 60,000 Units weekly.[23]

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

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

Pediatric Patients

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

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

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

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

[b] Adjusted 2 sided p <0.05

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

Surgery Patients

PROCRIT® has been studied in a placebo-controlled, double-blind trial enrolling 316 patients scheduled for major, elective orthopedic hip or knee surgery who were expected to require ≥2 units of blood and who were not able or willing to participate in an autologous blood donation program. Based on previous studies which demonstrated that pretreatment hemoglobin is a predictor of risk of receiving transfusion,[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 PROCRIT®, 100 Units/kg PROCRIT® or placebo by SC injection for 10 days before surgery, on the day of surgery, and for 4 days after surgery.[17] All patients received oral iron and a low-dose post-operative warfarin regimen.[17]

Treatment with PROCRIT® 300 Units/kg significantly (p = 0.024) reduced the risk of allogeneic transfusion in patients with a pretreatment hemoglobin of > 10 to ≤13; 5/31 (16%) of PROCRIT® 300 Units/kg, 6/26 (23%) of PROCRIT® 100 Units/kg, and 13/29 (45%) of placebo-treated patients were transfused.[17] There was no significant difference in the number of patients transfused between PROCRIT® (9% 300 Units/kg, 6% 100 Units/kg) and placebo (13%) in the > 13 to ≤15 g/dL hemoglobin stratum. There were too few patients in the ≤ 10 g/dL group to determine if PROCRIT® is useful in this hemoglobin strata. In the > 10 to ≤ 13 g/dL pretreatment stratum, the mean number of units transfused per PROCRIT®-treated patient (0.45 units blood for 300 Units/kg, 0.42 units blood for 100 Units/kg) was less than the mean transfused per placebo-treated patient (1.14 units) (overall p = 0.028). In addition, mean hemoglobin, hematocrit, and reticulocyte counts increased significantly during the presurgery period in patients treated with PROCRIT®.[17]

PROCRIT® was also studied in an open-label, parallel-group trial enrolling 145 subjects with a pretreatment hemoglobin level of ≥10 to ≤13 g/dL who were scheduled for major orthopedic hip or knee surgery and who were not participating in an autologous program.[18] Subjects were randomly assigned to receive one of two SC dosing regimens of PROCRIT® (600 Units/kg once weekly for 3 weeks prior to surgery and on the day of surgery, or 300 Units/kg once daily for 10 days prior to surgery, on the day of surgery and for 4 days after surgery). All subjects received oral iron and appropriate pharmacologic anticoagulation therapy.

From pretreatment to presurgery, the mean increase in hemoglobin in the 600 Units/kg weekly group (1.44 g/dL) was greater than observed in the 300 Units/kg daily group.[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

PROCRIT® is contraindicated in patients with:

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

WARNINGS

Pediatrics

Risk in Premature Infants

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

Adults

Increased Mortality, Serious Cardiovascular and Thromboembolic Events

Patients with chronic renal failure experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemoglobin levels (13.5 vs. 11.3 g/dL; 14 vs. 10 g/dL) in two 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. PROCRIT® 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]

Increased risk for serious cardiovascular events was also reported from a randomized, prospective trial of 1265 hemodialysis patients with clinically evident cardiac disease (ischemic heart disease or congestive heart failure). In this trial, patients were assigned to PROCRIT® treatment targeted to a maintenance hematocrit of either 42 ± 3% or 30 ± 3%.[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 3 - 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 PROCRIT® in adult patients who were undergoing coronary artery bypass surgery (7 deaths in 126 patients randomized to PROCRIT® versus no deaths among 56 patients receiving placebo). Four of these deaths occurred during the period of study drug administration and all four deaths were associated with thrombotic events.[42] ESAs are not approved for reduction of allogeneic red blood cell transfusions in patients scheduled for cardiac surgery.

Increased Mortality and/or Tumor Progression

Erythropoiesis-stimulating agents, when administered to target a hemoglobin of > 12 g/dL, shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy [Cancer Studies 3 and 4 (DAHANCA 10) in Table 1]. ESAs also shortened survival in patients with metastatic breast cancer (Cancer Study 1) and in patients with lymphoid malignancy (Cancer Study 2) receiving chemotherapy when administered to target a hemoglobin of > 12 g/dL. In addition, ESAs shortened survival in patients with non-small cell lung cancer and in a study enrolling patients with various malignancies who were not receiving chemotherapy or radiotherapy; in these two studies, ESAs were administered to target a hemoglobin of ≥12 g/dL (Cancer Studies 5 and 6 in Table 1). Although studies evaluated hemoglobin targets of ≥12 g/dL in these tumor types, the risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to target a hemoglobin of < 12 g/dL.

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 Lymphoid malignancy (n=344)	13-15 g/dL (M) 13-14 g/dL (F)	11.0 g/dL 9.8, 12.1 g/dL	Proportion of patients achieving a hemoglobin response	Decreased overall survival
Radiotherapy Alone				
Cancer Study 3 Head and neck cancer (n=351)	≥15 g/dL (M) ≥14 g/dL (F)	Not available	Locoregional progression-free survival	Decreased 5-year locoregional progression-free survival Decreased overall survival
Cancer Study 4 Head and neck cancer (n=522)	14-15.5 g/dL	Not available	Locoregional disease control	Decreased locoregional disease control
No Chemotherapy or Radiotherapy				
Cancer Study 5 Non-small cell lung cancer (n=70)	12-14 g/dL	Not available	Quality of life	Decreased overall survival
Cancer Study 6 Non-myeloid malignancy (n=989)	12-13 g/dL	10.6 g/dL 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 and Thromboembolic Events). Mortality at 4 months (8.7% vs. 3.4%) was significantly higher in the Epoetin alfa arm. The most common investigator-attributed cause of death within the first 4 months was disease progression; 28 of 41 deaths in the Epoetin alfa arm and 13 of 16 deaths in the placebo arm were attributed to disease progression. Investigator assessed time to tumor progression was not different between the two groups. 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 5 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 6 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 locoregional progression-free survival and overall survival:

Cancer Study 3 (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 4 (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).

Pure Red Cell Aplasia

Cases of pure red cell aplasia (PRCA) and of severe anemia, with or without other cytopenias, associated with neutralizing antibodies to erythropoietin have been reported in patients treated with PROCRIT®. This has been reported predominantly in patients with CRF receiving PROCRIT® by subcutaneous administration. Any patient who develops a sudden loss of response to PROCRIT®, accompanied by severe anemia and low reticulocyte count, should be evaluated for the etiology of loss of effect, including the presence of neutralizing antibodies to erythropoietin (see PRECAUTIONS: Lack or Loss of Response). If anti-erythropoietin antibody-associated anemia is suspected, withhold PROCRIT® and other erythropoietic proteins. Contact ORTHO BIOTECH (1 888 2ASK OBI or 1 888 227 5624) to perform assays for binding and neutralizing antibodies. PROCRIT® should be permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other erythropoietic proteins as antibodies may cross-react (see ADVERSE REACTIONS: Immunogenicity).

Albumin (Human)

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

Chronic Renal Failure Patients

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

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

It is recommended that the dose of PROCRIT® be decreased if the hemoglobin increase exceeds 1 g/dL in any 2-week period, because of the possible association of excessive rate of rise of hemoglobin with an exacerbation of hypertension. In CRF patients on hemodialysis with clinically evident ischemic heart disease or congestive heart failure, the dose of PROCRIT® should be carefully adjusted to achieve and maintain hemoglobin levels between 10-12 g/dL (see WARNINGS: Mortality, Serious Cardiovascular and Thromboembolic Events and DOSAGE AND ADMINISTRATION: Chronic Renal Failure Patients).

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

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

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

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

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

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

Zidovudine-treated HIV-infected Patients

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

PRECAUTIONS

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

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

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

Hematology

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

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

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

Lack or Loss of Response

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

1. Iron deficiency: Virtually all patients will eventually require supplemental iron therapy (see IRON EVALUATION).
2. Underlying infectious, inflammatory, or malignant processes.
3. Occult blood loss.
4. Underlying hematologic diseases (ie, thalassemia, refractory anemia, or other myelodysplastic disorders).
5. Vitamin deficiencies: Folic acid or vitamin 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 PROCRIT® therapy.

Iron Evaluation

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

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

Drug Interaction

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

Pregnancy Category C

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

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

Nursing Mothers

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

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

Pediatric Use

See WARNINGS: Pediatrics

Pediatric Patients on Dialysis: PROCRIT® is indicated in infants (1 month to 2 years), children (2 years to 12 years), and adolescents (12 years to 16 years) for the treatment of anemia associated with CRF requiring dialysis. Safety and effectiveness in pediatric patients less than 1 month old have not been established (see CLINICAL EXPERIENCE: CHRONIC RENAL FAILURE, PEDIATRIC PATIENTS ON DIALYSIS). The safety data from these studies show that there is no increased risk to pediatric CRF patients on dialysis when compared to the safety profile of PROCRIT® in adult CRF patients (see ADVERSE REACTIONS and WARNINGS). Published literature[27-30] provides supportive evidence of the safety and effectiveness of PROCRIT® in pediatric CRF patients on dialysis.

Pediatric Patients Not Requiring Dialysis: Published literature[30,31] has reported the use of PROCRIT® in 133 pediatric patients with anemia associated with CRF not requiring dialysis, ages 3 months to 20 years, treated with 50 to 250 Units/kg SC or IV, QW to TIW. Dose-dependent increases in hemoglobin and hematocrit were observed with reductions in transfusion requirements.

Pediatric HIV-infected Patients: Published literature[32,33] has reported the use of PROCRIT® in 20 zidovudine-treated anemic HIV-infected pediatric patients ages 8 months to 17 years, treated with 50 to 400 Units/kg SC or IV, 2 to 3 times per week. Increases in hemoglobin levels and in reticulocyte counts, and decreases in or elimination of blood transfusions were observed.

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

Geriatric Use

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

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

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

Information for Patients

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

Chronic Renal Failure Patients

Patients with CRF Not Requiring Dialysis

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

Hematology

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

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

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

Laboratory Monitoring

The hemoglobin should be determined twice a week until it has stabilized in the suggested 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 PROCRIT®, modest increases in serum uric acid and phosphorus were observed. While changes were statistically significant, the values remained within the ranges normally seen in patients with CRF.

Diet

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

Dialysis Management

Therapy with PROCRIT® results in an increase in hematocrit and a decrease in plasma volume which could affect dialysis efficiency. In studies to date, the resulting increase in hematocrit did not appear to adversely affect dialyzer function[8,9] or the efficiency of high flux hemodialysis.[10] During hemodialysis, patients treated with PROCRIT® may require increased anticoagulation with heparin to prevent clotting of the artificial kidney.

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

Renal Function

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

Zidovudine-treated HIV-infected Patients

Hypertension

Exacerbation of hypertension has not been observed in zidovudine-treated HIV-infected patients treated with PROCRIT®. However, PROCRIT® should be withheld in these patients if pre-existing hypertension is uncontrolled, and should not be started until blood pressure is controlled. In double-blind studies, a single seizure has been experienced by a patient treated with PROCRIT®.[23]

Cancer Patients on Chemotherapy

Hypertension

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

Seizures

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

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

Thrombotic Events

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

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

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

Surgery Patients

Hypertension

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

ADVERSE REACTIONS

Immunogenicity

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

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

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

Chronic Renal Failure Patients

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

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

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

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

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

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

Seizures: There have been 47 seizures in 1010 patients on dialysis treated with PROCRIT® in clinical trials, with an exposure of 986 patient-years for a rate of approximately 0.048 events per patient-year. However, there appeared to be a higher rate of seizures during the first 90 days of therapy (occurring in approximately 2.5% of patients) when compared to subsequent 90-day periods. The baseline incidence of seizures in the untreated dialysis population is difficult to determine; it appears to be in the range of 5% to 10% per patient-year.[34-36]

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

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

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

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

Zidovudine-treated HIV-infected Patients

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

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

In the 297 patients studied, PROCRIT® was not associated with significant increases in opportunistic infections or mortality.[23] In 71 patients from this group treated with PROCRIT® 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 PROCRIT® therapy.

Allergic Reactions: Two zidovudine-treated HIV-infected patients had urticarial reactions within 48 hours of their first exposure to study medication. One patient was treated with PROCRIT® and one was treated with placebo (PROCRIT® vehicle alone). Both patients had positive immediate skin tests against their study medication with a negative saline control. The basis for this apparent pre-existing hypersensitivity to components of the PROCRIT® formulation is unknown, but may be related to HIV-induced immunosuppression or prior exposure to blood products.

Seizures: In double-blind and open-label trials of PROCRIT® in zidovudine-treated HIV-infected patients, 10 patients have experienced seizures.[23] In general, these seizures appear to be related to underlying pathology such as meningitis or cerebral neoplasms, not PROCRIT® therapy.

Cancer Patients on Chemotherapy

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

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

* Statistically significant

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

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

Surgery Patients

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

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

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

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

[c] Determined by clinical symptoms

Thrombotic/Vascular Events: In three double-blind, placebo-controlled orthopedic surgery studies, the rate of deep venous thrombosis (DVT) was similar among Epoetin alfa and placebo-treated patients in the recommended population of patients with a pretreatment hemoglobin of > 10 g/dL to ≤ 13 g/dL.[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 PROCRIT® 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 PROCRIT® overdosage include signs and symptoms associated with an excessive and/or rapid increase in hemoglobin concentration, including any of the cardiovascular events described in WARNINGS and listed in ADVERSE REACTIONS. Patients receiving an overdosage of PROCRIT® should be monitored closely for cardiovascular events and hematologic abnormalities. Polycythemia should be managed acutely with phlebotomy, as clinically indicated. Following resolution of the effects due to PROCRIT® overdosage, reintroduction of PROCRIT® therapy should be accompanied by close monitoring for evidence of rapid increases in hemoglobin concentration (>1 gm/dL per 14 days). In patients with an excessive hematopoietic response, reduce the PROCRIT® dose in accordance with the recommendations described in DOSAGE AND ADMINISTRATION.

DOSAGE AND ADMINISTRATION

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

Chronic Renal Failure Patients

The recommended range for the starting dose of PROCRIT® is 50 to 100 Units/kg TIW for adult patients. The recommended starting dose for pediatric CRF patients on dialysis is 50 Units/kg TIW. Individualize dosing to achieve and maintain hemoglobin levels between 10-12 g/dL. The dose of PROCRIT® should be reduced as the hemoglobin approaches 12 g/dL or increases by more than 1 g/dL in any 2-week period. If hemoglobin excursions outside the recommended range occur, the PROCRIT® dose should be adjusted as described below.

PROCRIT® may be given either as an IV or SC injection. **In patients on hemodialysis, the IV route is recommended** (see WARNINGS: Pure Red Cell Aplasia). While the administration of PROCRIT® is independent of the dialysis procedure, PROCRIT® may be administered into the venous line at the end of the dialysis procedure to obviate the need for additional venous access. In adult patients with CRF not on dialysis, PROCRIT® may be given either as an IV or SC injection.

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

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 2. Hemoglobin decreases below 10 g/dL
Reduce Dose by 25% When:	1. Hemoglobin approaches 12 g/dL or, 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 PROCRIT® dose titrations over a 12-week period:

- do not administer higher PROCRIT® 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, PROCRIT® dose adjustments should be made as described above; discontinue PROCRIT® if responsiveness does not improve and the patient needs recurrent RBC transfusions.

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

Dose Adjustment: The dose should be adjusted for each patient to achieve and maintain 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 PROCRIT® may be increased by approximately 25% of the previous dose. Further increases may be made at 4-week intervals until the specified hemoglobin is obtained.

Maintenance Dose: The maintenance dose must be individualized for each patient on dialysis. In the US phase 3 multicenter trial in patients on hemodialysis, the median maintenance dose was 75 Units/kg TIW, with a range from 12.5 to 525 Units/kg TIW. Almost 10% of the patients required a dose of 25 Units/kg, or less, and approximately 10% of the patients required more than 200 Units/kg TIW to maintain their hematocrit in the suggested target range. In pediatric hemodialysis and peritoneal dialysis patients, the median maintenance dose was 167 Units/kg/week (49 to 447 Units/kg per week) and 76 Units/kg per week (24 to 323 Units/kg/week) administered in divided doses (TIW or BIW), respectively to achieve the target range of 30% to 36%.

If the transferrin saturation is greater than 20%, the dose of PROCRIT® may be increased. Such dose increases should not be made more frequently than once a month, unless clinically indicated, as the response time of the hemoglobin to a dose increase can be 2 to 6 weeks. Hemoglobin should be measured twice weekly for 2 to 6 weeks following dose increases. In adult patients with CRF not on dialysis, the dose should also be individualized to maintain hemoglobin levels between 10 to 12 g/dL. PROCRIT® doses of 75 to 150 Units/kg/week have been shown to maintain hematocrits of 36% to 38% for up to 6 months.

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

Zidovudine-treated HIV-infected Patients

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

In zidovudine-treated HIV-infected patients the dosage of PROCRIT® should be titrated for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for blood transfusion and not to exceed 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 PROCRIT® is 100 Units/kg as an IV or SC injection TIW for 8 weeks. For pediatric patients, see PRECAUTIONS: PEDIATRIC USE.

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

Maintenance Dose: After attainment of the desired response (ie, reduced transfusion requirements or increased hemoglobin), the dose of PROCRIT® should be titrated to maintain the response based on factors such as variations in zidovudine dose and the presence of intercurrent infectious or inflammatory episodes. If the hemoglobin exceeds 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

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

becomes stable. The dose of PROCRIT® should be titrated for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for blood transfusion and not to exceed the upper safety limit of 12 g/dL (See recommended Dose Modifications, below).

Recommended Dose: The initial recommended dose of PROCRIT® in adults is 150 Units/kg SC TIW or 40,000 Units SC Weekly. The initial recommended dose of PROCRIT® in pediatric patients is 600 Units/kg IV weekly. Discontinue PROCRIT® 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 12 g/dL and 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 8 weeks to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed the upper safety limit of 12 g/dL

Weekly Dosing

Starting Dose:	
Adults	40,000 Units SC
Pediatrics	600 Units/kg IV (maximum 40,000 Units)
Reduce Dose by 25% when:	Hemoglobin reaches a level needed to avoid transfusion or increases > 1 g/dL in any 2-weeks
Withhold Dose if:	Hemoglobin exceeds 12 g/dL and restart at 25% below the previous dose when the hemoglobin approaches a level where transfusions may be required
Increase Dose if: For Adults: 60,000 Units SC Weekly For Pediatrics: 900 Units/kg IV (maximum 60,000 Units) if:	Response is not satisfactory (no increase in hemoglobin by ≥1g/dL after 4 weeks of therapy, in the absence of a RBC transfusion) to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed the upper safety limit of 12 g/dL

Surgery Patients

Prior to initiating treatment with PROCRIT® a hemoglobin should be obtained to establish that it is > 10 to ≤ 13 g/dL.[17] The recommended dose of PROCRIT® is 300 Units/kg/day subcutaneously for 10 days before surgery, on the day of surgery, and for 4 days after surgery.

An alternate dose schedule is 600 Units/kg PROCRIT® subcutaneously in once weekly doses (21, 14, and 7 days before surgery) plus a fourth dose on the day of surgery.[18]

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

PREPARATION AND ADMINISTRATION OF PROCRIT®

1. Do not shake. It is not necessary to shake PROCRIT®. Prolonged vigorous shaking may denature any glycoprotein, rendering it biologically inactive.
2. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.
3. Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from the vial containing PROCRIT®, and wipe the septum with a disinfectant. Insert the needle into the vial, and withdraw into the syringe an appropriate volume of solution.
4. **Single-dose**: 1 mL vial contains no preservative. Use one dose per vial; do not re-enter the vial. Discard unused portions.

   Multidose: 1 mL and 2 mL vials contain preservative. Store at 2° to 8°C after initial entry and between doses. Discard 21 days after initial entry.
5. Do not dilute or administer in conjunction with other drug solutions. However, at the time of SC administration, preservative-free PROCRIT® from single-use vials may be admixed in a syringe with bacteriostatic 0.9% sodium chloride injection, USP, with benzyl alcohol 0.9% (bacteriostatic saline) at a 1:1 ratio using aseptic technique. The benzyl alcohol in the bacteriostatic saline acts as a local anesthetic which may ameliorate SC injection site discomfort. Admixing is not necessary when using the multidose vials of PROCRIT® containing benzyl alcohol.

HOW SUPPLIED

PROCRIT®, containing Epoetin alfa, is available in vials containing color coded labels and caps. Each dosage form is supplied in the following packages:

1 mL **Single-Dose, Preservative-free** Solution
Cartons containing six (6) **single-dose** vials:
- 2000 Units/mL (NDC 59676-302-01) (Purple)
- 3000 Units/mL (NDC 59676-303-01) (Magenta)
- 4000 Units/mL (NDC 59676-304-01) (Green)
- 10,000 Units/mL (NDC 59676-310-01) (Red)

Cartons containing four (4) **single-dose** vials:
- 40,000 Units/mL (NDC 59676-340-01) (Orange)

Trays containing twenty-five (25) **single-dose** vials:
- 2000 Units/mL (NDC 59676-302-02) (Purple)
- 3000 Units/mL (NDC 59676-303-02) (Magenta)
- 4000 Units/mL (NDC 59676-304-02) (Green)
- 10,000 Units/mL (NDC 59676-310-02) (Red)

2 mL **Multidose, Preserved** Solution
Cartons containing four (4) **multidose** vials:
- 10,000 Units/mL (NDC 59676-312-04) (Blue)

Cartons containing six (6) **multidose** vials:
- 10,000 Units/mL (NDC 59676-312-01) (Blue)

1 mL **Multidose, Preserved** Solution
Cartons containing four (4) **multidose** vials:
- 20,000 Units/mL (NDC 59676-320-04) (Lime)

Cartons containing six (6) **multidose** vials:
- 20,000 Units/mL (NDC 59676-320-01) (Lime)

STORAGE

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

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Appendix 2. Effect of Epoetin Alfa Treatment on Symptoms of Anemia in Patients Receiving Cancer Chemotherapy (Summary of Results From 5 Studies)

Study/Tumor Type	Epoetin Alfa Dose Regimen	Treatment Groups	Measures	Results	General Comments
Case et.al, 1993/Varied	150 IU/kg SC TIW x 12 weeks	Non-cisplatin or Cisplatin + EPO (n=63) or placebo (n=61)	LASA-Energy, Daily Activities and Overall QOL	ESA-treated patients had significant improvements in Energy and Daily Activities (P<0.05), and Overall QOL (P=0.083) as compared to baseline values	No intergroup comparisons between EPO-treated and placebo groups conducted
Littlewood et.al. 1999/Varied	150 IU/kg SC TIW x 6 cycles + 4 wk post-CT	Nonplatinum + EPO (n=238) or placebo (n=111)	LASA Energy, Daily Activities, Overall QOL, FACT-G, FACT-F, FACT-An, SF-36	ESA-treated patients had significant improvements in LASA Energy P<0.001, Daily Activities P<0.01, Overall QOL P=0.01, FACT-G P<0.05, FACT F P<0.01, FACT-An P<0.01, SF-36 NS	Adjustments for covariates not included.
Chang et.al./Breast	40K SC QW x 16 weeks (QOL at 12 weeks)	Nonplatinum+ EPO 40K QW (n=168), or SOC (n=170)	FACT-An, FACT-F, LASA Energy, Daily Activities, Overall QOL	ESA-treated patients had significant improvements in FACT-An and FACT-F P<.0001; LASA Energy P<.014, Daily Activities P<.01, Overall QOL P<.001	
Thatcher et.al./SCLC	150 IU/kg SC TIW X 6 cycles or 300 IU/kg SC TIW x 6 cycles	Platinum or Nonplatinum+EPO 150 IU TIW (n=42),EPO 300 TIW (n=44), or SOC (n=44)	LASA Energy, Daily Activities, Overall QOL, WHO Performance Score	Significant improvements in overall QOL P<0.05 for EPO 150 IU/kg group. All others NS	Open label design
Witzig et.al./ Varied	40K SC QW x 16 weeks	Platinum or Nonplatinum+ EPO (n=154) or placebo (n=151)	LASA Overall QOL, FACT-An, Symptom Distress Scale	ESA-treated patients had significant improvements in LASA Overall QOL P=0.27, FACT-An P=0.18, SDS NS	QOL higher in placebo group at baseline. Effect of increased transfusion rate in placebo group on Hb could have masked true QOL differences between groups.

CT=chemotherapy; EPO=epoetin alfa; FACT= Functional Assessment of Cancer Therapy; FACT-AN = FACT-anemia; FACT-F=FACT=fatigue; FACT-G= FACT-general; Hb=hemoglobin; LASA=linear analog self-assessment; NS=not significant; SC=subcutaneous; SOC=standard of care; QOL=quality of life; QW=once weekly SCLC=small-cell lung cancer; SDS=Symptom Distress Scale; SF-36; TIW=3 times weekly; 40K=40,000 IU

Appendix 3. European Summary of Product Characterstics

Excerpts from the European Summary of Product Characteristics (SPC) for Aranesp and Eprex are below.

Example 1: Aranesp 10 micrograms solution for injection in a pre-filled syringe.

Complete SPCs may be viewed at
http://medicines.org.uk/searchresult.aspx?search=aranesp

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Cancer patients receiving chemotherapy

In a prospective, randomised double-blind, placebo-controlled study conducted in 344 anaemic patients with lymphoproliferative malignancies receiving chemotherapy there was a significant reduction in transfusion requirements and an improvement in haemoglobin response ($p < 0.001$). Improvement in fatigue, as measured by the Functional Assessment of Cancer Therapy-fatigue (FACT-fatigue) scale, was also observed.

Example 2: EPREX, ERYPO 2000 IU/ml, solution for injection in pre-filled syringe.

Complete SPCs may be viewed at
http://www.medicines.org.uk/searchresult.aspx?search=eprex

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

In a prospective, randomised, double-blind, placebo-controlled trial conducted in 375 anaemic patients with various non-myeloid malignancies receiving non-platinum chemotherapy, there was a significant reduction of anaemia-related sequelae (eg, fatigue, decreased energy, and activity reduction), as measured by the following instruments and scales: Functional Assessment of Cancer Therapy-Anaemia (FACT-An) general scale, FACT-An fatigue scale, and Cancer Linear Analogue Scale (CLAS). Two other smaller, randomised, placebo-controlled trials failed to show a significant improvement in quality of life parameters on the EORTC-QLQ-C30 scale or CLAS

Appendix 4. US Patient Package Insert

AMGEN®

Aranesp®
(darbepoetin alfa)

Patient Information
Aranesp® (Air-uh-nesp)
darbepoetin alfa
Single-dose Vial/Single-dose Prefilled Syringe (SingleJect®)

This patient package insert contains information and directions for patients (and their caregivers) whose doctor has determined that they may receive injections of Aranesp® (Air-uh-nesp) at home. Please read it carefully. This patient package insert does not include all information about Aranesp® and does not replace talking with your doctor. You should discuss any questions about treatment with Aranesp® with your doctor. Only your doctor can prescribe Aranesp® and determine if it is right for you.

What is the most important information I should know about Aranesp®?

Aranesp® can cause serious side effects:

Chronic kidney failure patients:

- If your hemoglobin is kept too high, you have an increased chance of heart attack, stroke, heart failure, blood clots, and death. Your doctor should try to keep your hemoglobin between 10 and 12 g/dL.

Cancer patients:

- You may have an increased chance of dying sooner or your tumor (cancer) may grow faster if you take this drug.
- Your doctor should use the lowest dose of Aranesp® needed to help you avoid red blood cell transfusions.
- Once you have completed your chemotherapy course, Aranesp® treatment should be stopped.

All patients:

- Aranesp® treatment increases your chance of a blood clot. If you are scheduled for surgery, your doctor may prescribe a blood thinner to prevent blood clots.
- Blood clots can form at your vascular access if you are receiving hemodialysis. Call your doctor or dialysis center if you think your access is blocked.
- Blood clots can form in blood vessels (veins) in your leg (venous thrombosis). Blood clots may move from the legs to the lungs and block the blood circulation in the lungs (pulmonary embolus).

Call your doctor right away if you experience any of the following symptoms of a blood clot, while taking Aranesp®:

- chest pain
- shortness of breath
- pain in the legs with or without swelling

You will be asked to have blood tests that will check the number of red blood cells your body is producing. The blood tests will see if Aranesp® is working and if your hemoglobin level is getting too high. Your doctor may refer to the results of your blood tests as hemoglobin and hematocrit. The amount of time it takes to reach the red blood cell level that is right for you, and the dose of Aranesp® needed to make the red blood cell level rise, is different for each person. You may need Aranesp® dose adjustments before you reach your correct dose of Aranesp® and the correct dose may change over time. It is important to keep all appointments for blood tests to allow your doctor to adjust the dosage of Aranesp® as needed.

Please also read **"What are the possible side effects of Aranesp®?"** below.

What is Aranesp®?

Aranesp® is a man-made form of the protein human erythropoietin (ee-rith-row-po-eh-tin). Aranesp® works by stimulating your bone marrow to make red blood cells. After two to six weeks of treatment, your red blood cell counts may increase.

Aranesp® may be used to treat your anemia (a lower than normal number of red blood cells) if it is caused by:

- chronic kidney failure (you may or may not be on dialysis)
- chemotherapy used to treat cancer

Aranesp® does not improve symptoms of anemia, quality of life, or patient well-being for patients with cancer.

Before receiving Aranesp®, you should talk with your doctor about the benefits and risks of Aranesp®.

Who <u>should not take</u> Aranesp®?

You should not take Aranesp® if you have:

- High blood pressure that is not controlled (uncontrolled hypertension).
- Antibodies to Aranesp® or other erythropoietins.

Talk to your doctor if you are not sure if you have these conditions or if you have any questions about this information.

What should I tell my doctor before taking Aranesp®?

Tell your doctor about all your health conditions and all the medicines you take, including prescription and over-the-counter medicines, vitamins, supplements, and herbals. Be sure to tell your doctor if you have:

- Heart disease
- High blood pressure
- Any history of seizures or strokes
- Blood disorders (such as sickle cell anemia, blood clotting disorders)

Tell your doctor if you are:

- Pregnant or nursing
- Planning to become pregnant

Aranesp® has not been studied in pregnant women and its effects on developing babies are not known. It is also not known if Aranesp® can pass into human breast milk.

Talk to your doctor if you are not sure if you have these conditions or if you have any questions about this information.

Your doctor may monitor your blood pressure and the amount of iron in your blood before you start Aranesp® and while you are taking Aranesp®. You or your caregiver may also be asked to monitor your blood pressure every day and to report any changes. When the number of red blood cells increases, your blood pressure may also increase, so your doctor may prescribe new or more blood pressure medicine. You may be asked to have certain blood tests, such as hemoglobin, hematocrit or blood iron levels. Also, your doctor may prescribe iron for you to take. Follow your doctor's orders.

What are other possible side effects of Aranesp®?

Aranesp® may cause serious side effects. See **"What is the most important information I should know about Aranesp®?"**

Other side effects of Aranesp® include:

- Increased blood pressure; your doctor or caregiver may monitor your blood pressure more frequently.
- Infections
- Cough
- Chest pain
- Antibodies against Aranesp® that can block or reduce your body's ability to make red blood cells. If you experience unusual tiredness and lack of energy, **call your doctor**.
- Redness, swelling, pain, or itching at the site of injection. If you notice any signs of redness, swelling, or itching at the site of injection, talk to your doctor.
- Serious allergic reactions. These reactions can cause a rash over the whole body, shortness of breath, wheezing, a drop in blood pressure, swelling around the mouth or eyes, fast pulse, or sweating. If at any time a serious allergic reaction occurs, **stop using Aranesp® and call your doctor or emergency medical personnel immediately (for example, call 911)**.

The needle cover on the prefilled syringe contains a derivative of latex. If you know you are allergic to latex, talk to your healthcare provider before using Aranesp®.

The most common side effects you may have when taking Aranesp® are:

- Increased blood pressure
- Decreased blood pressure
- Body or muscle aches
- Headache
- Diarrhea
- Shortness of breath
- Swelling in your arms or legs
- Fever
- Nausea or vomiting
- Infections
- Chest pain

Some side effects are more common depending on the reasons for which you are taking Aranesp®. Talk to your doctor for more information about side effects. Make sure to report any side effects to your doctor.

Aranesp® has other side effects that are not listed here. For a complete list, talk to your doctor.

Call your doctor right away if:

- You take more than the amount prescribed.
- You are currently taking Aranesp® and experience any of these symptoms, which may be a sign of a serious problem:
  - Unusual tiredness and lack of energy
  - Redness, swelling, pain, or itching at the site of injection and spreading rash over the whole body, shortness of breath, wheezing, a drop in blood pressure, swelling around the mouth or eyes, fast pulse, or sweating
  - Convulsion, confusion, dizziness, loss of consciousness
  - Increased blood pressure, chest pain, irregular heartbeats
  - Stroke, chest pain, shortness of breath, or pain with or without swelling in the legs
  - Blood clots in your hemodialysis vascular access port

What important information do I need to know about taking Aranesp® at home?

After your doctor has determined that you can safely use Aranesp® at home, you or your caregiver will receive instructions on how much Aranesp® to use, how to inject it, how often it should be injected, and how to dispose of the unused portions of each vial or prefilled syringe. Your doctor will decide whether to use Aranesp® in vials or prefilled syringes. Do not change the way you use Aranesp® (including the dose of Aranesp®) without consulting your doctor. You should ask your doctor what to do if you miss a dose of Aranesp®. **You should always follow your doctor's instructions.**

Be sure to change the site for each injection to avoid soreness at any one site. Occasionally a problem may develop at the injection site. If there is a lump, swelling, or bruising at the injection site that does not go away, talk to your doctor.

If you have a hemodialysis vascular access, continue to check the access to make sure it is working. Call your doctor or dialysis center right away if you have any problems or questions.

How should I store Aranesp®?

Aranesp® should be kept in its original carton to protect it from light, and stored in the refrigerator at 2° to 8°C (36° to 46°F). Do not place Aranesp® in the freezer. Do not use a vial or prefilled syringe of Aranesp® that has been frozen, left in light, or improperly refrigerated. It is important that Aranesp® be stored and used as stated in these instructions. Contact your healthcare provider with any questions about storage.

When traveling, transport Aranesp® in its original carton in an insulated container with a coolant such as blue ice. To avoid freezing, make sure the Aranesp® vial or prefilled syringe does not touch the coolant. Once you arrive, your Aranesp® should be placed in a refrigerator as soon as possible.

How do I take Aranesp®?

When you receive your Aranesp®, always check to see that:

- The name Aranesp® appears on the package and vial or prefilled syringe label.
- The expiration date on the vial or prefilled syringe label has not passed. **You should not use a vial or prefilled syringe after the date on the label.**
- The strength of the Aranesp® vial or prefilled syringe (number of micrograms [mcg] in the colored square on the package and on the vial or prefilled syringe label) is the same as the doctor prescribed.
- The Aranesp® liquid in the vial or prefilled syringe is clear and colorless. Do not use Aranesp® if the liquid in the vial or prefilled syringe appears discolored or cloudy or if the liquid appears to contain lumps, flakes, or particles.

- The Aranesp® vial has a color cap on the top of the vial. Do not use a vial of Aranesp® if the color cap on the top of the vial has been removed or is missing.
- Do not use Aranesp® in a prefilled syringe if the grey cover on the needle is off, or the needle guard (yellow sleeve on the syringe) has been activated (pulled to extend over the needle). If you are using a vial of Aranesp®, only use the type of disposable syringe that your doctor prescribes.

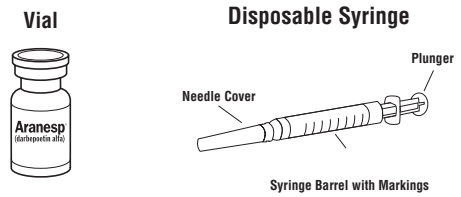
The doctor or nurse will give you instructions on how to measure your dose of Aranesp®. This dose will be measured in milliliters. You should only use a syringe that is marked in tenths of milliliters, or mL (for example, 0.2 mL). The doctor or nurse may refer to an "mL" as a "cc" (1 mL = 1 cc). Using an unmarked syringe can lead to a mistake in the dose. If you do not use the correct syringe, you could inject too much or too little Aranesp®.

Only use disposable syringes and needles. Use the syringes and needles only once and dispose of them as instructed by your healthcare provider.

IMPORTANT: TO HELP AVOID POSSIBLE INFECTION, FOLLOW THESE INSTRUCTIONS.

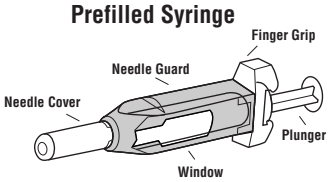
Setting up for an injection

1. Find a clean, flat work surface such as a table.
2. If you are using a vial, remove a vial of Aranesp® from the refrigerator. If you are using a prefilled syringe, tear off one syringe (in wrapper) from the strip and place the others back in the refrigerator. Keep the syringe in its wrapper until you are ready to prepare your dose. Do not freeze Aranesp® or use a vial or prefilled syringe that has been frozen. Do not shake Aranesp® or leave vials or syringes exposed to bright light. Vigorous shaking or exposure to light may denature Aranesp® causing it to become biologically inactive.
3. Remove the vial or prefilled syringe of Aranesp® from its carton and place it on your flat work surface. Allow it to reach room temperature. This should take about 30 minutes. During this time, cover the vial or prefilled syringe to protect the solution from light.
4. You should use a vial or prefilled syringe only once. Do not put the needle through the rubber stopper more than once. DO NOT SHAKE THE VIAL OR PREFILLED SYRINGE. Shaking may damage Aranesp®. If the Aranesp® vial or prefilled syringe has been shaken vigorously, the solution may appear foamy and it should not be used.
5. Assemble the supplies you will need for an injection:
   - Aranesp® vial and the correct disposable syringe and needle



OR

   - Aranesp® prefilled syringe with a transparent (clear) yellow plastic needle guard attached



   - Two alcohol swabs and one cotton ball or gauze. Open one alcohol wipe if you are using a prefilled syringe. Open two alcohol wipes if you are using a vial and disposable syringe.

   - Puncture-proof disposal container

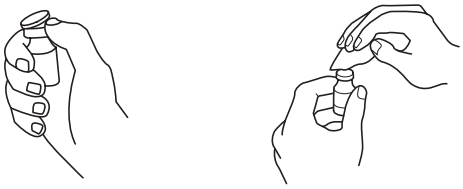
6. Wash your hands with soap and warm water.

How to prepare the dose of Aranesp®

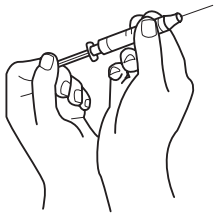
If you are using Aranesp® in a vial, follow the instructions in Section A. If you are using Aranesp® in a prefilled syringe, follow the instructions in Section B.

Section A. Preparing the dose of Aranesp® using a vial and disposable syringe

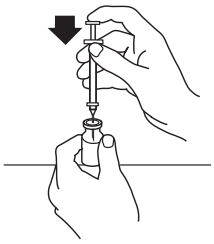
1. Take the color cap off the vial. Clean the rubber stopper with one alcohol swab.



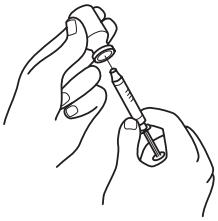
2. Check the package containing the syringe. If the package has been opened or damaged, do not use that syringe. You should dispose of that syringe in the puncture-proof disposal container. If the syringe package is undamaged, open the package and remove the syringe.
3. Pull the needle cover straight off the syringe. Then, pull back on the plunger to draw air into the syringe. The amount of air drawn into the syringe should be the same amount (mL or cc) as the dose of Aranesp® that your doctor prescribed.



4. Keep the vial on your flat work surface and insert the needle straight down through the rubber stopper.
5. Push the plunger of the syringe down to inject the air from the syringe into the vial of Aranesp®.



6. Keeping the needle inside the vial, turn the vial upside down. Make sure that the tip of the needle is in the Aranesp® liquid.



7. Keeping the vial upside down, slowly pull back on the plunger to fill the syringe with Aranesp® liquid to the number (mL or cc) that matches the dose your doctor prescribed.
8. Keeping the needle in the vial, check for air bubbles in the syringe. If there are air bubbles, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe. Then slowly push the plunger up to force the air bubbles out of the syringe. Keep the tip of the needle in the liquid and once again pull the plunger back to the number on the syringe that matches your dose. Check again for air bubbles. The air in the syringe will not hurt you, but too large an air bubble can reduce your dose of Aranesp®. If there are still air bubbles, repeat the steps above to remove them.
9. Check again to make sure that you have the correct dose in the syringe. It is important that you use the exact dose prescribed by your doctor.
10. Lay the vial on its side with the needle still in it until after you have selected and prepared a site for injection. This will keep the needle from touching anything before you use it.

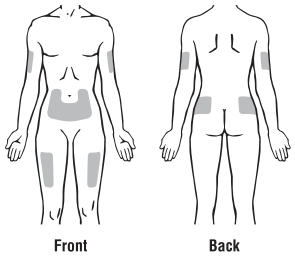
Go directly to the section "Selecting and preparing the injection site."

Section B. Preparing the dose of Aranesp® using a prefilled syringe

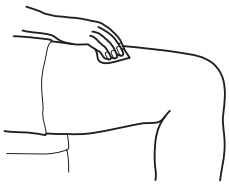
1. Open the package and remove the syringe from the tray. Check to see that the needle cover is on and the yellow needle guard is covering the barrel of the syringe. If the needle guard is covering the needle, then it has already been activated. DO NOT use that syringe. Dispose of that syringe in the puncture-proof disposal container. Use a new syringe. DO NOT slide the needle guard over the needle cover before injection. This will "activate" or lock the needle guard.
2. Hold the syringe with the needle pointing up to prevent the Aranesp® from leaking out of the needle. Carefully pull the needle cover straight off.
3. Still holding the syringe up, slowly push the plunger to the line on the syringe that matches the dose your doctor has prescribed.
4. Check the syringe for air bubbles. If there are air bubbles, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe. Slowly push the plunger up to force the air bubbles out of the syringe.
5. Check again to make sure that you have the correct dose in the syringe. It is important that you use the exact dose prescribed by your doctor.
6. When you put the syringe down on your working surface, be careful not to allow the needle to touch anything.

Selecting and preparing the injection site

1. Choose an injection site. Four recommended injection sites for Aranesp® include:
   - The outer area of the upper arms
   - The abdomen (except for the two-inch area around the navel)
   - The front of the middle thighs
   - The upper outer areas of the buttocks



   Choose a new site each time you inject Aranesp®. Choosing a new site can help avoid soreness at any one site. Do not inject Aranesp® into an area that is tender, red, bruised, hard, or that has scars or stretch marks.
2. Clean the injection site with a new alcohol swab.

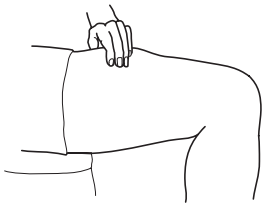


Injecting the dose of Aranesp® from a vial or prefilled syringe

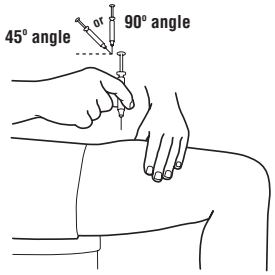
For patients not on hemodialysis:

1. Hold the syringe in the hand that you will use to inject Aranesp®. Use the other hand to pinch a fold of skin at the cleaned injection site.

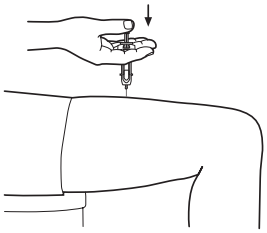
Note: If using a prefilled syringe with a needle guard, hold the syringe barrel through the two needle guard windows when giving the injection.



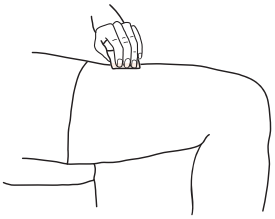
2. Holding the syringe like a pencil, use a quick "dart like" motion to insert the needle either straight up and down (90 degree angle) or at a slight angle (45 degrees) into the skin.



3. After the needle is inserted, let go of the skin. Pull the plunger back slightly. If no blood appears, slowly push the plunger all the way down, until all the Aranesp® is injected. If blood comes into the syringe, do not inject Aranesp® because the needle has entered a blood vessel. Withdraw the syringe and discard it in the puncture-proof disposal container. Repeat the steps to choose and clean a new injection site and prepare a new syringe. Remember to check again for blood before injecting Aranesp®.



4. When the syringe is empty, pull the needle out of the skin and place a cotton ball or gauze over the injection site and press for several seconds.



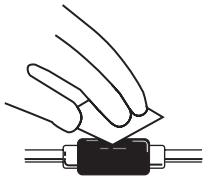
5. You should ONLY use a disposable syringe and Aranesp® vial or prefilled syringe once. You should discard the disposable syringe and vial or prefilled syringe with any remaining Aranesp®.

If a prefilled syringe was used, go directly to the section "Activation of the needle guard on used prefilled syringes."

If a disposable syringe was used with a vial of Aranesp®, go directly to the section "Disposal of syringes and needles."

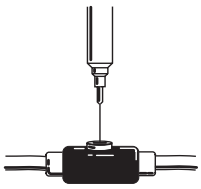
For patients on hemodialysis:

1. Clean the venous port of the hemodialysis tubing with a new alcohol swab.

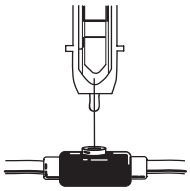


2. Insert the needle of the syringe into the cleaned venous port and push the plunger all the way down to inject all the Aranesp®.

Using disposable syringe



Using prefilled syringe with needle guard

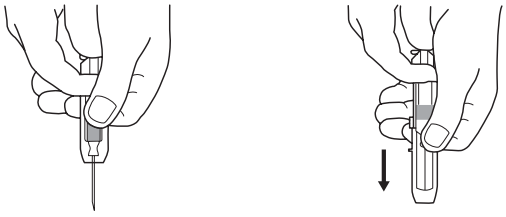


Remove the syringe from the venous port.

If a disposable syringe was used with a vial of Aranesp®, go directly to the section "Disposal of syringes and needles."

Activation of the needle guard on used prefilled syringes

1. After injecting Aranesp® from the prefilled syringe, do not recap the needle. Keep your hands behind the needle at all times. To activate the needle guard, hold the finger grip of the syringe with one hand and grasp the needle guard with your free hand, sliding it completely over the needle until the needle guard clicks into place. **NOTE: If an audible click is not heard, the needle guard may not be completely activated.**



Disposal of syringes and needles

Dispose of the syringe and needle or the syringe with activated needle guard as instructed by your healthcare provider, or by following these steps:

- Do not throw the needle or syringe in the household trash or recycle.
- DO NOT put the needle cover back on the needle. Place the used needle, needle cover, and syringe in a hard plastic disposal container with a screw-on cap or a metal container with a plastic lid, such as a coffee can, labeled "used syringes." If a metal container is used, cut a small hole in the plastic lid and tape the lid to the metal container. If a hard plastic container is used, always screw the cap on tightly after each use.
- Do not use glass or clear plastic containers.
- When the container is full, tape around the cap or lid to make sure the cap or lid does not come off.
- **Always** keep the container out of the reach of children.
- You should always check first with your healthcare provider for instructions on how to properly dispose of a filled disposal container. There may be special state and local laws for disposing of used needles and syringes. **Do not throw the disposal container in household trash. Do not recycle.**

General Information about Aranesp®

Doctors can prescribe medicines for conditions that are not in this leaflet. Use Aranesp® only for what your doctor prescribed. Do not give it to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet gives the most important information about Aranesp®. For more information, talk with your doctor or healthcare provider. You can also access more information at the following website: www.aranesp.com.

Active ingredient: darbepoetin alfa

Inactive ingredients: polysorbate solution or albumin solution

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AMGEN®

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v11 – Issue Date: 11/2007

Patient Information
PROCRIT® *(PRO' – KRIT)*
Epoetin Alfa
For Injection

This patient package insert contains information and directions for patients (and their caregivers) whose doctor has determined that they may receive injections of PROCRIT® *(PRO' – KRIT)* at home. Please read it carefully. This patient package insert does not include all information about PROCRIT® and does not replace talking with your doctor. You should discuss any questions about treatment with PROCRIT® with your doctor. Only your doctor can prescribe PROCRIT® and determine if it is right for you.

What is the most important information I should know about PROCRIT®?

PROCRIT® can cause serious side effects:

Chronic kidney failure patients:

- If your hemoglobin is kept too high, you have an increased chance of heart attack, stroke, heart failure, blood clots, and death. Your doctor should try to keep your hemoglobin between 10 and 12 g/dL.

Cancer patients:

- You may have an increased chance of dying sooner or your tumor (cancer) may grow faster if you take this drug.
- Your doctor should use the lowest dose of PROCRIT® needed to help you avoid red blood cell transfusions.
- Once you have completed your chemotherapy course, PROCRIT® treatment should be stopped.

All patients:

- PROCRIT® treatment increases your chance of a blood clot. If you are scheduled for surgery, your doctor may prescribe a blood thinner to prevent blood clots.
- Blood clots can form at your vascular access if you are receiving hemodialysis. Call your doctor or dialysis center if you think your access is blocked.
- Blood clots can form in blood vessels (veins) in your leg (venous thrombosis). Blood clots may move from the legs to the lungs and block the blood circulation in the lungs (pulmonary embolus).

Call your doctor right away if you experience any of the following symptoms of a blood clot, while taking PROCRIT®:

- chest pain
- shortness of breath
- pain in the legs with or without swelling

You will be asked to have blood tests that will check the number of red blood cells your body is producing. The blood tests will see if PROCRIT® is working and if your hemoglobin level is getting too high. Your doctor may refer to the results of your blood tests as hemoglobin and hematocrit. The amount of time it takes to reach the red blood cell level that is right for you, and the dose of PROCRIT® needed to make the red blood cell level rise, is different for each person. You may need PROCRIT® dose adjustments before you reach your correct dose of PROCRIT® and the correct dose may change over time. It is important to keep all appointments for blood tests to allow your doctor to adjust the dosage of PROCRIT® as needed.

Please also read **'What are the possible side effects of PROCRIT®?'** below.

What is PROCRIT®?

PROCRIT® is a man-made form of the protein human erythropoietin (ee-rith-row-po-eh-tin). PROCRIT® works by stimulating your bone marrow to make red blood cells. After two to six weeks of treatment, your red blood cell counts may increase.

PROCRIT® may be used to treat your anemia (a lower than normal number of red blood cells) if it is caused by:

- chronic kidney failure (you may or may not be on dialysis)
- chemotherapy used to treat cancer
- a medicine called zidovudine (AZT), used to treat HIV infection

PROCRIT® may be given prior to certain types of operations where the chances of significant blood loss and blood transfusions is high, in order to reduce the need for blood transfusions during and after surgery.

PROCRIT® does not improve symptoms of anemia, quality of life, fatigue, or patient well-being for patients with cancer or with HIV.

PROCRIT® increases hemoglobin levels and improves exercise tolerance and physical functioning in chronic kidney failure patients on dialysis.

Before receiving PROCRIT®, you should talk with your doctor about the benefits and risks of PROCRIT®.

Who <u>should not take</u> PROCRIT®?

You should not take PROCRIT® if you have:

- High blood pressure that is not controlled (uncontrolled hypertension).
- Antibodies to PROCRIT® or other erythropoietins.

Talk to your doctor if you are not sure if you have these conditions or if you have any questions about this information.

What should I tell my doctor before taking PROCRIT®?

Tell your doctor about all your health conditions and all the medicines you take including prescription and over-the-counter medicines, vitamins, supplements, and herbals. Be sure to tell your doctor if you have:

- Heart disease
- High blood pressure
- Any history of seizures or strokes
- Blood disorders (such as sickle cell anemia, blood clotting disorders)

Tell your doctor if you are:

- Pregnant or nursing
- Planning to become pregnant

PROCRIT® has not been studied in pregnant women and its effects on developing babies are not known. It is also not known if PROCRIT® can pass into human breast milk.

Talk to your doctor if you are not sure if you have these conditions or if you have any questions about this information.

Your doctor may monitor your blood pressure and the amount of iron in your blood before you start PROCRIT® and while you are taking PROCRIT®. You or your caregiver may also be asked to monitor your blood pressure every day and to report any changes. When the number of red blood cells increases, your blood pressure may also increase, so your doctor may prescribe new or more blood pressure medicine. You may be asked to have certain blood tests, such as hemoglobin, hematocrit or blood iron levels. Also, your doctor may prescribe iron for you to take. Follow your doctor's orders.

What are other possible side effects of PROCRIT®?

PROCRIT® may cause serious side effects. See **'What is the most important information I should know about PROCRIT®?'**

Other side effects of PROCRIT® include:

- Increased blood pressure; your doctor or caregiver may monitor your blood pressure more frequently.
- Infections
- Cough
- Chest pain
- Antibodies against PROCRIT® that can block or reduce your body's ability to make red blood cells. If you experience unusual tiredness and lack of energy, **call your doctor.**
- Redness, swelling, pain, or itching at the site of injection. If you notice any signs of redness, swelling, or itching at the site of injection, talk to your doctor.
- Serious allergic reactions. These reactions can cause a rash over the whole body, shortness of breath, wheezing, a drop in blood pressure, swelling around the mouth or eyes, fast pulse, or sweating. If at any time a serious allergic reaction occurs, **stop using PROCRIT® and call your doctor or emergency medical personnel immediately (for example, call 911).**

The most common side effects you may have when taking PROCRIT® are:

- Increased blood pressure
- Headache
- Body aches
- Diarrhea
- Nausea
- Vomiting
- Swelling in your legs and arms
- Shortness of breath
- Fever

Some side effects are more common depending on the reasons for which you are taking PROCRIT®. Talk to your doctor for more information about side effects. Make sure to report any side effects to your doctor.

PROCRIT® has other side effects that are not listed here. For a complete list, talk to your doctor.

Call your doctor right away if:

- You take more than the amount prescribed.
- You are currently taking PROCRIT® and experience any of these symptoms which may be a sign of a serious problem.
  - Unusual tiredness and lack of energy
  - Redness, swelling, pain, or itching at the site of injection and spreading rash over the whole body, shortness of breath, wheezing, a drop in blood pressure, swelling around the mouth and or eyes, fast pulse, or sweating
  - Convulsion, confusion, dizziness, loss of consciousness
  - Increased blood pressure, chest pain, irregular heartbeats
  - Stroke, chest pain, shortness of breath, or pain with or without swelling in the legs
  - Blood clots in your hemodialysis vascular access port

How should I take PROCRIT®?

After your doctor has determined that you, as a home dialysis patient, or your caregiver can administer PROCRIT® at home, ***always follow the instructions of your doctor concerning the dose, how to administer and how often to administer PROCRIT®.*** Ask your doctor what to do if you miss a dose of PROCRIT®.

Always keep an extra syringe and needle on hand.

When you receive your PROCRIT® from the dialysis center, doctor's office or pharmacy, always check to see that:

1. The name PROCRIT® appears on the carton and vial label.
2. You will be able to use PROCRIT® before the expiration date stamped on the package.

The PROCRIT® solution in the vial should always be clear and colorless. Do not use PROCRIT® if the contents of the vial appear discolored or cloudy, or if the vial appears to contain lumps, flakes, or particles. If the vial has been shaken vigorously, the solution may appear to be frothy and should not be used. Do not shake the PROCRIT® vial before use.

Always use the correct syringe.

Your doctor has instructed you on how to give yourself the correct dosage of PROCRIT®. This dosage will usually be measured in Units per milliliter or cc's. It is important to use a syringe that is marked in tenths of milliliters (for example, 0.2 mL or cc). Using the wrong syringe can lead to a mistake in your dose, and you may receive too much or too little PROCRIT®. Too little PROCRIT® may not be effective in increasing the number of red blood cells. Too much PROCRIT® may lead to serious problems because too many red blood cells are being produced (a hemoglobin or hematocrit that is too high).

Only use disposable syringes and needles. Use the syringe once and dispose of it as instructed by your doctor.

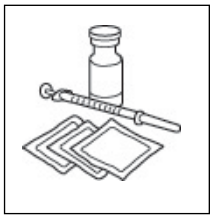
Unless you have been prescribed Multidose PROCRIT® (1 mL or 2 mL vials with a big "M" on the label, each containing a total of 20,000 Units of PROCRIT®), vials of PROCRIT® are for single use. Single use means the vial cannot be used more than once, and any unused portion of the vial should be discarded as directed by your doctor.

However, Multidose PROCRIT® can be used to inject multiple doses as prescribed by your doctor, and may be stored between doses in the refrigerator (but not the freezer) for up to 21 days. Follow your doctor's or dialysis center's instructions on what to do with the used vials.

IMPORTANT: TO HELP AVOID CONTAMINATION AND POSSIBLE INFECTION, FOLLOW THESE INSTRUCTIONS EXACTLY.

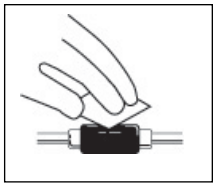
Preparing the dose:

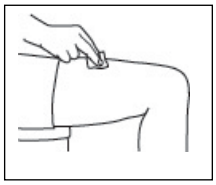
1. Remove the vial of PROCRIT® from the refrigerator and allow it to reach room temperature. Do not leave the vial in direct sunlight. Each PROCRIT® vial is designed to be used only once, unless you are using a Multidose vial. Do not shake PROCRIT®. Assemble the other supplies you will need for your injection (vial; syringe; alcohol antiseptic wipes and a container for disposing the needle).



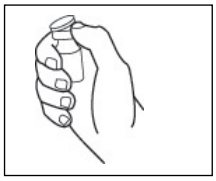
2. Check the date on the PROCRIT® vial to be sure that the drug has not expired.
3. Wash your hands thoroughly with soap and water before preparing the medication.

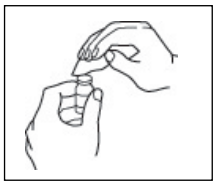
4. Wipe off the venous port of the hemodialysis tubing with an antiseptic swab or cleanse the skin with an antiseptic swab where the injection is to be made. Be careful not to touch the area that has been wiped with the antiseptic.



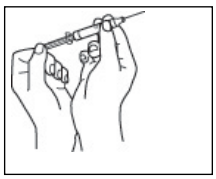


5. Flip off the protective cap but do not remove the gray rubber stopper. Wipe the top of the gray rubber stopper with an antiseptic swab.

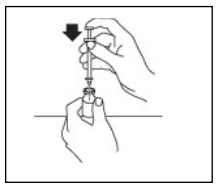




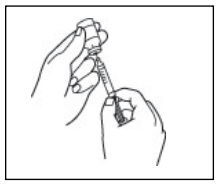
6. Using a syringe and needle that has been ordered by your doctor, carefully remove the needle cover. Then, draw air into the syringe by pulling back on the plunger. The amount of air should be equal to your PROCRIT® dose/volume.



7. With the vial on a flat work surface, put the needle through the gray rubber stopper of the PROCRIT® vial.



8. Push the plunger in to discharge air into the vial. The air injected into the vial will allow PROCRIT® to be easily withdrawn into the syringe.
9. Turn the vial and syringe upside down in one hand. Be sure the tip of the needle is in the PROCRIT® solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw the correct dose of PROCRIT® into the syringe.

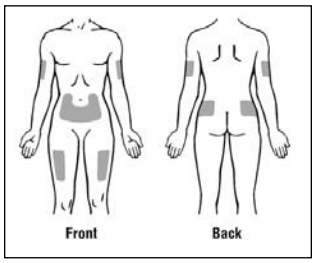


10. Check for air bubbles. A small amount of air is harmless, but too large an air bubble will reduce the PROCRIT® dose. To remove air bubbles, gently tap the syringe with your fingers to move the air bubbles to the top of the syringe, then use the plunger to push the solution and the air back into the vial. Keeping the tip of the needle in the PROCRIT® solution, refill the syringe with your correct dose of PROCRIT®.
11. Double-check that you have the correct dose in the syringe. Remove the needle from the vial. Do not lay the syringe down or allow the needle to touch anything.

Injecting the dose:

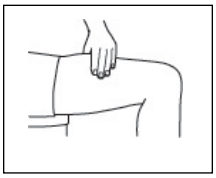
PROCRIT® can be injected into your body using two different ways as described below. Make sure you discuss with your doctor and understand which way is best for you. In patients on hemodialysis, the IV route is recommended.

1. SUBCUTANEOUS Route: PROCRIT® can be injected directly into a layer of fat under your skin. This is called a subcutaneous injection. When receiving subcutaneous injections, always change the site for each injection as directed by your doctor. You may wish to record and track the site where you have injected. Do not inject PROCRIT® into an area that is tender, red, bruised, hard, or has scars or stretch marks. Recommended sites for injection are presented in the figure above, including the outer area of the upper arm, the abdomen (except for the two-inch area around the navel), the front of the middle thighs, and the outer area of the buttocks.

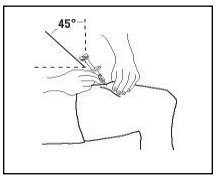


2. INTRAVENOUS Route: PROCRIT® can be injected in your vein through a special access port put in by your doctor. This type of PROCRIT® injection is called an intravenous injection. This route is usually for hemodialysis patients. If you have a dialysis vascular access, to make sure it is working, continue to check your access as your doctor or nurse has shown you. Be sure to let your healthcare provider know right away if you are having any problems, or if you have any questions.

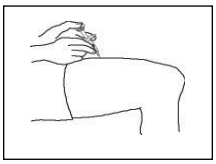
Using the subcutaneous route:



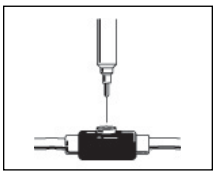
1. With one hand, hold the area surrounding the cleaned skin either by spreading it or by pinching up a large area. Do not touch the cleansed area.
2. Double-check that the correct amount of PROCRIT® is in the syringe.



3. Hold the syringe with the other hand, as you would a pencil, insert the needle into the skin at a 45-degree angle. Let go of the skin and pull the plunger back slightly. If blood comes into the syringe, do not inject PROCRIT®, as the needle has entered a blood vessel; withdraw the syringe, clean a new area, follow steps 1 and 2 and inject at a different site. If blood does not enter the syringe, inject the PROCRIT® by pushing the plunger all the way down.



4. Pull the needle straight out of the skin and immediately press the antiseptic swab over the injection site for several seconds.



Using the intravenous injection route (hemodialysis patients):

1. Insert the needle of the syringe into the clean venous port and inject the PROCRIT®.

How should I dispose of syringes and needles?

Remove the syringe and dispose of the whole unit WITHOUT RECAPPING THE NEEDLE. Use the disposable syringe only once. Dispose of syringes and needles as directed by your doctor, by following these simple steps:

- Place all used needles and syringes in a labeled hard-plastic container with a screw-on-cap, or a labeled metal container with a plastic lid, such as a coffee can properly labeled as to content. If a metal container is used, cut a small hole in the plastic lid and tape the lid to the metal container. If a hard-plastic container is used, always screw the cap on tightly after each use. When the container is full, tape around the cap or lid, and ***dispose of according to your doctor's instructions.***
- Do not use glass or clear plastic containers, or any container that will be recycled or returned to a store.
- ALWAYS store the container out of the reach of children.
- Please check with your doctor, nurse, or pharmacist for other suggestions. There may be special state and local laws that they will discuss with you. DO NOT THROW THE CONTAINER IN YOUR HOUSEHOLD TRASH.

How should I store PROCRIT®?

PROCRIT® should be stored in the refrigerator, but NEVER in the freezer. Do not use a vial of PROCRIT® that has been frozen. Do not leave the vial in direct sunlight. If you have any questions about PROCRIT® that has been exposed to temperature extremes, be sure to check with your doctor. When traveling, transport PROCRIT® in its original carton in an insulated container with a coolant such as blue ice. To avoid freezing, make sure the PROCRIT® vial does not touch the coolant. Once you arrive, your PROCRIT® should be placed in a refrigerator as soon as possible.

General information about PROCRIT®

Doctors can prescribe medicines for conditions that are not in this leaflet. Use PROCRIT® only for what your doctor prescribed. Do not give it to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet gives the most important patient information about PROCRIT®. For more information talk to your doctor or Healthcare provider. You can also visit www.procrit.com or call 1 888 2ASK OBI or 1-888-227-5624.

Active Ingredients: Epoetin alfa

Inactive Ingredients: All formulations include Albumin (human), sodium citrate, sodium chloride, and citric acid in water for injection. In addition, certain formulations may contain: benzyl alcohol, sodium phosphate monobasic monohydrate or sodium phosphate dibasic anhydrate.

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