PRODUCT MONOGRAPH

PrEPREX®

epoetin alfa

Sterile Solution

Single-use pre-filled syringes with PROTECS® needle guard:
1,000 IU/0.5 mL, 2,000 IU/0.5 mL, 3,000 IU/0.3 mL,
4,000 IU/0.4 mL, 5,000 IU/0.5 mL, 6,000 IU/0.6 mL,
8,000 IU/0.8 mL, 10,000 IU/mL,
20,000 IU/0.5 mL,
30,000 IU/0.75 mL, 40,000 IU/mL

Erythropoiesis Regulating Hormone

Janssen Inc.
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Toronto, Ontario
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Date of Preparation:
February 16, 1990

Date of Revision:
October 3, 2017

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Erythropoiesis Regulating Hormone

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	**Dosage Form: Sterile Colourless Solution / Strength**	**Clinically Relevant Nonmedicinal Ingredients**
Polysorbate-80 Containing (Human Serum Albumin [HSA]-free formulation) Intravenous / Subcutaneous	1,000 IU/0.5 mL, 2,000 IU/0.5 mL, 3,000 IU/0.3 mL, 4,000 IU/0.4 mL, 5,000 IU/0.5 mL, 6,000 IU/0.6 mL, 8,000 IU/0.8 mL, 10,000 IU/mL, 20,000 IU/0.5 mL, 30,000 IU/0.75 mL, 40,000 IU/mL	Glycine, polysorbate 80, sodium chloride, sodium phosphate monobasic dihydrate, sodium phosphate dibasic dihydrate, in water for injection.

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. EPREX® (epoetin alfa) is a 165 amino acid glycoprotein manufactured by recombinant DNA technology. 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.

INDICATIONS AND CLINICAL USE

EPREX® (epoetin alfa) 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. EPREX® therapy is not intended for patients who require immediate correction of severe anemia. EPREX® may obviate the need for maintenance transfusions but is not a substitute for emergency transfusion. Blood pressure should be adequately controlled prior to initiation of EPREX® therapy and must be closely monitored and controlled during treatment. EPREX® therapy is not indicated for other specific causes of anemia with established treatments such as iron or folate deficiencies, hemolysis or gastrointestinal bleeding which should be managed appropriately.

Treatment of Anemia of Chronic Renal Failure

Adults: EPREX® therapy is indicated in the treatment of anemia associated with chronic renal failure, including patients on dialysis (end-stage renal disease) and patients not on dialysis (see **DOSAGE AND ADMINISTRATION, CRF PATIENTS**).

Pediatrics: EPREX® is indicated in infants and children from 1 month old up to 16 years of age 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 **WARNINGS AND PRECAUTIONS** and ***Product Monograph Part II***, **CLINICAL TRIALS, CRF PATIENTS, Pediatric Chronic Renal Failure Patients on Dialysis**).

Treatment of Anemia in Zidovudine-Treated/HIV-Infected Patients

EPREX® therapy is indicated for the treatment of transfusion-dependent anemia related to therapy with zidovudine in HIV-infected patients. EPREX® is effective in HIV-infected patients treated with zidovudine, when the endogenous serum erythropoietin level is ≤ 500 mU/mL and when patients are receiving a dose of zidovudine ≤ 4200 mg/week.

Treatment of Anemia Due to Chemotherapy in Patients With Non-Myeloid Malignancies

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

- In patients with a long life expectancy, the decision to administer ESAs should be based on a benefit-risk assessment with the participation of the individual patient. This should take into account the specific clinical context such as (but not limited to) the type of tumor and its stage, the degree of anemia, life expectancy, the environment in which the patient is being treated and known risks of transfusions and ESAs.
- If appropriate, red blood cell transfusion should be the preferred treatment for the management of anemia in patients with a long life expectancy and who are receiving myelosuppressive chemotherapy.

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

Surgery Patients
EPREX® therapy is indicated in the following elective surgery regimens:

Use of EPREX® to Reduce Allogeneic Blood Exposure
EPREX® therapy is indicated to treat patients who are undergoing major elective surgery (including patients who do not wish to or are not eligible to participate in an autologous blood donation (ABD) program) and have a pretreatment hemoglobin of > 100 to ≤ 130 g/L. EPREX® therapy is indicated to reduce allogeneic blood transfusions and hasten erythroid recovery in these patients.

Combined Use of EPREX® and ABD
EPREX® is indicated to facilitate autologous blood collection within a predeposit program and may decrease the risk of receiving allogeneic blood transfusions in patients with hemoglobin of 100-130 g/L who are scheduled for major elective surgery and are expected to require more blood than that which can be obtained through autologous blood collection techniques in the absence of EPREX®.

Geriatrics (> *65* years of age): No data available.

CONTRAINDICATIONS

EPREX® (epoetin alfa) is contraindicated in patients:

- who develop pure red cell aplasia (PRCA) following treatment with any erythropoiesis regulating hormone (see **WARNINGS AND PRECAUTIONS, ALL PATIENTS, Immune**);
- with uncontrolled hypertension;
- with known hypersensitivity to mammalian cell-derived products or any component of the product; (see **DOSAGE FORMS, COMPOSITION AND PACKAGING**);
- who for any reason cannot receive adequate antithrombotic treatment.

The use of EPREX® in patients scheduled for elective surgery and not participating in an autologous blood donation program is contraindicated in patients with severe coronary, peripheral arterial, carotid, or cerebral vascular disease, including patients with recent myocardial infarction or cerebral vascular accident.

Contraindications defined by the guidelines and methods of practice for ABD programs should be respected in patients receiving EPREX®.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

ALL PATIENTS

- To minimize the risks for death, serious adverse cardiovascular reactions and stroke, follow the recommended dosage for each indication for EPREX® and other erythropoiesis stimulating agents (ESAs) (see **WARNINGS AND PRECAUTIONS: Increased Mortality, Serious Adverse Cardiovascular Reactions, Thromboembolic Events and Stroke** and **DOSAGE AND ADMINISTRATION).**
- In surgical patients treated with EPREX® for reduction of allogeneic red blood cell transfusions, adequate antithrombotic prophylaxis, as per current standard of care, is recommended in order to reduce the incidence of deep venous thrombosis.
- Patients with uncontrolled hypertension should not be treated with EPREX®; blood pressure should be controlled adequately before initiation of therapy.
- EPREX® should be used with caution in patients with a history of seizures.
- Antibody-mediated pure red cell aplasia (PRCA) has been reported after months to years of treatment with ESAs.

CHRONIC RENAL FAILURE PATIENTS

- In controlled trials patients experienced greater risks for death, serious adverse cardiovascular reactions and stroke when administered ESAs to target hemoglobin levels of 130 g/L and above. Individualize dosing to achieve and maintain hemoglobin levels within the range of 100 to 115 g/L, not to exceed 120 g/L.

CANCER PATIENTS

- ESAs increased the risks for death and serious adverse cardiovascular reactions and thromboembolic events in some controlled clinical trials.
- ESAs shortened overall survival and/or increased the risk of tumour progression or recurrence in some clinical studies in patients with breast, head and neck, lymphoid, cervical and non-small cell lung cancers when dosed to target a hemoglobin of ≥120 g/L.
- To minimize the above risks, use the lowest dose needed to avoid red blood cell (RBC) transfusions.
- Use ESAs only for treatment of anemia due to concomitant myelosuppressive chemotherapy.
- If appropriate, red blood cell transfusion should be the preferred treatment for the management of anemia in patients with a long life expectancy and who are receiving myelosuppressive chemotherapy.
- Discontinue EPREX® following completion of a chemotherapy course.

ALL PATIENTS

General
In order to improve the traceability of erythropoiesis-stimulating agents (ESAs), the trade name of the administered ESA should be clearly recorded (or stated) in the patient file.

Patients should only be switched from one ESA to another under appropriate supervision.

Carcinogenicity, Mutagenicity
Long-term carcinogenicity studies have not been carried out. Epoetin alfa does not induce bacterial gene mutation (Ames Test), chromosomal aberrations in mammalian cells, micronuclei in mice, or gene mutation at the HGPRT locus.

Cardiovascular
Hypertension
Patients with uncontrolled hypertension should not be treated with EPREX® (epoetin alfa). Blood pressure may rise during EPREX® therapy, often during the early phase of treatment when the hemoglobin is increasing, especially in CRF patients.

For patients who respond to EPREX® therapy with a rapid increase in hemoglobin (e.g., more than 10 g/L in any two-week period), the dose of EPREX® should be reduced because of the possible association of excessive rate of rise of hemoglobin with an exacerbation of hypertension.

All patients on EPREX® should have hematocrit/hemoglobin levels measured at least once a week until a stable level is achieved and periodically thereafter.

In all patients receiving EPREX®, blood pressure should be closely monitored and controlled as necessary. During EPREX® therapy, patients should be advised of the importance of compliance with antihypertensive therapy and dietary restrictions.

It may be necessary to initiate or increase antihypertensive treatment during EPREX® therapy. If blood pressure cannot be controlled, EPREX® should be discontinued until blood pressure control is re-established.

Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care have occurred also during EPREX® treatment in patients with previously normal or low blood pressure. Particular attention should be paid to the development of unusual headaches (such as, a sudden stabbing migraine-like headache) or an increase in headaches as a possible warning signal (see **ADVERSE REACTIONS, ALL PATIENTS, Hypertension**).

Immune
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 EPREX®. This has been reported predominantly in CRF patients receiving EPREX® by

subcutaneous administration. Any patient who develops a sudden loss of response to EPREX®, 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. If anti-erythropoietin antibody-associated anemia is suspected, withhold EPREX® and other erythropoietic proteins. Contact Janssen Inc. at 1-800-567-3331 to perform assays for binding and neutralizing antibodies. EPREX® 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)**.

Increased Mortality, Serious Adverse Cardiovascular Reactions, Thromboembolic Events and Stroke

During hemodialysis, patients treated with EPREX® may require increased anticoagulation with heparin to prevent clotting of the artificial kidney. Clotting of the vascular access (A-V fistula) has occurred at an annualized rate of about 0.25 events per patient-year on EPREX® therapy. Overall, for patients with CRF (whether on dialysis or not), other thrombotic events (e.g., myocardial infarction, cerebrovascular accident, transient ischemic attack) have occurred at an annualized rate of less than 0.04 events per patient-year of EPREX® therapy. Patients with pre-existing vascular disease should be monitored closely.

Patients with CRF experienced greater risks for death, serious adverse cardiovascular reactions and stroke when administered ESAs to target hemoglobin levels of 130 g/L and above in clinical studies. No trial has identified a hemoglobin target level, dose or dosing strategy that does not increase these risks. Patients with CRF and an insufficient hemoglobin response to ESA therapy may be at even greater risk for adverse cardiovascular reactions and mortality than other patients. EPREX® and other ESAs increased the risks for death and for serious adverse cardiovascular reactions and thromboembolic events in controlled clinical trials of patients with cancer. These reactions included myocardial infarction, stroke, congestive heart failure and an increased risk of serious arterial and venous thromboembolic events including hemodialysis vascular access thrombosis. A rate of hemoglobin rise of >10 g/L over 2 weeks may contribute to these risks (see ***Product Monograph Part II,*** **CLINICAL TRIALS, CRF PATIENTS; CANCER PATIENTS**).

CRF patients with hypo-responsiveness to ESAs may be at an increased risk for mortality and adverse cardiovascular reactions. These patients should be evaluated for treatable conditions (see **WARNINGS AND PRECAUTIONS: Lack or Loss of Response** and **DOSAGE AND ADMINISTRATION: CRF PATIENTS**). These risks should be carefully weighed against the benefit to be derived from treatment with ESAs, particularly in cancer patients with increased risk factors of thrombotic vascular events (TVEs), such as patients with a prior history of TVEs (e.g. deep venous thrombosis or pulmonary embolism) (see ***Product Monograph Part II,*** **CLINICAL TRIALS** and **DOSAGE AND ADMINISTRATION, CRF PATIENTS; CANCER PATIENTS RECEIVING CHEMOTHERAPY**).

To minimize the risks for death and serious adverse cardiovascular reactions, EPREX® and other ESAs should follow the recommended dose for each indication. For CRF patients, individualize dosing to achieve and maintain hemoglobin levels within the recommended range of 100-115 g/L. The hemoglobin concentrations should not exceed 120 g/L; the rate of hemoglobin increase should not exceed 10 g/L in any 2-week period. For patients with cancer, use the lowest dose sufficient to avoid blood transfusions (see **DOSAGE AND ADMINISTRATION**).

Hematologic
The safety and efficacy of EPREX® therapy have not been established in patients with underlying hematologic disease (e.g., sickle cell anemia, myelodysplastic syndromes, or hypercoagulable disorders).

Neurologic
Seizures
EPREX® should be used with caution in patients with a history of seizures or medical conditions associated with a predisposition to seizure activity such as CNS infections and brain metastases. Additional close monitoring of all possible risk factors is advisable if the decision is made to use EPREX® to treat such patients.
Given the potential for an increased risk of seizures in CRF patients during the first 90 days of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely, and CRF patients should be cautioned to avoid potentially hazardous activities such as driving or operating heavy machinery during this period.

It is recommended that the dose of EPREX® be decreased if the hemoglobin increase exceeds 10 g/L in any two-week period.

The safety and efficacy of EPREX® therapy have not been established in patients with a known history of a seizure disorder.

Sensitivity/Resistance
The parenteral administration of any biologic product should be attended by appropriate precautions in case allergic or other untoward reactions occur. If an anaphylactoid reaction occurs, EPREX® should be immediately discontinued and appropriate therapy initiated.

Hypersensitivity reactions, including cases of rash, urticaria, anaphylactic reaction, and angioneurotic edema have been reported.

Severe Cutaneous Reactions
Blistering and skin exfoliation reactions including erythema multiforme and Stevens-Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN), have been reported in a small number of patients treated with EPREX®. Discontinue EPREX® therapy immediately if a severe cutaneous reaction, such as SJS/TEN, is suspected.

Lack or Loss of Response
Inadequate response to EPREX® should prompt an investigation for causative factors. If the patient fails to respond or to maintain a response, the following etiologies should be considered and evaluated:

1. Iron deficiency: Virtually all patients will eventually require supplemental iron therapy (see **Monitoring and Laboratory Tests**, **Iron Evaluation**);
2. Underlying infectious, inflammatory, or malignant processes;
3. Occult blood loss;
4. Underlying hematologic diseases (i.e., 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. Inflammatory or traumatic episodes;
10. Pure Red Cell Aplasia (PRCA).

Special Populations

Use in Patients with Known Porphyria:

The initial presentation or exacerbation of porphyria has been observed rarely in EPREX® - treated patients. EPREX® should be used with caution in patients with known porphyria.

Use in Patients with a History of Gout:

Increased serum uric acid (and phosphorus) levels have been observed in both normal volunteers and dialysis independent CRF patients treated with EPREX® who experienced a rapid rate of rise of hemoglobin. This effect may be related to an increased rate of nucleic acid synthesis in the bone marrow. Consequently, EPREX® should be administered with caution to patients with a history of gout.

Hepatic Dysfunction:

The safety of EPREX® has not been established in patients with hepatic dysfunction.

Use in Pregnancy:

Although EPREX® has been shown to have adverse effects in rats when given in doses greater than five times the human dose, it is not known whether it can affect reproduction capacity or cause fetal harm when administered to pregnant women. EPREX® should be given to a pregnant woman only if potential benefit justifies the potential risk to the fetus.

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

Nursing Mothers:

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

In pregnant or lactating surgical patients participating in an autologous blood predonation program, the use of EPREX® is not recommended.

Use in Children:

Pediatric Patients on Dialysis

EPREX® is indicated in infants and children from 1 month old up to 16 years of age 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 ***Product Monograph Part II,*** **CLINICAL TRIALS, CRF PATIENTS, Pediatric Chronic Renal Failure 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 EPREX® in adult CRF patients (see **ADVERSE REACTIONS**). Published literature provides supportive evidence of the safety and effectiveness of EPREX® in pediatric patients on dialysis.

Monitoring and Laboratory Tests

Hematology

All patients receiving EPREX® should have hematocrit/hemoglobin levels measured once a week until hematocrit/hemoglobin has been stabilized, and measured periodically thereafter (see **CHRONIC RENAL FAILURE PATIENTS, Monitoring and Laboratory Tests, Hematology** for additional laboratory monitoring in CRF patients).

There may be a moderate dose-dependent rise in the platelet count, within the normal range, during treatment with EPREX®. This regresses during the course of continued therapy. In addition, thrombocythemia above the normal range has been reported. The platelet count should be regularly monitored during the first eight weeks of therapy.

Iron Evaluation

In most chronic renal failure, cancer, and HIV-infected patients, the serum ferritin concentrations fall concomitantly with the rise in packed cell volume. Therefore, prior to and during EPREX® 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 serum ferritin levels should be at least 100 ng/mL. Supplemental iron, e.g., oral elemental iron or intravenous iron, is recommended to increase and maintain transferrin saturation to levels that will adequately support EPREX®-stimulated erythropoiesis.

All surgery patients being treated with EPREX® should receive adequate iron replacement throughout the course of therapy in order to support erythropoiesis and avoid depletion of iron stores. If possible, iron supplementation should be initiated prior to starting EPREX® therapy to achieve adequate iron stores.

Vitamin B_{12} and Folate Evaluation

Prior to starting EPREX® therapy, the patient's serum vitamin B_{12} and serum folate should be assessed. A deficiency in vitamin B_{12} and/or folate may blunt the response and should be investigated as per standard clinical practice.

CHRONIC RENAL FAILURE (CRF) PATIENTS

General

Hemoglobin levels during treatment with ESAs should not exceed 120 g/L in both men and women. The dose of EPREX® should be reduced as the hemoglobin approaches 120 g/L or increases by more than 10 g/L in any 2-week period. Patients with CRF experienced greater risks for death, serious cardiovascular events and stroke when administered ESAs to target hemoglobin levels of 130 g/L and above. Individualize dosing to achieve and maintain hemoglobin levels within the range of 100 to 115 g/L (see **DOSAGE AND ADMINISTRATION**).

Renal

Dialysis Management

Therapy with EPREX® results in an increase in hemoglobin and a decrease in plasma volume, which could potentially affect dialysis efficiency. In studies to date, the resulting increase in hemoglobin did not appear to adversely affect dialyzer function or the efficiency of high flux hemodialysis. During hemodialysis, chronic renal failure patients treated with EPREX® may require increased anticoagulation with heparin to prevent clotting of the artificial kidney.

Shunt thromboses have occurred in hemodialysis patients, especially in those who have a tendency to hypotension or whose arteriovenous fistulae exhibit complications (e.g., stenoses, aneurisms, etc.). Early shunt revision and thrombosis prophylaxis by administration of acetylsalicylic acid, for example, is recommended in these patients.

Chronic renal failure patients who are marginally dialyzed may require adjustments in their dialysis prescription. As with all patients on dialysis, the serum chemistry values [including blood urea nitrogen (BUN), creatinine, phosphorus, and potassium] in patients treated with EPREX® should be monitored regularly to assure the adequacy of the dialysis prescription.

Diet

As the hemoglobin increases and patients experience an improved sense of well-being and quality of life, the importance of compliance with dietary and dialysis prescriptions should be reinforced. In particular, hyperkalemia is not uncommon in patients with CRF.

Predialysis Management

Blood pressure and hemoglobin should be monitored in predialysis patients no less frequently than for ESRD patients maintained on dialysis. Renal function and fluid and electrolyte balance should be closely monitored, as an improved sense of well-being may obscure the need to initiate dialysis in some patients.

Based on information to date, the use of EPREX® in predialysis patients does not accelerate the rate of progression of renal insufficiency.

Monitoring and Laboratory Tests

Hematology

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of EPREX® before adjusting the dose. The hemoglobin should be determined weekly until it has stabilized in the recommended range and the maintenance dose has been established. After any dose adjustment, the hemoglobin should also be measured weekly for at least 2-6 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 order to avoid reaching the recommended hemoglobin range of 100-115 g/L too rapidly, or exceeding 120 g/L, the guidelines for dose and frequency of dose adjustments (see **DOSAGE AND ADMINISTRATION**) should be followed.

The elevated bleeding time characteristic of chronic renal failure (CRF) decreases toward normal after correction of anemia in patients treated with EPREX®. Reduction of bleeding time also occurs after correction of anemia by transfusion.

Biochemistry

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 patients on dialysis, modest increases were seen in BUN, creatinine, phosphorus, and potassium. In some CRF patients not on dialysis who were treated with EPREX®, 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.

In adult patients with CRF not on dialysis, renal function and fluid and electrolyte balance should be closely monitored, as an improved sense of well-being may obscure the need to initiate dialysis in some patients. In patients with CRF not on dialysis, placebo-controlled studies of the progression of renal dysfunction over periods of greater than one 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 EPREX®, compared with placebo-treated patients. Analysis of the slope of 1/serum creatinine vs. time plots in these patients indicates no significant change in the slope after the initiation of EPREX® therapy.

SURGERY PATIENTS

General

Combined Use of EPREX® and ABD

Warnings and precautions defined by the guidelines and methods of practice for ABD programs should be respected in patients receiving EPREX®.

Use of EPREX® to Reduce Allogeneic Blood Exposure

Thrombotic/Vascular Events

In patients scheduled for major elective orthopedic surgery, thrombotic events can be a risk and this possibility should be carefully weighed against the benefit to be derived from the treatment in this patient group. Patients scheduled for elective surgery should receive adequate antithrombotic prophylaxis as per current standard of care.

An increased incidence of deep vein thrombosis (DVT) was observed in patients receiving EPREX® who were undergoing spinal surgery and not receiving prophylactic anticoagulation. Patients should receive adequate antithrombotic prophylaxis in order to reduce the incidence of DVT (see ***Product Monograph Part II,*** **CLINICAL TRIALS, SURGERY PATIENTS, Use of EPREX® to Reduce Allogeneic Blood Exposure**).

In a randomized, placebo-controlled study of EPREX® in adult patients who were undergoing coronary artery bypass surgery and not participating in an autologous blood donation program,

increased mortality was observed (7 deaths in 126 patients randomized to EPREX® versus no deaths among 56 patients receiving placebo). Among the seven deaths in the EPREX®-treated patients, three were related to intercurrent infectious episodes and four of these deaths occurred during the period of study drug administration. All four deaths were associated with thrombotic events and a causative role for EPREX® cannot be excluded.

Cardiovascular

Rarely, blood pressure may rise in the perioperative period in patients being treated with EPREX®. Therefore, blood pressure should be monitored.

Thrombotic/Vascular Events

Independent of EPREX® treatment, thrombotic and vascular events may occur in surgical patients with underlying cardiovascular disease following repeated phlebotomy. Therefore, routine volume replacement should be performed in such patients in autologous blood donation programs.

CANCER PATIENTS

General

In cancer patients receiving chemotherapy, the 2 to 3 week delay between ESA administration and the appearance of erythropoietin-induced red cells should be taken into account when assessing if epoetin alfa therapy is appropriate (in particular for patients at risk of transfusion).

Increased Mortality and/or Increased Risk of Tumour Progression or Recurrence

ESAs, when administered to target a hemoglobin of > 120 g/L, shortened the time to tumour progression in patients with advanced head and neck cancer receiving radiation therapy. ESAs also shortened survival in patients with metastatic breast cancer and in patients with lymphoid malignancy receiving chemotherapy when administered to target a hemoglobin of ≥ 120 g/L.

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 level of ≥ 120 g/L.

An increased risk of death was observed in a clinical study when ESAs were administered to target hemoglobin of 120 g/L in patients with active malignant disease not being treated with either chemotherapy or radiation therapy. EPREX® is not indicated for use in cancer patients who have anemia that is not associated with chemotherapy (see ***Product Monograph Part II,* CLINICAL TRIALS, CANCER PATIENTS,** Tumour Progression, Increased Mortality and Thromboembolic Events).

In view of the above, where appropriate red blood cell transfusion should be the preferred treatment for the management of anemia in patients with cancer. The decision to administer ESAs should be based on a benefit-risk assessment with the participation of the individual patient. This should take into account the specific clinical context such as (but not limited to) the type of tumor and its stage, the degree of anemia, life-expectancy, the environment in which the patient is being treated, and known risks of transfusion and ESAs.

Neurologic

Seizures

In a placebo-controlled, double-blind trial utilizing once weekly dosing with EPREX®, 1.2% (n = 2/168) of safety-evaluable patients treated with EPREX® and 0% (n = 0/165) of placebo-treated patients had seizures. Seizures in the patients treated with weekly EPREX® occurred in the context of a significant increase in hemoglobin from baseline values but significant increases in blood pressure were not seen. Both patients may have had other CNS pathology which may have been related to the seizures.

ADVERSE REACTIONS

ALL PATIENTS

Hypertension

The most frequent adverse reaction during treatment with EPREX® (epoetin alfa) is a dose-dependent increase in blood pressure or aggravation of existing hypertension. This occurred most commonly in chronic renal failure patients (see **WARNINGS AND PRECAUTIONS**).

Hypertensive crises with encephalopathy and seizures have occurred in isolated patients, including previously normotensive patients.

Thrombotic/Vascular Events

Serious adverse drug reactions include venous and arterial thromboses and embolism (including some with fatal outcomes), such as deep venous thrombosis, arterial thrombosis, pulmonary emboli, aneurysms, retinal thrombosis, clotting of vascular access (A-V fistula) and shunt thrombosis (including dialysis equipment). Additionally, cerebrovascular accidents (including cerebral infarction and cerebral hemorrhage) and transient ischemic attacks have been reported in patients receiving EPREX®.

In clinical studies conducted in surgery patients with a pretreatment hemoglobin of > 100 to ≤ 130 g/L (the recommended population) and not participating in an ABD program, the rate of deep venous thrombosis (DVT) was similar among patients treated with EPREX® and placebo. However, in patients with a pretreatment hemoglobin of >130 g/L, the rate of DVTs was higher in the group treated with EPREX® than in the placebo-treated group, but within the range of that reported in the literature for orthopedic surgery patients (47-74% without anticoagulant therapy and 3-37% with use of anticoagulant therapy).

In a study examining the use of EPREX® in 182 patients scheduled for coronary artery bypass graft surgery, 23% of patients treated with EPREX® and 29% treated with placebo experienced thrombotic/vascular events. There were four deaths among the patients treated with EPREX® that were associated with a thrombotic/vascular event and a causative role of EPREX® cannot be excluded.

Influenza-like Illness

Influenza-like illness including headaches, joint pains, myalgia and pyrexia may occur, especially at the start of treatment.

Hypersensitivity Reactions
Hypersensitivity reactions, including cases of rash (including urticaria), angio-edema and anaphylactic reaction have been reported.

Immune Reactions
In post-marketing reports, very rare cases of pure red cell aplasia (PRCA) have been reported predominantly in chronic renal failure patients after months to years of treatment with recombinant erythropoietins including EPREX®. Most of these reports have been associated with the subcutaneous route of administration. Cases have been rarely reported in patients with hepatitis C treated with interferon and ribavirin, when ESAs are used concomitantly. ESAs are not authorized in the management of anaemia associated with hepatitis C. Neutralizing antibodies to erythropoietins have been reported in most of these patients (see **WARNINGS AND PRECAUTIONS, ALL PATIENTS, Immune**).

Seizures
Seizures have been reported in patients treated with EPREX®.

CRF PATIENTS

Studies analyzed to date indicate that EPREX® is generally well tolerated irrespective of the route of administration. The adverse events reported are frequent sequelae of CRF and are not necessarily attributable to EPREX® therapy. In double-blind, placebo-controlled studies involving 335 patients with CRF (both predialysis and treated with dialysis), the events reported in greater than 5% of patients treated with EPREX® (n=200) during the blinded phase were:

Table 1.1

Adverse Events	EPREX® (n=200)	Placebo (n=135)
Hypertension	24.0%	18.5%
Headache	16.0%	11.9%
Arthralgias	11.0%	5.9%
Nausea	10.5%	8.9%
Edema	9.0%	10.4%
Fatigue	9.0%	14.1%
Diarrhea	8.5%	5.9%
Vomiting	8.0%	5.2%
Chest Pain	7.0%	8.8%
Skin Reaction at Administration Site	7.0%	11.9%
Asthenia	7.0%	11.9%
Dizziness	7.0%	12.6%
Clotted Access	6.8%	2.3%

Pediatric CRF Patients on Dialysis:

EPREX® is generally well tolerated in pediatric dialysis patients. The adverse events reported are typical sequelae for patients on dialysis, and relationship to EPREX® therapy has not been

established. In double-blind clinical studies involving 123 pediatric dialysis patients, only one event, myalgia, occurred with a statistically significant higher frequency in patients treated with EPREX® (20%) than in placebo-treated patients (6%), p=0.03. Adverse events reported in greater than 5% of patients treated with EPREX® were:

Table 1.2

Adverse Events	EPREX® (n=59)	Placebo (n=64)
Hypertension	25.4%	17.2%
Vomiting	22.0%	21.9%
Headache	22.0%	29.7%
Myalgia	20.3%	6.3%
Abdominal Pain	20.3%	25.0%
Access Infection	20.3%	12.5%
Peritonitis	16.9%	14.1%
Fever	13.6%	15.6%
Pruritus	11.9%	3.1%
Upper Respiratory Infection	11.9%	14.1%
Hyperkalemia	11.9%	10.9%
Nausea	11.9%	12.5%
Pharyngitis	10.2%	7.8%
Cough	10.2%	9.4%
Constipation	10.2%	6.3%
Chest Pain	10.2%	3.1%
Access Complication	10.2%	6.3%
Dizziness	8.5%	10.9%
Convulsions	8.5%	6.3%
Hypotension	8.5%	14.1%
Influenza-like Symptoms	8.5%	6.3%
Access Catheter Clotted	8.5%	1.6%
Thrombosis Vascular Access	6.8%	1.6%
Pneumonia	6.8%	3.1%
Increased Nonprotein Nitrogen	5.1%	0.0%
Arthralgia	5.1%	3.1%
Hyperphosphatemia	5.1%	1.6%
Otitis	5.1%	1.6%
Malaise	5.1%	7.8%

Adverse events reported at > 5% in pediatric patients (Table 1.2) that were not previously reported in adult patients include: myalgia, abdominal pain, access infection, peritonitis, fever, pruritus, upper respiratory infection, hyperkalemia, pharyngitis, cough, constipation, access complication, convulsions, hypotension, influenza-like symptoms, thrombosis vascular access, pneumonia, increased nonprotein nitrogen, hyperphosphatemia, otitis, malaise.

The following adverse experiences have been reported at an incidence greater than 1% and less than 5%. No adverse events were reported at an incidence of <1%.

Application Site: injection site reaction
Body as a Whole: rigors, organ transplant rejection, dialysis complication, syncope, incisional pain, hot flushes, fatigue, edema peripheral, edema periorbital, edema circumoral, access pain, access erythema, access edema, access drainage, access cellulitis
Cardiovascular: hypertension aggravated, cardiac failure
CNS/PNS: vertigo, somnolence, paresthesia, migraine, encephalopathy hypertensive
Endocrine Disorders: glucocorticoids increased
Gastrointestinal: hemorrhage GI, increased saliva, gastroenteritis, gastrointestinal disorder, gastritis, flatulence, dyspepsia, diarrhea, anorexia
Hearing/Vestibular: otitis media, earache
Heart Rate/Rhythm: cardiac arrest
Hematologic: thrombocythemia, lymphedema, ecchymosis
Liver and Biliary: infectious hepatitis
Metabolic/Nutrition: hypokalemia, hypocalcemia, hypercalcemia, SGPT increased, hypertriglyceridemia
Musculo-Skeletal: limb pain, back pain, skeletal pain, musculo-skeletal disorder, muscle weakness, arthrosis
Myo/Endo/Pericardial: heart murmur, heart disorder
Psychiatric Disorder: hallucination
Reproductive: vaginitis (female), breast mass (male)
Resistance Mechanism: sepsis, infection, viral infection, fungal infection
Respiratory: wheezing, upper respiratory tract congestion, sinusitis, epistaxis, dyspnea, bronchospasm, atelectasis
Skin and Appendages: rash, dry skin, maculo-papular rash, folliculitis, erythema, cellulitis, acne
Urinary Disorders: uremia, urinary tract infection, albuminuria
Vascular Disorders: superior vena cava syndrome
Vision Disorders: conjunctivitis, abnormal vision

ZIDOVUDINE-TREATED/HIV-INFECTED PATIENTS

Adverse experiences reported in clinical trials with EPREX® in zidovudine-treated/HIV-infected patients were consistent with the progression of HIV infection. In double-blind, placebo-controlled studies of 3-month duration involving approximately 300 zidovudine-treated/HIV-infected patients, adverse experiences with an incidence of ≥ 10% in either patients treated with EPREX® (n=144) or placebo-treated patients were:

Table 1.3

Adverse Experience	EPREX® (n=144)	Placebo (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 at Administration Site	10%	7%
Dizziness	9%	10%

There were no statistically significant differences between treatment groups in the incidence of the above events.

EPREX® does not appear to potentiate progression of HIV disease as measured by: incidence of opportunistic infections; mortality; serum p24 antigen levels; or HIV replication in infected cell lines in vitro.

CANCER PATIENTS

Adverse experiences reported in clinical trials with EPREX® administered thrice weekly in cancer patients were consistent with the underlying disease state. In double-blind, placebo-controlled studies of up to three months duration involving 413 cancer patients, adverse events with an incidence ≥ 10% in either patients treated with EPREX® or placebo-treated patients were:

Table 1.4

Adverse Experience	EPREX® (n=213)	Placebo (n=200)
Nausea	23%	29%
Pyrexia	22%	21%
Asthenia	17%	16%
Fatigue	15%	20%
Vomiting	15%	18%
Diarrhea	15%	9%
Edema	14%	8%
Dizziness	10%	9%
Skin Reaction at Administration Site	10%	10%
Constipation	10%	9%
Shortness of Breath	8%	15%*
Decreased Appetite	8%	12%
Trunk Pain	8%	12%
Chills	7%	10%

*Significantly higher incidence for placebo patients (p=0.030).

There were no statistically significant differences in the percentage of patients treated with EPREX® reporting these adverse events compared to the corresponding incidence in placebo-treated patients, except for shortness of breath which occurred at a higher incidence in placebo-treated patients than in patients treated with EPREX®.

Thrombotic vascular events can occur in cancer patients as a consequence of their disease, comorbidities, and treatment. An increased incidence of thromboembolic events has been reported in cancer patients receiving ESAs, including EPREX®.

In a placebo-controlled, double-blind trial utilizing once-weekly (QW) dosing with EPREX® for up to 4 months involving 333 safety-evaluable cancer patients, adverse events were reported using the NCI Common Toxicity Criteria. Adverse events with an incidence > 10% in either patients treated with EPREX® or placebo-treated patients were as indicated in the table below. The safety profile of EPREX® administered QW was similar to placebo; adverse events in both groups appeared consistent with events expected in advanced cancer or associated with cancer treatment.

Table 1.5

Percent of Patients in the Weekly Dosing Study Reporting Event		
CTC Category Adverse Experience (all grades)	EPREX® (n=168)	Placebo (n=165)
Fatigue	51%	52%
Nausea	35%	30%
Alopecia	25%	29%
Neurosensory	23%	23%
Vomiting	20%	16%
Diarrhea - no colostomy	20%	22%
Anorexia	18%	19%
Constipation	18%	22%
Dyspnea	16%	22%
Pain	9%	11%
Anemia	8%	13%

Based on comparable survival data and on the percentage of patients treated with EPREX® QW and placebo-treated patients who discontinued therapy due to death (7% vs 5%), disease progression (7% vs 8%), or adverse experiences (1% vs 1%), the clinical outcome in patients treated with EPREX® and placebo-treated patients appeared to be similar.

SURGERY PATIENTS

Use of EPREX® to Reduce Allogeneic Blood Exposure

Adverse events were combined for all groups treated with EPREX® and the placebo-treated groups from four orthopedic surgery studies where subjects received EPREX® at a dose of 300 or 100 IU/kg daily, 600 IU/kg weekly, or placebo. Adverse events reported by at least 10% of subjects in any treatment group were:

Table 1.6: Percent of Patients Reporting Event[a]

Adverse Event	300[b] or 100[c] IU/kg EPREX® (Daily) (n=546)	600[d] IU/kg EPREX® (Weekly) (n=73)	Placebo (n=250)
Pyrexia	45%	47%	52%
Skin reaction, injection site	42%	26%	40%
Nausea	37%	45%	34%
Constipation	34%	51%	32%
Vomiting	17%	21%	11%
Skin pain	17%	5%	19%
Insomnia	14%	21%	11%
Headache	13%	10%	9%
Pruritus	12%	14%	10%
Dizziness	10%	11%	9%
Diarrhea	9%	10%	9%
Urinary tract infection	8%	11%	10%
Edema	8%	11%	8%
Arthralgia	8%	10%	6%
Urinary retention	7%	11%	7%
Confusion	5%	12%	6%
Flatulence	4%	10%	4%
Anxiety	3%	11%	6%

[a] All patients participating in orthopedic surgery studies regardless of baseline hemoglobin
[b] 300 IU/kg daily for either 5 or 10 days prior to surgery, on the day of surgery and either 3 or 4 days following surgery (either 9, 14 or 15 daily doses)
[c] 100 IU/kg daily for 10 days prior to surgery, on the day of surgery and 4 days following surgery (15 daily doses)
[d] 600 IU/kg once a week beginning 3 weeks prior to surgery and on the day of surgery (4 weekly doses)

Similar proportions of patients treated with EPREX® and placebo-treated patients reported each adverse event.

Combined Use of EPREX® and ABD

The incidence of adverse events was calculated across five double-blind, placebo-controlled studies and one single-blind study, combining all patients treated with EPREX® (n=402), regardless of dose administered, and all placebo patients (n=242). Adverse experiences with an incidence of ≥ 5% in either patients treated with EPREX® or placebo-treated patients were:

Table 1.7

Event	EPREX® (n = 402)	Placebo (n = 242)
Fatigue	18.41%	19.01%
Dizziness	12.19%	13.64%
Nausea	11.44%	9.09%
Headache	9.20%	11.98%
Asthenia	5.47%	3.72%
Diarrhea	3.48%	7.02%

In general, there were no notable differences between patients treated with EPREX® and placebo-treated patients in the incidence of any adverse event.

POST-MARKET ADVERSE DRUG REACTIONS

Blood & Lymphatic System Disorders:
Cases of erythropoietin Antibody-Mediated Pure Red Cell Aplasia and thrombocythemia have been reported.

Skin and Appendages System Disorders:
Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with epoetin treatment (see **WARNINGS AND PRECAUTIONS, Severe Cutaneous Reactions**).

DRUG INTERACTIONS

Drug-Drug Interactions
No evidence exists that indicates that treatment with EPREX® alters the metabolism of other drugs. Drugs that decrease erythropoiesis may decrease the response to EPREX®.

Since cyclosporine is bound by red blood cells, there is potential for a drug interaction. If EPREX® is given concomitantly with cyclosporine, blood levels of cyclosporine should be monitored and the dose of cyclosporine adjusted as necessary.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

IMPORTANT: See WARNINGS AND PRECAUTIONS: SERIOUS WARNINGS AND PRECAUTIONS Box, and Increased Mortality, Serious Adverse Cardiovascular Reactions, Thromboembolic Events and Stroke. Follow the recommended dosage for each indication for EPREX®.

EPREX® (epoetin alfa) may be given either as an IV or SC injection (see **Recommended Dose and Dosage Adjustment; CRF PATIENTS**).

In order to ensure optimum response to EPREX®, adequate iron stores should be assured and iron supplementation should be administered if necessary (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Iron Evaluation**).

Self-Administration and Information for the Patient

In those situations in which the physician determines that a patient can safely and effectively self-administer EPREX® injection, the patient should be instructed as to the proper dosage and administration. The first few doses should be administered under supervision. Following the initial laboratory and clinical assessment, all patients, including those deemed capable of self-administration, should be monitored for their response to EPREX®, their blood pressure and serum levels as indicated in the **WARNINGS AND PRECAUTIONS** section. Patients should be referred to the full ***Product Monograph PART III*: CONSUMER INFORMATION** section. It is not a disclosure of all possible effects. Patients should be informed of the signs and symptoms of allergic drug reaction and advised of appropriate actions.

If home use is prescribed, 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 for the disposal of used syringes and needles should be available to the patient. The full container should be disposed of according to the directions provided by the physician.

Recommended Dose and Dosage Adjustment

CRF PATIENTS

The treatment of anemia in chronic renal failure patients should be individualized. The choice of the treatment modality (iron, erythropoiesis-stimulating agent, blood transfusion) and of the amount of therapeutic product administered should take into consideration the overall condition and treatment plan for the patient (e.g., presence of concomitant conditions, risk factors, plan for renal transplant, etc.) as well as national guidelines. EPREX® therapy should only be initiated if hemoglobin is less than 100 g/L.

The recommended dose to initiate therapy of EPREX® is 50 to 100 IU/kg three times per week (TIW) for adult patients. The recommended starting dose for pediatric CRF patients on dialysis is 50 IU/kg three times weekly (TIW). The dose of EPREX® should be reduced as the hemoglobin approaches 120 g/L or increases by more than 10 g/L in any 2-week period.

The dosage of EPREX® should be individualized to achieve and maintain the hemoglobin within the recommended range of 100-115 g/L and not to exceed 120 g/L. If hemoglobin excursions outside the recommended range occur, EPREX® dose should be adjusted using the dosing recommendations below.

It should be recognized that subcutaneous administration of recombinant human proteins may increase the risk of immunogenicity. In patients on hemodialysis, the IV route is recommended.

When used intravenously, EPREX® Sterile Solution usually has been administered as a slow IV bolus three times per week. While the administration of EPREX® is independent of the dialysis

procedure, EPREX® solution may be administered into the venous port at the end of the dialysis procedure to obviate the need for additional venous access. Following the change from intravenous to subcutaneous route of administration, the patient should be monitored carefully to ensure that the hemoglobin response is appropriate. Available data suggests that patients with a baseline hemoglobin < 60 g/L may require higher maintenance doses than those with a baseline hemoglobin > 80 g/L. EPREX® therapy is not intended for patients who require immediate correction of severe anemia.

During therapy, hematological parameters should be monitored regularly.
Table 1.8 provides general therapeutic guidelines.

Table 1.8

Starting Dose	Reduce Dose When (Starting with 25 IU/kg/dose decrement)	Increase Dose If (Starting with 25 IU/kg/dose increment)	Maintenance Dose	Recommended Hb Range
Adults: 50-100 IU/kg three times per week IV or SC Pediatric patients: 50 IU/kg three times per week IV or SC	1) Hb approaches 120 g/L or 2) Hb increases >10 g/L in any 2-week period.	Hb does not increase by 10 g/L after 8-12 weeks of therapy, and Hb is below range.	Individually titrate.	100-115 g/L not to exceed 120 g/L

Dose Adjustment
Following EPREX® therapy, a period of time is required for erythroid progenitors to mature and be released into circulation resulting in an eventual increase in hemoglobin. Additionally, red blood cell survival time affects hemoglobin and may vary due to uremia. As a result, the time required to elicit a clinically significant change in hemoglobin (increase or decrease) following any dose adjustment may be 2-6 weeks.

Dose adjustment should not be made more frequently than once a month, unless clinically indicated. After any dose adjustment, the hemoglobin should be determined weekly for at least 2-6 weeks (see **WARNINGS AND PRECAUTIONS, CHRONIC RENAL FAILURE (CRF) PATIENTS, Monitoring and Laboratory Tests**).

- If the hemoglobin is increasing and approaching 120 g/L, the dose should be decreased by approximately 25 IU/kg three times per week. If the reduced dose does not stop the rise in hemoglobin, or the hemoglobin is 120 g/L doses should be temporarily withheld until the hemoglobin begins to decrease, at which point therapy should be re-initiated at a lower dose.
- At any time, if the hemoglobin increases by more than 10 g/L in a two-week period, the dose should be immediately decreased. After the dose reduction, the hemoglobin should be

monitored weekly for 2-6 weeks, and further dose adjustments should be made (see **Maintenance Dose**).

- If a hemoglobin increase of 10 g/L is not achieved after an eight-week period and iron stores are adequate (see **Lack or Loss of Response** in this section), the dose of EPREX® may be increased in increments of 25 IU/kg three times per week. Further increases of 25 IU/kg three times per week may be added at 4-6 week intervals until the desired response is attained.

Maintenance Dose

The maintenance dose must be individualized for each chronic renal failure patient.

If the hemoglobin remains below, or falls below, the recommended range, iron stores should be re-evaluated. If the transferrin saturation is less than 20%, supplemental iron should be administered. If the transferrin saturation is greater than 20%, the dose of EPREX® may be increased by 25 IU/kg three times per week. 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 2-6 weeks. Hemoglobin should be measured for 2-6 weeks following dose increases.

Lack or Loss of Response

Over 95% of patients with chronic renal failure responded with clinically significant increases in hemoglobin; virtually all patients were transfusion-independent within approximately two months of initiation of EPREX® therapy.

If a patient fails to respond or maintain a response, other etiologies should be considered and evaluated as clinically indicated (see **WARNINGS AND PRECAUTIONS**).

For patients whose hemoglobin does not attain a level within the range of 100 to 120 g/L despite the use of appropriate EPREX® dose titrations over a 12-week period:

- do not administer higher EPREX® 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 **WARNINGS AND PRECAUTIONS**: **Lack or Loss of Response**), and
- thereafter, hemoglobin should continue to be monitored and if responsiveness improves, EPREX® dose adjustments should be made as described above; use caution when increasing the dose for patients with lack or loss of response,
- discontinue EPREX® if responsiveness does not improve and the patient needs recurrent RBC transfusions.

ZIDOVUDINE-TREATED/HIV-INFECTED PATIENTS

Prior to beginning EPREX® therapy, it is recommended that the endogenous serum erythropoietin level be determined (prior to transfusion). Available evidence suggests that

patients receiving zidovudine with levels > 500 mU/mL are unlikely to respond to therapy with EPREX® unless the dose of zidovudine is reduced or temporarily stopped.

Starting Dose
For patients with serum erythropoietin levels ≤ 500 mU/mL, the recommended starting dose of EPREX® is 100 IU/kg as an intravenous or subcutaneous injection three times weekly for eight weeks.

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 eight weeks of therapy, the dose of EPREX® can be increased by 50-100 IU/kg three times per week. Response should be evaluated every 4-8 weeks thereafter and the dose adjusted accordingly by 50-100 IU/kg increments three times per week. If patients have not responded satisfactorily to an EPREX® dose of 300 IU/kg three times per week up to month 12 of therapy, further continuation of treatment is not warranted as it is unlikely that they will respond to higher doses of EPREX®.

Maintenance Dose
After attainment of the desired response (i.e., reduced transfusion requirements or increased hemoglobin), the dose of EPREX® 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 120 g/L, the dose should be temporarily withheld until the hemoglobin falls below 120 g/L. Resume dosing at 25% less than the previous dose and titrate the dose to maintain the desired hemoglobin.

Hemoglobin Range
Maximum benefit from EPREX® therapy appears to occur when the hemoglobin is maintained in the range of 120-130 g/L; however, the hemoglobin for zidovudine-treated/HIV-infected patients should not exceed 120 g/L.

CANCER PATIENTS RECEIVING CHEMOTHERAPY

EPREX® should not be initiated at hemoglobin levels ≥ 100 g/L. EPREX® administration should be discontinued following completion of a chemotherapy course.

Starting Dose
Two EPREX® dosing regimens may be used in adults: 150 IU/kg subcutaneously three times per week or 40,000 IU subcutaneously once per week.

Dose Adjustment

Three times per week (TIW)

Starting dose	150 IU/kg SC (TIW)

Increase dose to 300 IU/kg for four weeks	If the response is not satisfactory i.e., if after four weeks of therapy, no reduction in transfusion requirements or the hemoglobin has not increased by ≥ 10 g/L
Reduce Dose by 25%	If the hemoglobin reaches a level needed to avoid transfusions or increases > 10 g/L in any 2 week period
Withhold dose	If hemoglobin exceeds a level needed to avoid transfusions or exceeds 120 g/L. Restart dosing at 25% below the previous dose.
Discontinue	Discontinue EPREX® if after 8 weeks of therapy there is no response as measured by increase hemoglobin levels or decrease need for RBC transfusions.

Once per week (QW)

Starting Dose	40,000 IU SC (QW)
Increase dose to 60,000 IU/week for four weeks	If the response is not satisfactory i.e., if after four weeks of therapy, no reduction in transfusion requirements or the hemoglobin has not increased by ≥ 10 g/L
Reduce Dose by 25%	If the hemoglobin reaches a level needed to avoid transfusions or increases > 10 g/L in any 2 week period
Withhold dose	If hemoglobin exceeds a level needed to avoid transfusions or exceeds 120 g/L. Restart dosing at 25% below the previous dose.
Discontinue	Discontinue EPREX® if after 8 weeks of therapy there is no response as measured by increase hemoglobin levels or decrease need for RBC transfusions.

Endogenous Serum Erythropoietin Levels

In patients being treated with cyclic chemotherapy, there does not appear to be a significant relationship between the endogenous serum erythropoietin level and response to EPREX® therapy.

Use of EPREX® is not recommended in patients with grossly elevated serum erythropoietin levels (e.g., > 200 mU/mL).

SURGERY PATIENTS

Use of EPREX® to Reduce Allogeneic Blood Exposure

The recommended dose regimen is 600 IU/kg subcutaneously given once weekly for three weeks (Days -21, -14, and -7) prior to surgery and on the day of surgery.

If the period prior to surgery is less than three weeks, 300 IU/kg subcutaneously may be given as an alternative dosing regimen for 10 consecutive days prior to surgery, on the day of surgery, and for four consecutive days immediately thereafter.

Combined Use of EPREX® and ABD

EPREX® should be administered twice weekly for three weeks prior to surgery if the presurgical predonation interval permits. At each patient visit, a unit of blood is collected and stored for autologous transfusion if the patient has an acceptable hematocrit or hemoglobin for predonation.

The recommended dosage regimen is 600 IU/kg intravenously twice weekly.

Administration

NOTE: All strengths of EPREX® Pre-filled Syringes now contain a "peelable" label on the barrel of the syringe. The peelable portion of the label should be removed from the syringe barrel and affixed to the patient's chart. The peelable label will be used to track Lot numbers and use of EPREX® Pre-filled syringes.

1. **Do Not Shake.** Shaking may denature the 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 pre-filled syringes exhibiting particulate matter or discoloration.

3. Intravenous Injection: EPREX® Sterile Solution should be administered over at least one to five minutes, depending on the total dose. While the administration of EPREX® is independent of the dialysis procedure, EPREX® may be administered into the venous line at the end of the dialysis procedure to obviate the need for additional venous access. A slower injection may be preferable in patients who develop flu-like symptoms.

4. Subcutaneous Injection: The maximum volume per injection site should be 1 mL. In case of larger volumes, more than one injection site should be used. The injections should be given in the limbs or the anterior abdominal wall. The patient should always alternate the site for each injection.

5. Pre-filled Syringe: Contains no preservative. Discard unused portions.

6. Do not administer by intravenous infusion or mix with other drugs.

7. The phosphate-buffered formulation has been found to mitigate injection site discomfort.

OVERDOSAGE

The maximum amount of EPREX® (epoetin alfa) that can be safely administered in single or multiple doses has not been determined. Doses of up to 1500 IU/kg three times per week for three to four weeks have been administered to adults without any direct toxic effects of EPREX®

itself. Humans have received EPREX® doses as high as 3000 IU/kg in a single day without acute toxic effects.

EPREX® therapy can result in polycythemia if the hemoglobin is not carefully monitored and the dose appropriately adjusted. If the recommended range is exceeded, EPREX® therapy may be temporarily withheld until the hemoglobin returns to the recommended range; EPREX® therapy may then be resumed using a lower dose (see **DOSAGE AND ADMINISTRATION**). If polycythemia is of concern, phlebotomy may be indicated to decrease the hemoglobin to within acceptable ranges. Supportive care should be provided for hypertensive or convulsive events that may be related to overdosing with EPREX®.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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.

Pharmacodynamics

CRF PATIENTS

Erythropoietin is a glycoprotein which stimulates red blood cell production. 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. In normal subjects, plasma erythropoietin levels range from 0.01 to 0.03 U/mL and increase up to 100 to 1000-fold during hypoxia or anemia. 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.

EPREX® (epoetin alfa) has been shown to stimulate erythropoiesis in anemic patients with CRF, including both patients on dialysis and those who do not require regular dialysis. The first evidence of a response to EPREX® is an increase in the reticulocyte count within 10 days, followed by increases in the red cell count, hemoglobin and hematocrit, usually within 2-6 weeks.

Because several days are required 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 recommended range (30-36%), that level can be sustained by EPREX® in the absence of iron deficiency and concurrent illnesses.

The rate of hematocrit increase varies between patients and is dependent upon the dose of EPREX®, within a therapeutic range of approximately 50-300 IU/kg three times per week. Other factors affecting the rate and extent of response include availability of iron stores, the baseline hematocrit, and the presence of concurrent medical problems.

Intravenously administered EPREX® is eliminated at a rate consistent with first order kinetics with a circulating half-life ranging from approximately 4 to 13 hours in adult and 6.2 to 8.7 hours in pediatric patients with CRF. Within the therapeutic dose range, detectable levels of plasma erythropoietin are maintained for at least 24 hours. After subcutaneous administration of EPREX® to patients with CRF, peak serum levels are achieved within 5-24 hours after administration and decline slowly thereafter. In comparison with intravenous administration, subcutaneously administered EPREX® is more slowly absorbed and results in lower serum levels which are maintained for 48 hours. The estimated AUC_{0-48} for subcutaneous administration is approximately 15% of the AUC_{0-48} for the same dose given intravenously. Despite these differences, EPREX® exhibits a dose-related effect on hematological parameters which is independent of route. There is no apparent difference in half-life between adult patients not on dialysis whose serum creatinine levels were greater than 264 μmol/L (3 mg/dL), and adult patients maintained on dialysis. In normal volunteers, the half-life of intravenously administered EPREX® Sterile Solution is approximately 20% shorter than the half-life in CRF patients.

The pharmacokinetic profile of EPREX® in children and adolescents appears to be similar to that of adults. Limited data are available in neonates.

ZIDOVUDINE-TREATED/HIV-INFECTED PATIENTS

Response to EPREX® in zidovudine-treated/HIV-infected patients is manifested by reduced transfusion requirements and increased hematocrit. Responsiveness to EPREX® therapy in HIV-infected patients is dependent upon the endogenous serum erythropoietin levels prior to treatment. Zidovudine-treated/HIV-infected patients with endogenous serum erythropoietin levels ≤ 500 mU/mL respond to EPREX® therapy. Patients with endogenous serum erythropoietin levels > 500 mU/mL do not appear to respond to EPREX® therapy. It appears likely that endogenous serum erythropoietin levels in HIV-infected patients receiving zidovudine are related to the severity of the zidovudine-induced damage to erythroid precursors in the bone marrow.

CANCER PATIENTS

Anemia in cancer patients may be related to the effect of concomitantly administered chemotherapeutic agents. EPREX® administered three times a week (TIW) has been shown to increase hemoglobin and decrease transfusion requirements (after the first month of therapy) in anemic cancer patients. In addition, EPREX® administered once weekly (QW) has been shown to increase hemoglobin and decrease transfusion requirements after the first month of therapy (months 2, 3 and 4) in anemic cancer patients.

In a series of clinical trials enrolling 413 anemic cancer patients who received EPREX® TIW, 289 of whom were receiving cyclic chemotherapy, approximately 75 percent of the patients had endogenous serum erythropoietin levels ≤150 mU/mL, and approximately 5 percent of patients

had endogenous serum erythropoietin levels > 500 mU/mL. In patients who were being treated with cyclic chemotherapeutic regimens, there was not a statistically significant relationship between response to EPREX® therapy and the prestudy endogenous serum erythropoietin level; however, treatment of patients with grossly elevated serum erythropoietin levels (e.g., > 200 mU/mL) is not recommended.

In a Phase 1 PK/PD study comparing 150 IU/kg subcutaneous thrice weekly (TIW) dosing to 40,000 IU subcutaneous once weekly (QW) dosing in healthy subjects, the following parameters were estimated using data corrected for predose endogenous erythropoietin concentration during Week 4: mean C_{max} (SD) was 191 (100.1) and 785 (427.3) mIU/mL, respectively; mean (SD) C_{min} was 39 (17.9) and 13 (9.5) mIU/mL, respectively, and mean $t_{1/2}$ was 31.8 and 39.3 hours, respectively, after the 150 IU/kg TIW dosing (n=24) and 40,000 IU QW (n=22) dosing regimens were administered. Bioavailability of epoetin alfa after the 40,000 IU/week dosing regimen relative to the 150 IU/kg thrice weekly dosing regimen, based on AUC comparison, was 176%.

In another Phase 1 PK/PD study, pharmacokinetic parameters were estimated using data corrected for predose endogenous erythropoietin concentration comparing 150 IU/kg TIW and 40,000 IU QW dosing regimens in healthy subjects (n=6 per arm) and anemic cancer subjects (n=9 per arm). The respective mean (SD) parameters for the 150 IU/kg TIW and 40,000 IU QW regimens in healthy subjects were: C_{max} 163 (53.6) and 1036 (237.9) mIU/mL; C_{min} 29 (10.4) and 9.2 (5.71) mIU/mL; t_{max} 9.0 (3.29) and 21 (7.1) hours; $t_{1/2}$ 25.2 (6.76) [n=4] and 28.9 (7.98) hours, and CL/F 31.2 (11.48) and 12.6 (3.05) mL/h/kg. The respective mean (SD) parameters for the 150 IU/kg TIW and 40,000 IU QW regimens in the anemic cancer subjects were: C_{max} 263 (179.1) and 931 (596.9) mIU/mL; C_{min} 54 (41.8) and 34 (32.3) mIU/mL; t_{max} 8.3 (8.58) and 43 (16.0) hours; $t_{1/2}$ 29.9 (2.43) [n=4] and 22.9 (7.55) [n=7] hours and CL/F 45.8 (58.81) and 11.3 (6.45) mL/h/kg. It appeared that the pharmacokinetics of epoetin alfa in anemic cancer subjects were similar to those in healthy subjects.

However, the degree of variability associated with the pharmacokinetic parameters was higher in anemic cancer patients.

Pharmacodynamics

In a PK/PD study comparing the 150 IU/kg thrice weekly and 40,000 IU once weekly dosing regimens in healthy subjects (n = 6 per arm) and in anemic cancer subjects (n = 9 per arm), the time profiles of changes in percent reticulocytes, hemoglobin, and total red blood cells were similar between the two dosing regimens in both healthy and anemic cancer subjects. The AUCs of the respective pharmacodynamic parameters were similar between the 150 IU/kg TIW and 40,000 IU QW dosing regimens in healthy subjects and also in anemic cancer subjects, although the extent of increase in hemoglobin and RBC count was slightly lower in anemic cancer subjects than in healthy subjects (in terms of AUC of hemoglobin and RBC over the study period).

ESAs are growth factors that primarily stimulate red cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells.

SURGERY PATIENTS

Use of EPREX® to Reduce Allogeneic Blood Exposure

Patients undergoing major elective surgery frequently require transfusion of allogeneic blood, both intraoperatively and postoperatively, resulting from blood loss experienced during and after surgery. In patients with a pretreatment hemoglobin of > 100 to ≤ 130 g/L, EPREX® has been shown to decrease the risk of receiving allogeneic transfusions and hasten erythroid recovery (i.e., increased hemoglobin levels, hematocrit levels, and reticulocyte counts).

Combined Use of EPREX® and Autologous Blood Donation (ABD)

EPREX® has been shown to stimulate red blood cell production in order to augment autologous blood collection, and to limit the decline in hematocrit in adult patients scheduled for major elective surgery who are not expected to predeposit their complete perioperative blood needs. The greatest effects are observed in patients with low hematocrit (≤ 39%).

Pharmacokinetics and Hematological Responses

Measurement of epoetin alfa following multiple dose intravenous administration revealed a half-life of approximately 4 hours in normal volunteers and a somewhat more prolonged half-life in renal failure patients, approximately 5 hours (ranging to 13 hours). Within the therapeutic dose range, detectable levels of plasma erythropoietin are maintained for at least 24 hours. There is no apparent difference in half-life between patients not on dialysis whose serum creatinine levels were greater than 264 µmol/L (3 mg/dL), and patients maintained on dialysis.

After subcutaneous administration of EPREX® to normal subjects, peak serum levels are achieved within 5-24 hours after administration. In comparison with intravenous administration, subcutaneously administered EPREX® is more slowly absorbed and results in lower serum levels which are maintained for 48 hours. In normal subjects, there was no significant epoetin alfa accumulation when administered under the clinical trial conditions. After multiple doses, similar blood levels were obtained after initial and subsequent injections in normal subjects. In these subjects, the half-life was estimated to be about 24 hours. The bioavailability of subcutaneous epoetin alfa is approximately 20% of that of the intravenously injected epoetin alfa. Despite these differences, EPREX® exhibits an injection-route independent, dose-related effect on hematological parameters.

In normal volunteers, C_{max} values for 40,000 IU once weekly determined in four-week studies were 6 times and $AUC_{(0\text{-}168\ h)}$ were 3 times that of the 150 IU/kg thrice weekly dosing regimen. Mean hemoglobin increases are similar with 3.1±0.86 and 3.1±0.84 g/dL for the 150 IU/kg thrice weekly and 40,000 IU once weekly, respectively. The time profiles of changes in hemoglobin and total red blood cells over the one-month study period were similar between the two dosing regimens.

However, statistically significant differences between genders for the AUC_{HEMO} and AUC_{RBC} pharmacodynamic response parameters at 40,000 IU once weekly dosing were noted. Clinical consequences of these differences were not studied as the normal volunteers were not scheduled subject to surgical procedures. When demographic data for the 40,000 IU once weekly and 150 IU/kg t.i.w. regimens were examined separately, or combined and stratified by gender, a significant difference in weight between males and females was detected in each treatment group. Dosing should be individualized on an IU/kg basis (see **DOSAGE AND ADMINISTRATION**).

Special Populations and Conditions

Pediatrics: No data available.

Geriatrics: No data available.

Gender: No data available.

Race: No data available.

Hepatic Insufficiency: The safety of EPREX® has not been established in patients with hepatic dysfunction.

Renal Insufficiency: Based on information to date, the use of EPREX® in predialysis patients does not accelerate the rate of progression of renal insufficiency.

STORAGE AND STABILITY

Store at 2° - 8°C. Protect from exposure to light. **Do Not Freeze. Do Not Shake.**

When the pre-filled syringe is about to be used, it may be removed from the refrigerator and stored at room temperature (not above 25°C) for one single period of maximum 7 days.

SPECIAL HANDLING INSTRUCTIONS

Store at 2° - 8°C. Protect from exposure to light. **Do Not Freeze. Do Not Shake.**

DOSAGE FORMS, COMPOSITION AND PACKAGING

Polysorbate-80 Containing (HSA-free) Formulation Pre-filled Syringes with PROTECS® needle guard

Polysorbate-80 Containing (HSA-free) Formulation Pre-filled Syringes contain the active ingredient epoetin alfa and the following inactive ingredients:

Stabilizer:	Glycine and polysorbate 80
Other Inactives:	Sodium chloride, sodium phosphate monobasic dihydrate, sodium phosphate dibasic dihydrate, water for injection.

The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex).

EPREX® (epoetin alfa) Injection is supplied as a sterile solution in the following formats:

Single-Use Pre-filled Syringe with PROTECS® needle guard (phosphate-buffered)

1,000 IU/0.5 mL
2,000 IU/0.5 mL
3,000 IU/0.3 mL
4,000 IU/0.4 mL
5,000 IU/0.5 mL
6,000 IU/0.6 mL
8,000 IU/0.8 mL
10,000 IU/mL
20,000 IU/0.5 mL
30,000 IU/0.75 mL
40,000 IU/mL

To reduce the risk of accidental needle sticks to users, each pre-filled syringe is equipped with the PROTECS®-needle guard that is automatically activated to cover the needle after complete delivery of the syringe content.

For packaging configuration see published price list.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: EPREX®

Chemical name: epoetin alfa

Molecular formula and molecular mass: Approximately 30,400 daltons when fully glycosylated. (Approximately 18,000 daltons for the peptide chain.)

Structural formula: Peptide chain of 165 amino acids. Sequence identical to that of human urinary erythropoietin.

Physicochemical properties: Bulk product is a clear colourless liquid with a pH of 6.9 ± 0.3 at 23°C ± 5°C consisting of epoetin alfa in buffer.

Product Characteristics

Epoetin alfa is a purified glycoprotein hormone of recombinant DNA origin that stimulates erythropoiesis. It is produced from mammalian Chinese hamster ovary (CHO) cells that have been transfected with the human gene coding for erythropoietin.

EPREX® (epoetin alfa) is formulated as a sterile, colourless liquid for intravenous (IV) or subcutaneous (SC) administration.

CLINICAL TRIALS

CRF PATIENTS

Response to EPREX® (epoetin alfa) was consistent across all studies. In the presence of adequate iron stores (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**, **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 EPREX® dose administered and individual patient variation. In clinical trials at starting doses of 50-150 IU/kg three times per week, patients responded with an average rate of hematocrit rise of:

Table 2.1: Hematocrit Increase

Starting Dose Three times/week, IV	Hematocrit percentage points/day	Hematocrit percentage points/2 weeks
50 IU/kg	0.11	1.5
100 IU/kg	0.18	2.5
150 IU/kg	0.25	3.5

Over this dose range, approximately 95% of all patients responded with a clinically significant increase in hematocrit. By the end of approximately two months of therapy, virtually all patients were transfusion-independent. Once the target hematocrit was achieved, the maintenance dose was individualized for each patient.

Adult Patients on Dialysis

Thirteen clinical studies were conducted, involving intravenous administration to a total of 1010 anemic patients on dialysis for 986 patient-years of EPREX® therapy. In the three largest of these clinical trials, the median maintenance dose necessary to maintain the hematocrit between 30-36% was approximately 75 IU/kg given three times per week. In a U.S. multicentre Phase III study (n=412), approximately 65% of the patients required doses of 100 IU/kg, or less, three times per week to maintain their hematocrit at approximately 35%. Almost 10% of patients required a dose of 25 IU/kg, or less, and approximately 10% required a dose of more than 200 IU/kg three times per week to maintain their hematocrit at this level.

Among the 99 patients treated in the double-blind, placebo-controlled, Canadian multicentre, quality of life study, clinically and statistically ($p<0.05$) significant improvement was shown in the patients treated with EPREX® compared to the placebo group when measuring fatigue, relationships and depression (Kidney Disease Questionnaire), distance walked (Six Minute Walk Test) and time on the Naughton Treadmill test after six months of therapy. Sixty-seven patients from the group treated with EPREX® were then enrolled in an open-label extension study where 62 patients maintained their quality of life improvements for an additional 12 months.

A multicentre study was also conducted in 152 patients receiving peritoneal dialysis who self-administered EPREX® Sterile Solution subcutaneously for approximately 132.9 patient-years of experience. Patients responded to EPREX® administered subcutaneously in a manner similar to patients receiving intravenous administration.

Pediatric Chronic Renal Failure 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 EPREX®. The largest study (EPO-9002) was a placebo-controlled, randomized trial in 113 children with anemia (hematocrit ≤ 27%) undergoing peritoneal dialysis or hemodialysis. The patient demographics for this study are presented in Table 2.2. The initial dose of EPREX® was 50 IU/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.

Table 2.2: Patient Demographics for Study EPO-9002

Variable		Hemodialysis		Peritoneal Dialysis		Total (N=113)	
		EPREX® (N=24) %	Placebo (N=24) %	EPREX® (N=31) %	Placebo (N=34) %	EPREX® (N=55) %	Placebo (N=58) %
Age Group	0 - < 5	0.0	4.2	16.1	32.4	9.1	20.7
	5 - < 15	54.2	50.0	51.6	55.9	52.7	53.4
	15 - < 18	45.8	45.8	32.3	11.8	38.2	25.9
Sex	Male	54.2	62.5	64.5	55.9	60.0	58.6
	Female	45.8	37.5	35.5	44.1	40.0	41.4
Race	Caucasian	37.5	25.0	35.5	41.2	36.4	34.5
	Black	37.5	41.7	19.4	20.6	27.3	29.3
	Hispanic	25.0	33.3	35.5	38.2	30.9	36.2
	Asian	0.0	0.0	6.5	0.0	3.6	0.0
	Other	0.0	0.0	3.2	0.0	1.8	0.0

At the end of the initial 12 weeks, a statistically significant rise in mean hematocrit (9.4% vs 0.9%) was observed in the EPREX® 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 EPREX® arm (96% vs 58%). Within 12 weeks of initiating EPREX® therapy, 92.3% of the pediatric patients were transfusion-independent as compared to 71% who received placebo. Among patients who received 36 weeks of EPREX®, hemodialysis patients required a higher median maintenance dose (167 IU/kg/week [n=28] vs 76 IU/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. Additional information regarding the number of patients who experienced an increase of 6 or more hematocrit points from baseline, versus attaining a target hematocrit of 30% to 36 % can be found in detail in Table 2.3.

Table 2.3: Achievement of a Hematocrit Increase of 6 or More Points Above Baseline in the Study EPO-9002 (First 12 Study Weeks)

		EPREX®			Placebo		
Dialysis Type	**Age Group (Years)**	**No. of Patients**	**No. Achieved**	**% Achieved**	**No. of Patients**	**No. Achieved**	**% Achieved**
Hemodialysis	0 - < 5	0	0	0.0	1	0	0.0
	5 - < 15	13	13	100.0	11	6	54.5
	15 - < 18	11	8	72.7	11	3	27.3
	Subtotal	24	21	87.5	23	9	39.1
Peritoneal Dialysis	0 - < 5	5	5	100.0	11	7	63.6
	5 - < 15	16	16	100.0	19	13	68.4
	15 - < 18	10	10	100.0	4	2	50.0
	Subtotal	31	31	100.0	34	22	64.7
All Dialysis Types	0 - < 5	5	5	100.0	12	7	58.3
	5 - < 15	29	29	100.0	30	19	63.3
	15 - < 18	21	18	85.7	15	5	33.3
	Total	55	52	94.5	57	31	54.4

CRF Patients Not Requiring Dialysis

Four clinical trials were conducted in patients with CRF not on dialysis involving 181 patients treated with EPREX® for approximately 67 patient-years of experience. The average duration of therapy was nearly five months. These patients responded to EPREX® 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 EPREX® Sterile Solution was administered by either an intravenous or subcutaneous route. Similar rates of rise of hematocrit were noted when EPREX® Solution was administered by either route. Moreover, EPREX® doses of 75-150 IU/kg per week have been shown to maintain hematocrits of 36-38% for up to six months. Correcting the anemia of progressive renal failure will allow patients to remain active even though their renal function continues to decrease.

Increased Mortality, Serious Adverse Cardiovascular Reactions, Thromboembolic Events and Stroke

A randomized prospective trial of 1265 hemodialysis patients with clinically evident cardiac disease (ischemic heart disease or congestive heart failure) was conducted in which patients were assigned to EPREX® treatment targeted to a maintenance hematocrit of either 42 ± 3% or 30 ± 3%. 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 increased mortality observed in this study is unknown; however, the incidence of non-fatal myocardial infarctions (3.1% vs. 2.3%), vascular access thrombosis (39% vs. 29%) and all other thrombotic events (22% vs. 18%) was also higher in the group randomized to achieve a hematocrit of 42%.

A randomized prospective trial (CHOIR) evaluated 1432 anemic chronic renal failure patients who were not undergoing dialysis. Patients were assigned to EPREX® treatment targeting a maintenance hemoglobin concentration of 135 g/L or 113 g/L. A major adverse cardiovascular reaction (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).

In a randomized, double-blind, placebo-controlled study of 4038 patients, there was an increased risk of stroke when darbepoetin alfa was administered to patients with anemia, type 2 diabetes, and CRF who were not on dialysis. Patients were randomized to darbepoetin alfa treatment targeted to a hemoglobin level of 130 g/L or to placebo. Placebo patients received darbepoetin alfa only if their hemoglobin levels were less than 90 g/L. A total of 101 patients receiving darbepoetin alfa experienced stroke compared to 53 patients receiving placebo (5% vs. 2.6%; HR 1.92, 95% CI: 1.38, 2.68; p < 0.001).

ZIDOVUDINE-TREATED/HIV-INFECTED PATIENTS

EPREX® has been studied in four placebo-controlled trials enrolling 297 anemic (hematocrit < 30%) HIV-infected (AIDS) patients receiving concomitant therapy with zidovudine. In the subgroup of patients (n=89) with prestudy endogenous serum erythropoietin levels ≤ 500 mU/mL, EPREX® significantly reduced the mean cumulative number of units of blood transfused per patient by approximately 40%. Among those patients who required transfusions

at baseline, 43% of patients treated with EPREX® versus 18% of placebo-treated patients were transfusion-independent during the second and third months of therapy. EPREX® also resulted in statistically significant increases in hematocrit in comparison to placebo (6.9% vs. 0.6% in placebo group, p=0.0167). When examining the results according to the weekly dose of zidovudine received during Month 3 of therapy, statistically significant effects of EPREX® on Month 3 transfusion requirements were limited to patients with endogenous serum erythropoietin levels ≤ 500 mU/mL who were taking ≤ 4200 mg/week of zidovudine. Approximately 17% of the patients with endogenous serum erythropoietin levels ≤ 500 mU/mL receiving EPREX® in doses from 100-200 IU/kg three times weekly achieved the target hematocrit of 38% unrelated to transfusion or to a significant reduction in zidovudine dose. In the subgroup of patients whose prestudy endogenous serum erythropoietin levels were > 500 mU/mL, EPREX® did not reduce transfusion requirements or increase hematocrit compared to the corresponding responses in placebo-treated patients.

Clinical experience with EPREX® administered for more than one year to HIV-infected (AIDS) patients receiving concomitant zidovudine therapy suggests that additional benefit, in terms of raising hematocrit and decreasing transfusion requirements, may be obtained by increasing the EPREX® dose in a stepwise fashion above initial dose levels in patients whose prestudy endogenous serum erythropoietin levels are ≤ 500 mU/mL.

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

CANCER PATIENTS

Three times per week dosing

EPREX® has been studied in a series of placebo-controlled, double-blind trials in a total of 289 anemic cancer patients. Within the group, 157 patients were treated with concomitant non-cisplatin-containing chemotherapy regimens and 132 patients were treated with concomitant cisplatin-containing chemotherapy regimens. Patients were randomized to EPREX® doses of 150 IU/kg or placebo subcutaneously three times per week for 12 weeks.

In each of the study populations tested, EPREX® therapy was associated with a significantly ($p<0.005$) greater hematocrit response than in the corresponding placebo-treated patients. In all patients treated with concomitant chemotherapy, transfusion requirements in patients treated with EPREX® (1.04 units in Months 2, 3) were reduced by approximately 43 percent compared to transfusion requirements in placebo-treated patients (1.81 units in Months 2, 3) after the first month of therapy.

Comparable intensity of chemotherapy in the EPREX® and placebo groups in the chemotherapy trials was demonstrated by a similar area under the neutrophil time curve in patients treated with EPREX® and placebo-treated patients, as well as by a similar proportion of patients in groups treated with EPREX® and placebo-treated groups whose absolute neutrophil counts fell below 1000 and 500 cells/μL.

In the above studies, the double-blind phase was followed by an open-label phase during which all patients received EPREX®. During total EPREX® exposure, in each of the studies, a significant improvement ($p \leq 0.05$) in hematocrit from baseline to final reported value was observed. In addition, the percentage of patients requiring transfusion declined from 30.9% and 26.2% in the chemotherapy and cisplatin groups, respectively, during the month prior to initiating therapy to 11.5% and 6.1%, respectively, during Month 5 of therapy. The following table details the transfusion rates in the open-label phase from one month prior to therapy through to Month 5 of therapy.

Table 2.4: Proportion of Patients Transfused During Open-Label Phase

Period	Chemotherapy		Cisplatin	
	N[a]	Percent[b] Transfused	N[a]	Percent[b] Transfused
Baseline				
Month 1	139	30.94	103	26.21
On-Therapy				
Month 1	139	25.18	103	42.72
Month 2	117	17.09	85	15.29
Month 3	107	14.02	71	15.49
Month 4	78	12.82	45	6.67
Month 5	61	11.48	33	6.06

[a] Number of patients participating during the interval.
[b] Percent of patients requiring transfusion during that interval.

Available evidence suggests that patients with hematologic and solid cancers respond equivalently to EPREX® therapy, and that patients with or without tumour infiltration of the bone marrow respond equivalently to EPREX® therapy.

EPREX® significantly improved energy level (by 21% relative to placebo), increased daily activities (by 24% relative to placebo) and improved overall quality of life (by 25% relative to placebo), as measured on a 100 mm Visual Analog Scale, in cancer patients whose hematocrit increased at least 6 percentage points from baseline.

EPREX® was also studied in a large open label trial of 2030 anemic cancer patients on chemotherapy who were treated with EPREX® doses of 150 IU/kg subcutaneously three times a week for up to four months. Functional capacity parameters, i.e., energy level, activity level and overall quality of life, improved significantly ($p<0.001$) over baseline levels (38%, 32%, 24% improvement, respectively); these improvements correlated ($p<0.001$) directly with hemoglobin change from baseline. Patients whose hemoglobin increased the most, experienced the greatest improvements in energy level, activity level, and overall quality of life.

Once Weekly Dosing

Epoetin alfa was also studied in a placebo-controlled, double-blind trial utilizing QW dosing in a total of 344 anemic cancer patients. In this trial, 285 patients were treated with concomitant non

cisplatin-containing chemotherapy regimens and 59 patients were treated with concomitant cisplatin-containing chemotherapy regimens.

Of those patients treated with non cisplatin-containing chemotherapy regimens, 79 received carboplatin and 11 received oxaliplatin. Patients were randomized to EPREX® 40,000 IU/week or placebo SC for a planned treatment period of 16 weeks. If after 4 weeks of therapy hemoglobin had not increased by > 1 g/dL independent of RBC transfusion or the patients received RBC transfusion during the first 4 weeks of therapy, study drug was to be increased to 60,000 IU/week. 43% of patients in the EPREX® group had their dose of study drug increased to 60,000 IU over the entire study.

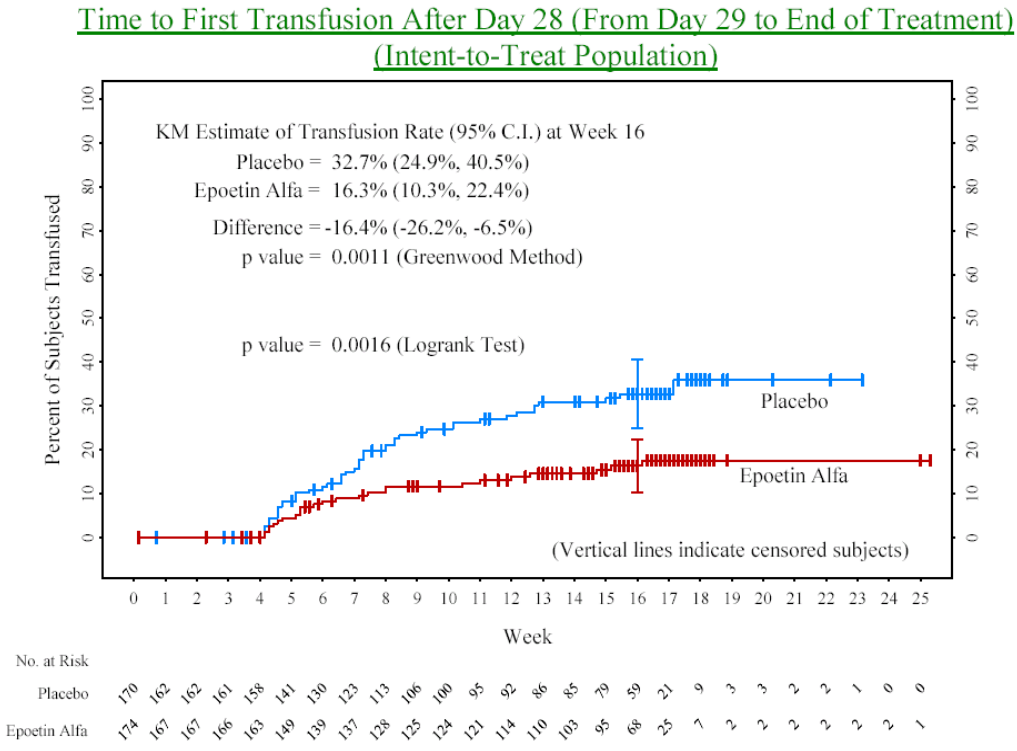
Results demonstrated that EPREX® therapy was associated with a significantly greater hemoglobin response than in the corresponding placebo-treated patients. The mean change from baseline to final hemoglobin value was 2.8 g/dL in patients treated with EPREX® and 0.9 g/dL in patients treated with placebo ($p < 0.0001$) (see Table 2.5).

Table 2.5: Hemoglobin (g/dL): Mean Change from Baseline to Last Value

	EPREX® (n)	Placebo (n)
Baseline	9.5 (174)	9.4 (170)
Last Value	12.2 (166)	10.3 (164)
Mean Change	2.8 (166)	0.9 (164)

In addition, the mean number of units of blood transfused per 100 patient-days on the study was significantly ($p < 0.0001$) lower in patients treated with EPREX® (0.76 units per 100 patient-days on study) than in corresponding placebo-treated patients (1.54 units per 100 patient-days on study). Moreover, the proportion of patients transfused after study day 29 through week 16 (day 112) was significantly ($p = 0.0011$) lower in the patients treated with EPREX® than in the corresponding placebo-treated patients. Estimates of the proportion of patients receiving transfusions over this period, using Kaplan-Meier analysis, indicated transfusion rates of 16% for patients in the EPREX® group versus 33% for patients randomized to placebo (see Figure 2.1).

Figure 2.1



Vertical marks represent subjects whose data was "censored" at that point, i.e., no longer available for analysis because the subjects were off study without transfusion. It should be noted that because this analysis starts after day 28; the horizontal lines are at 0 for the first 4 weeks of treatment. The vertical bars after Week 16 indicate the points at which subjects whose treatment extended beyond 16 weeks discontinued treatment.

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.

Tumour Progression, Increased Mortality and Thromboembolic Events

A randomized, placebo-controlled trial was conducted in 224 chemotherapy-naïve, non-anemic patients with small cell lung cancer receiving cisplatin-based combination chemotherapy, to investigate whether the concurrent use of EPREX® stimulated tumour growth as assessed by impact on overall response rate. Patients were randomized to receive EPREX® 150 units/kg or placebo subcutaneously TIW during chemotherapy. The overall response rates, after 3 cycles of treatment, were 72% and 67%, in the EPREX® and placebo arms, respectively. Complete response rates (17% vs. 14%) and median overall survival (10.5 mos vs. 10.4 mos) were similar in the EPREX® and placebo arms.

A systematic review of 57 randomized controlled trials (including the BEST and ENHANCE studies) evaluating 9353 patients with cancer compared ESAs plus transfusion with transfusion alone for prophylaxis or treatment of anaemia 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. Use of ESAs for treatment of anaemia in cancer patients on chemotherapy was associated with an overall survival odds ratio of 0.99 (95% CI: 0.72, 1.36). Sub-group analysis of anaemic cancer patients receiving chemotherapy from this systematic review demonstrates an odds ratio of 0.92 (95% CI: 0.78, 1.09) for platinum based chemotherapy and 1.10 (95% CI: 0.96, 1.24) for chemotherapy without platinum.

Studies of ESAs in patients with cancer exploring the effect on survival and/or progression of administrations of exogenous erythropoietin with higher hemoglobin targets beyond the treatment of anemia, and in patients not receiving chemotherapy or radiation therapy, and showing safety signals are presented below.

A randomized controlled clinical study EPO-INT-76 (referred to as the 'BEST' study) evaluated 939 mainly non-anemic women with metastatic breast cancer receiving chemotherapy. Patients received either weekly EPREX® or placebo for up to a year. This study was designed to show that survival was superior when EPREX® was administered to prevent anemia (maintain hemoglobin levels between 120 and 140 g/L). The study was terminated prematurely when interim results demonstrated that higher mortality at 4 months (8.7% EPREX® vs 3.4% placebo) and a higher rate of fatal thrombotic events (1.1% EPREX® vs 0.2% placebo) were observed among patients treated with EPREX®. Based on Kaplan-Meier estimates, at the time of study termination, the 12-month survival was lower in the EPREX® group than in the placebo group (70% vs 76%, HR 1.37, 95% CI: 1.07,1.75, p = 0.012).

A randomized, non-inferiority, open-label, multicenter study evaluated the impact of epoetin alfa on progression free survival (PFS) when used to treat anemia in patients receiving first or second line of chemotherapy for metastatic breast cancer. The study was designed to rule out a 15% risk increase in tumor progression or death of epoetin alfa plus standard of care (SOC) as compared with SOC alone. Of the 2098 anemic women randomized into the study, 1048 received SOC that included packed red blood cell (RBC) transfusions and 1050 received the SOC plus 40,000 IU epoetin alfa given subcutaneously. Randomization was stratified by line of chemotherapy (first-line or second-line) and HER-2/*neu* status. Demographic and baseline characteristics were generally well-balanced across the 2 treatment groups. The median age was 52 years, and most subjects were white (67.5%) or Asian (30.5%). Most subjects (56.1%) were postmenopausal at initial disease diagnosis. Overall, 31.1% of subjects were initially diagnosed with Stage IV disease. The extent and location of metastatic disease at baseline was similar across treatment groups. Most subjects (79.4%) were receiving first-line chemotherapy; 20.6% second-line chemotherapy. Baseline hormone receptor positive/HER-2/neu negative status was similar in both groups (epoetin alfa: 42.5%; SOC: 41.2%). Positive HER-2/*neu* status was reported for 38.8% of the overall population. At the clinical cutoff date, there were 841 (80%) subjects with a PFS event in the epoetin alfa treatment arm compared to 818 (78%) subjects in the SOC arm as per investigator assessment. The median PFS was 7.4 months in each arm (HR 1.09, 95% CI: 0.99, 1.20). The study did not achieve the non-inferiority objective of ruling out a 15% increased risk in PD/death. At clinical cutoff, 1337 deaths were reported. Median overall survival in the epoetin alfa group was 17.2 months compared with 17.4 months in the SOC group (HR 1.06, 95% CI: 0.95, 1.18). The OS data was not mature at the time of the PFS analysis and should be interpreted with caution. The proportion of subjects with RBC transfusions was 5.8% (61/1050) for subjects in the epoetin alfa group compared 11.4% (119/1048) for subjects in the SOC group.

Thrombotic vascular events occurred in 2.8% (29/1050) of subjects in epoetin alfa versus 1.4% (15/1048) of subjects in the SOC. The higher overall incidence of TVEs in the epoetin alfa group was especially evident for TVEs with notable clinical relevance, including ischemic stroke, pulmonary embolism and acute coronary syndrome.

In another placebo-controlled study using epoetin beta in 351 patients with head and neck cancer (referred to as the ENHANCE study), study drug was administered to maintain the hemoglobin levels of 140 g/L in women and 150 g/L in men. Locoregional progression-free survival was significantly shorter in patients receiving epoetin beta.

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

In a multicentre, randomized, double-blind placebo-controlled trial (EPO-CAN-20), patients with advanced non-small-cell lung cancer unsuitable for curative therapy were treated with EPREX® targeting hemoglobin levels between 120 and 140 g/L or placebo. Following an interim analysis of 70 of 300 patients planned, a significant difference in median survival in favour of patients in the placebo group was observed (63 vs 129 days, HR 1.84, p = 0.04).

A recently-completed phase III double-blind, randomized, placebo-controlled trial evaluating 989 cancer patients with active malignant disease but not being treated with either chemotherapy or radiation therapy showed no statistically significant reduction in the proportion of patients receiving red blood cell transfusions, and more deaths in the darbepoetin alfa group than in the placebo group (26% vs 20%) at 16 weeks (completion of treatment phase). With a median survival follow-up of 4.3 months, the absolute number of deaths at the end of the study was also higher in the darbepoetin alfa group (49% vs 46%, HR 1.29, 95% CI: 1.08, 1.55).

Randomized, controlled trials with decreased survival and/or decreased locoregional control are summarized in Table 2.6.

Table 2.6: 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				
BEST Metastatic breast cancer (n=939)	120-140 g/L	129 g/L 122, 133 g/L	12-month overall survival	Decreased 12-month survival
20000161 Lymphoid malignancy (n=344)	130-150 g/L (M) 130-140 g/L (F)	110 g/L 98, 121 g/L	Proportion of patients achieving a hemoglobin response	Decreased overall survival
PREPARE Early breast cancer (n=733)	125-130 g/L	131 g/L 125, 137 g/L	Relapse-free and overall survival	Decreased 3 yr. relapse-free and overall survival
GOG 191 Cervical Cancer (n=114)	120-140 g/L	127 g/L 121, 133 g/L	Progression-free and overall survival and locoregional control	Decreased 3 yr. progression-free and overall survival and locoregional control
Radiotherapy Alone				
ENHANCE Head and neck cancer (n=351)	≥150 g/L (M) ≥140 g/L (F)	Not available	Locoregional progression-free survival	Decreased 5-year locoregional progression-free survival Decreased overall survival
DAHANCA 10 Head and neck cancer (n=522)	140-155 g/L	Not available	Locoregional disease control	Decreased locoregional disease control
No Chemotherapy or Radiotherapy				
EPO-CAN-20 Non-small cell lung cancer (n=70)	120-140 g/L	Not available	Quality of life	Decreased overall survival
20010103 Non-myeloid malignancy (n=989)	120-130 g/L	106 g/L 94, 118 g/L	RBC transfusions	Decreased overall survival

SURGERY PATIENTS

Use of EPREX® to Reduce Allogeneic Blood Exposure

EPREX® 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. Patients were stratified into one of three groups based on their pretreatment hemoglobin [≤ 100 (n=2), >100 to ≤ 130 (n=96), and >130 to ≤ 150 g/L (n=218)] and then randomly assigned to receive EPREX® doses of 300 IU/kg, 100 IU/kg or placebo by subcutaneous injection for 10 days before surgery, on the day of surgery, and for four days after surgery.

Treatment with EPREX® 300 IU/kg significantly (p=0.024) reduced the risk of allogeneic transfusion in patients with a pretreatment hemoglobin of >100 to ≤ 130 g/L; 16% of EPREX® 300 IU/kg, 23% of EPREX® 100 IU/kg and 45% of placebo-treated patients were transfused. There was no significant difference in number of patients transfused between EPREX® (9% 300 IU/kg, 6% 100 IU/kg) and placebo (13%) in the > 130 to ≤ 150 g/L hemoglobin stratum. In the >100 to ≤ 130 g/L pretreatment stratum, the mean number of units transfused per patient treated with EPREX® (0.45 units 300 IU/kg, 0.42 units 100 IU/kg) was less than the mean transfused per placebo-treated patient (1.14 units) (overall p=0.028).

During the pretreatment to presurgery period, for both the > 100 to ≤ 130 g/L and > 130 to ≤ 150 g/L strata, mean increases in hemoglobin (among-group difference, p=0.0001) and hematocrit (among-group difference, p=0.0001) were observed in both groups treated with EPREX®, while no changes were observed in the placebo-treated group. In addition, greater mean increases in reticulocyte counts were observed in the groups treated with EPREX® compared to the placebo-treated groups (p=0.0001). These increases were maintained postoperatively.

EPREX® has also been studied in two additional placebo-controlled trials enrolling patients scheduled to undergo major elective orthopedic surgery. In one study (n=208), patients received either EPREX® 300 IU/kg or placebo for 9 or 14 days. In the second study (n=200) patients received either EPREX® 300 IU/kg, 100 IU/kg, or placebo for 15 days. Results of analyses comparing the risk of transfusion according to baseline hemoglobin for intent-to-treat patients are as follows:

Table 2.7: Percent of Patients Who Required Transfusions, Stratified by Baseline Hemoglobin

Baseline Hemoglobin	300 IU/kg 14/15 Days	300 IU/kg 9 Days	100 IU/kg 15 Days	Placebo 14/15 Days
EPREX® 300 IU/kg or placebo for 9 or 14 days				
>100 to 130 g/L	(N=25) 32%	(N=18) 61%	-	(N=23) 74%
>130 g/L	(N=52) 19%	(N=35) 14%	-	(N=55) 31%
EPREX® 300 IU/kg, 100 IU/kg or placebo for 15 days				
>100 to 130 g/L	(N=22) 14%	-	(N=25) 44%	(N=27) 78%
>130 g/L	(N=29) 14%	-	(N=37) 11%	(N=39) 36%

Results from both orthopedic surgery studies indicate that in patients with a baseline hemoglobin level of > 100 to ≤ 130 g/L, the risk that placebo-treated patients will require an allogeneic blood transfusion is two- to three-fold greater than that of patients treated with EPREX®.

EPREX® was also studied in an open-label, parallel-group trial enrolling 145 subjects with a pretreatment hemoglobin level of ≥ 100 to ≤ 130 g/L who were scheduled for major orthopedic hip or knee surgery. Subjects were randomly assigned to receive one of two dosing regimens of EPREX® (600 IU/kg once weekly for three weeks prior to surgery and on the day of surgery or 300 IU/kg once daily for 10 days prior to surgery, on the day of surgery and for four days after surgery), administered subcutaneously. All subjects received oral iron and appropriate pharmacologic anticoagulation therapy.

From pretreatment to presurgery, the mean increase in hemoglobin in the 600 IU/kg weekly group (14.4 g/L) was greater than observed in the 300 IU/kg daily group (7.3 g/L). The mean increase in absolute reticulocyte count was smaller in the weekly group (0.11 x 106/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 (16% in the 600 IU/kg weekly group and 20% in the 300 IU/kg daily group). The mean number of units transfused per EPREX®-treated subject was approximately 0.3 units in both treatment groups. The transfusion rates were substantially lower than that for placebo-treated patients (45%), and similar to the transfusion rate for the EPREX® 300 IU/kg-treated patients (16%) whose baseline hemoglobin was ≥ 100 to ≤ 130 g/L in the first study referenced in this section.

A randomized controlled study (SPINE) in which 681 adult patients not receiving prophylactic anticoagulation and undergoing spinal surgery received either 4 doses of 600 U/kg EPREX® (7, 14 and 21 days before surgery and on the date of surgery) and standard of care treatment, or standard of care treatment alone. Preliminary analysis showed a higher incidence of deep vein

thrombosis, determined by either Colour Flow Duplex Imaging or by clinical symptoms in the EPREX® group [16 patients (4.7%)] compared to the standard of care group [7 patients (2.1%)]. In addition, 12 patients in the epoetin group and 7 patients in the standard of care group had other thrombotic vascular events.

Combined Use of EPREX® and ABD

A double-blind study was conducted in 204 patients scheduled to undergo elective orthopedic surgery with hematocrits ≤ 39% and no underlying anemia due to iron deficiency. On average, patients treated with EPREX® 600 IU/kg were able to predeposit significantly more units of blood (4.5 units) than placebo-treated patients (3.0 units) ($p<0.001$). Also, significantly more patients treated with EPREX® ($p\leq 0.05$) were able to predeposit between 3 to 6 units, inclusively, of autologous blood than the corresponding placebo-treated patients. Virtually all (98%) of the patients treated with EPREX® predeposited 3 or more units compared with 69% of placebo-treated patients. While 37% of the placebo patients were able to predeposit 4 or 5 units, 81% of the EPREX® patients predeposited 4 or more units. Among the evaluable patients, fewer patients who received EPREX® required allogeneic transfusions (19.8%) than patients who received placebo (31.0%).

DETAILED PHARMACOLOGY

Pharmacodynamics

Table 2.8 summarizes the in vitro biological activity of epoetin alfa.

Table 2.8

Test System	Species	Concentration Tested	Observations
Iron incorporation into bone marrow cells in culture	Rat	0.5 - 5.0 IU/mL	Increased ^{59}Fe incorporation into heme in cell cultures treated with epoetin alfa. Dose response curve identical to that of u-HuEPO.
Colony forming units (CFU-E) assay	Mouse	0.075 - 0.75 IU/mL	The number of CFU-E units formed was directly proportional to amount of epoetin alfa
Burst forming units (BFU-E) assay	Mouse	0.1 - 3.0 IU/mL	Epoetin alfa produced dose-dependent increases in the number of BFU-E.
BFU-E Assay	Human	0.5 - 3.0 IU/mL	Epoetin alfa was able to support the growth and differentiation of human erythroid progenitors.
Assay for colony stimulating factor (CSF) activity	Mouse	10 IU/mL	No increase in non-erythroid colony formation with epoetin alfa.
Bursting-promoting activity assay	Human	0.63 and 1.25 IU/mL	No effect of epoetin alfa on the burst promoting activity in human mononuclear cells.
Megakaryocyte development assay	Mouse	Up to 3.2 IU/mL	Increased number of megakaryocytes in response to epoetin alfa in mouse bone marrow cell culture.
Radioimmunoassay (RIA)	Rabbit Antisera (U/anti-U) (R/anti-U) (R/anti-R)		Parallel curves suggesting immunological identity of epoetin alfa and u-HuEPO.
Non-pregnant uterus	Rat	10 - 1000 IU/mL	No significant effect on spontaneous contractions compared to vehicle.
Pregnant uterus	Rat	10 - 1000 IU/mL	No significant difference between drug and vehicle effects on spontaneous or oxytocin-induced contractions.
Ileum	Guinea Pig	10 - 1000 IU/mL	Epoetin alfa occasionally produced ileal contraction at 1000 IU/mL.
Trachea	Guinea Pig	10 - 1000 IU/mL	No effect on the resting tension or response to histamine.
Vas deferens	Guinea Pig	10 - 1000 IU/mL	No effect on the response to exogenous adrenaline.
Atria	Guinea Pig	10 - 1000 IU/mL	No difference between drug and vehicle treatments on contractile force or rate.
Blood	Rabbit	10 - 1000 IU/mL	No increase in hemolysis in blood of rabbits treated *in vitro*.

In general pharmacological testing, epoetin alfa is devoid of pharmacological activity up to 1000 IU/mL in *in vivo* studies on the cardiopulmonary system, isolated smooth muscle and the blood clotting system.

In addition, epoetin alfa reacts identically to u-HuEPO in RIAs using a variety of different antisera. Urinary erythropoietin (u-HuEPO) and recombinant epoetin alfa appear indistinguishable from each other in the parameters of biological and immunological reactivity measured by these assay systems. Table 2.9 summarizes the *in vivo* biological activity of epoetin alfa.

Table 2.9

Test System	Species	Doses Tested	Observations
Exhypoxic Poly-cythemia	Mouse	1.5 IU/mL	Increased hematopoiesis due to epoetin alfa administration.
Hematocrit	Mouse	50 - 1500 IU/kg i.p.	Increased hematocrit with epoetin alfa administration which was statistically significant at doses equal to or greater than 150 IU/kg.
Sub-total Nephrectomy	Rat	10 IU/day, 5 days/week for 2 weeks, i.m.	Increased hematocrit with epoetin alfa treatment compared to vehicle control.
Hematocrit	Dog	280 or 2800 IU/kg, i.v.	Dose-related increases in hematocrit, reticulocyte and RBC count with epoetin alfa treatment as compared to vehicle control.
r-HuEPO effect on platelet levels	Mouse	300 - 1200 IU/kg i.p. daily for 5 days	Increased hematocrit with no effect on platelet numbers. Increased megakaryocytes in the spleen.
Melphalan - Induced Anemia	Dog	100 or 300 IU/kg	Melphalan-induced anemia is attenuated by epoetin alfa as evidenced by prevention of decreased RBC and reticulocytes
Intestinal Charcoal Meal Propulsion	Mouse	20 - 2000 IU/kg i.v.	No significant effect observed.
Renal Function	Rat	20 - 2000 IU/kg i.v.	No significant effect on urine volume or electrolytes.
Blood Coagulation	Rat	20 - 2000 IU/kg i.v.	No effect on prothrombin time, activated partial thromboplastin time or recalcification time.
Fibrinolysis	Rat	20 - 2000 IU/kg i.v.	No significant effect on euglobulin lysis time.
Cardiopulmonary	Anesthetized Dog	20 - 2000 IU/kg i.v.	No significant alterations observed on blood pressure, heart rate, ECG, blood flow, respiratory rate.
Cardiopulmonary	Conscious Dog	20 - 2000 IU/kg i.v.	No significant difference in blood pressure, heart rate, ECG between vehicle and drug treatments.
CNS	Mouse	20 - 2000 IU/kg i.v.	No effect on general behaviour, motor coordination, acetic acid-induced writhing, hexobarbital sleeping time anticonvulsant effect. No statistically significant effect on locomotor activity. Significant decrease in body temperature produced by 2000 IU/kg at 4 hrs. after treatment.
CNS	Rat	20 - 2000 IU/kg i.v.	No effect on pain threshold, mono- or polysynaptic spinal reflexes, no antipyretic effect.
CNS	Rabbit	20 - 2000 IU/kg i.v.	No effect on E.E.G.

In general pharmacological testing, epoetin alfa is devoid of significant pharmacological activity up to 2000 IU/kg *in vivo*. The only noted pharmacological effect was a decrease in body temperature in mice after the 2000 IU/kg i.v. dose of epoetin alfa. This dose is in excess of the clinically effective dose (20-500 IU/kg i.v.) and therefore this finding should pose no problem to the use of epoetin alfa clinically. Therefore, epoetin alfa, as tested in various pharmacological systems, appears to be devoid of significant pharmacological activity which could affect its clinical safety.

Non-Clinical Pharmacokinetics

Administration:

In the primary studies of the pharmacokinetics and metabolism of exogenously administered epoetin alfa in animals, the intravenous (i.v.) route was the mode of drug administration. Consequently, the rate and extent of absorption was not a parameter under investigation. However, it has been shown in a uremic rabbit model that ^{125}I-epoetin alfa is almost completely absorbed from the empty peritoneal cavity.

In one multiple dose study in cynomolgus monkeys, enhanced serum levels of epoetin alfa over baseline were found after subcutaneous (s.c.) administration at 1000 IU/kg, the only s.c. dose given. Epoetin alfa was absorbed slowly from the injection site, which resulted in a much slower decline in serum epoetin alfa levels than observed after i.v. administration. These issues and their clinical relevance are examined in the human clinical pharmacology section, where the kinetics of epoetin alfa after administration by i.v. and s.c. routes are compared.

Distribution:

In studies in which radiotracer techniques were utilized, tissue concentrations of radioactivity following i.v. administration of ^{125}I-epoetin alfa to rats were highest in the bone marrow, spleen and kidneys.

Other organ systems in which radioactivity was detected (in addition to the plasma) included the pituitary, lungs, liver and adrenals.

Radioactivity levels in the thyroid increased over time. This was attributed to the uptake of free ^{125}I and was not unexpected since no measures were taken to block uptake into the thyroid gland.

The initial volume of distribution of i.v. administered ^{125}I-epoetin alfa approximated that of the plasma volume.

The distribution of exogenously administered epoetin alfa was examined in the rat by whole-body autoradiography and monitoring of individual tissue levels.

In the whole-body autoradiography experiments animals were sacrificed at 0.5, 1, 4 and 24 hours post-dose. The highest radioactivity was detected in the bone marrow 30 minutes after treatment. Relatively high radioactivity was also present in the thyroid, blood, renal cortex, spleen, lungs, liver and adrenals. Almost no activity was present in the brain, gastrointestinal tract, muscle or spinal cord. The radioactivity distribution pattern was similar 30 minutes and 1 hour after treatment. Twenty-four hours after treatment, radioactivity decreased to the background level in all tissues other than the thyroid.

These findings were very consistent with measured radioactivity levels in various tissues, with animals being sacrificed at 0.5, 1, 4, 8 and 24 hours. Thirty minutes after treatment, the highest radioactivity was determined in the bone marrow. Radioactivity was also present at high levels in the spleen and kidneys 30 minutes after treatment, followed in descending order by the pituitary, liver and adrenals. Radioactivity in these organs decreased over time in parallel with plasma radioactivity levels. In contrast, radioactivity levels were low in the brain, thymus, skin and mesenteric lymph nodes. No radioactivity was detected in erythrocytes at any time point.

Radioactivity levels in the thyroid increased over the 24-hour study period. This was attributed to the uptake of free ^{125}I and was not unexpected since no measures were taken to block uptake into the thyroid gland.

Since erythropoietin is the primary regulator of erythropoiesis, it is not surprising that labelled epoetin alfa was promptly transferred to the bone marrow.

The initial volume of distribution of i.v. administered iodinated epoetin alfa approximated that of the plasma volume. Thereafter, the labelled hormone was cleared from the plasma in a biphasic manner. Using labelled albumin as a marker for vascular space, there was insufficient accumulation of ^{125}I-epoetin alfa in the liver, kidney, spleen or bone marrow to account for the initial component of the plasma disappearance curve. This suggests that this component was due to distribution of the hormone between the plasma and the extravascular space from which elimination subsequently occurred.

Metabolism and Excretion:

The metabolism of both endogenous native and exogenously administered epoetin alfa appears to occur primarily in the liver. Studies in the rat have shown this is due to the fact that desialylated hormone is cleared very efficiently by hepatic galactosyl receptors. Consequently, the bulk of the desialylated hormone is sequestered in the liver where it is rapidly catabolized to smaller, unidentified products which are released back into the plasma and subsequently excreted by the kidney.

Urinary excretion data substantiate the hepatic clearance observations in the rat. Approximately 90% of the administered dose was recovered in the urine but only about 3% of this constituted immunoreactive material.

Endogenous erythropoietin is synthesized as a pro-form that contains a 27 amino acid leader which is processed during secretion. The biologically active hormone has a molecular weight of around 34,000 daltons, is heavily glycosylated and is particularly rich in sialic acid residues. The sialic acid residues of erythropoietin are not required for the expression of biological activity *in vitro* but are required for its expression *in vivo*. The hormone's sialic acid residues serve to prevent its premature removal from the circulation. Any reduction of the sialic acid content results in a drastically reduced biological half-life. This is due to the fact that desialylated erythropoietin/epoetin alfa is cleared very efficiently by galactosyl receptors in the liver. These aspects of the metabolism of erythropoietin have been reviewed and the data obtained in rats for epoetin alfa are described below.

On administration of ^{125}I labelled desialylated epoetin alfa to male Sprague-Dawley rats, only 24% of the material was recovered in the plasma as TCA-precipitable radioactivity within 2 minutes after injection and 96% of the hormone was cleared from the plasma with a half-life of 2 minutes. There was a reciprocal increase in hepatic acid-precipitable radioactivity as plasma acid-precipitable radioactivity declined. At the peak organ accumulation, 87% of the acid-precipitable radioactivity was sequestered in the liver.

Following the uptake of radiolabelled protein by the liver, there was a rapid increase in the intracellular radioactivity which was acid-soluble and this was followed by a similar increase in plasma acid-soluble radioactivity after a delay of approximately 14 minutes.

Asialo-orosomucoid, but not orosomucoid yeast mannan or Dextran sulfate 500, inhibited the rapid clearance and hepatic accumulation of desialylated erythropoietin. This suggests that uptake by the liver is regulated in part by hepatocyte galactosyl receptors. Oxidation of the desialylated hormone restored its plasma recovery and clearance to that of epoetin alfa but rendered it biologically inactive. Other determinants which may serve as recognition sites for the metabolism of epoetin alfa are as yet unknown.

Metabolism has also been studied by incubating ^{125}I-epoetin alfa with various rat tissue homogenates at 37°C. Almost 100% of the added radioactivity was recovered from the TCA-precipitable fraction in liver, spleen and muscle at all sampling times (0, 0.5 hr, 1 hr, 2 hr, 4 hr). In the kidneys, however, acid-precipitable radioactivity decreased over time, and the recovery rate was 80.7% four hours after the start of incubation.

The recovery of immunoreactive radioactivity decreased over the course of the experiment in all tissues when incubated at 37^{o}C. Decreases were relatively fast in the kidneys and liver.

The fact that intact hormone and not desialylated epoetin alfa was used in these *in vitro* studies probably influenced the rate at which epoetin alfa was metabolized. Also, although the *in vitro* results implicate the kidney as a metabolic organ in the rat, it necessitates that epoetin alfa is accumulated into kidney cells for this organ to have an inactivation role *in vivo*.

Urinary excretion data for ^{125}I-epoetin alfa substantiated the hepatic clearance observations presented above. The excretion of ^{125}I radioactivity in urine and feces of normal and partially nephrectomized rats has been compared. In normal rats, 86.9% and 5.7% of the dose was excreted into urine and feces, respectively, by 96 hours after treatment. Only 5.6% of the dose was recovered in the TCA-precipitable fraction of the urine and only 2.8% of the total dose was found as immunoreactive radioactivity in the urine. In partially nephrectomized rats, 81.5% and 4.8% of the total dose was excreted into urine and feces, respectively, over the same time frame.

Excretion was slightly delayed compared to normal rats. In urine, acid-precipitable radioactivity accounted for 3.6% and 3.3% of the dose, respectively.

The erythropoietin content of 24-hour urine collections has been assayed in a number of clinical conditions and healthy subjects. Low erythropoietin levels (mean values) were found in polycythemia vera (<10 mU/mL), and anemia associated with uremia (<16 mU/mL) and rheumatoid arthritis (<20 mU/mL). Higher levels were found in association with hypoxic polycythemia and anemia (>75 mU/mL) due to iron deficiency (80 mU/mL), blood loss (>100 mU/mL) and marrow hypoplasia (aplastic anemia; >14,000 mU/mL). Hence, urinary excretion of intact endogenous erythropoietin also appears to contribute minimally to the overall clearance of the hormone in man under normal conditions.

TOXICOLOGY

Epoetin alfa has a very low potential for acute toxicity when administered intravenously to rats, mice and dogs, and orally or intramuscularly to rats and mice. There was no mortality or other signs of toxicity when administered at single doses up to 20,000 IU/kg.

Table 2.10: Acute Toxicity Studies

Strain Species	# Animal Group	Route	Vehicle	Dose Level IU/KG	Lethality	Summary Toxic Signs
Mice	8/sex	i.v.	0.25%/HSA	0 (vehicle)	0/16	None
				20000	0/16	None
		p.o.	0.25%/HSA	20000	0/16	None
		i.m.	0.25%/HSA	20000	0/16	None
Rats	8/sex	i.v.	0.25%/HSA	0 (vehicle)	0/16	None
				20000	0/16	None
		p.o.	0.25%/HSA	20000	0/16	None
		i.m.	0.25%/HSA	20000	0/16	None
Rats	10/sex	i.v.	0.25%/HSA	0 (vehicle)	0/20	None
				80	0/20	None
				240	0/20	None
				800	0/20	None
				2400	0/20	None
				8000	0/20	None
Dogs	2 males	i.v.	0.25%/HSA	0 (vehicle)	0/20	None
				10000	0/20	None
				20000	0/20	None

Most of the changes associated with intravenous (i.v.) and subcutaneous (s.c.) multidose studies represent the expected pharmacologic actions of epoetin alfa, as shown in Table 2.11

Table 2.11: Multidose Studies Results

Key to Abbreviations

RBC	Red blood cells	SGOT	Serum glutamic-oxaloacetic transaminase
Hct	Hematocrit	LDH	Lactic acid dehydrogenase
Hgb	Hemoglobin	CPK	Creatinine phosphokinase
MCH	Mean corpuscular hemoglobin	A/G Ratio	Albumin/Globulin Ratio
MCV	Mean corpuscular volume	M:E Ratio	Myeloid:Erythrocytes Ratio
MCHC	Mean corpuscular hemoglobin concentration	TL	Total lipids
APTT	Activated partial thromboplastin time	TCHO	Total cholesterol
		PL	Phospholipid
		PT	Prothrombin time

Study	Lethality	Toxic Signs	Clinical Path	Gross/Micro
Rats i.v. 4weeks/ 4week recovery	No drug-related deaths	Reddening of pinnae, and extremities in females @ 400 and in both sexes @ 2000 IU/kg. Reduced body weight gains and food consumption in males @ 2000 IU/kg	Increased RBC, Hct, Hgb, reticulocytes, SGOT, LDH, bilirubin. MCH and MCV @ 16, 80 IU/kg in females and 80 IU/kg in males. Decreased MCV, MCHC and MCH @ higher doses except MCHC in females in all treated groups. Platelets in most treated groups, glucose, cholesterol and prolongation of APTT and PT. Urine spec. grav. in males @ 400, 2000 IU/kg. All changes were partially reversible.	Enlarged spleens. Increased erythropoiesis of bone marrow. Extra-medullary erythropoiesis in spleen and liver.
Rats i.v. 13 weeks/ 5week recovery	2 rats @ 500 IU/kg on Days 85 and 87	Decreased body weight gains @ 500 IU/kg. Dilation of vessels of eyes, reddening of retinas @ 100, 500 IU/kg.	Increased RBC, Hct, Hgb, reticulocytes, MCV, MCH, SGOT, CPK, LDH, bilirubin, potassium and phosphorus. Urine occult blood and RBCs in females @ 500 IU/kg. Prolongation of APTT. Decreased urine spec. grav. MCHC, platelets, glucose, albumin, total protein, cholesterol and calcium. Everything reversible.	Enlarged spleens, heart, kidneys, adrenals. Erosion of glandular stomach. Increased erythropoiesis in bone marrow. Extra-medullary hematopoiesis. Reversible.
Rats s.c. 2 weeks	None	None	Increased RBC, Hct, Hgb, reticulocytes, WBC, MCV, nucleated RBC, bilirubin, total protein, calcium, chloride, sodium, albumin and globulin. Decreased MCH, MCHC, BUN, glucose and cholesterol. Low titer antibodies on day 15 in 4 rats @ 200 and 1 rat @ 2000 IU/kg.	Enlarged spleens. Erythroid hyperplasia of bone marrow. Extra-medullary hematopoiesis.

Table 2.11: Multidose Studies Results (cont'd)

Study	Lethality	Toxic Signs	Clinical Path	Gross/Micro
Dogs i.v. 4 weeks	None	Conjunctival injection and reddening of oral mucosa @ 200, 2000 IU/kg.	Increased RBC, Hct, Hgb, reticulocytes, LDH, total protein, triglycerides, potassium, bilirubin and giant platelets. Decreased MCH, MCHC, MCV, glucose @ 200, 2000 IU/kg.	Enlarged spleens. Myelofibrosis @ 2000 IU/kg. Extramedullary erythropoiesis and megakaryopoiesis. Prostates smaller @ 2000 IU/kg.
Dogs i.v. 4 weeks	None	Conjunctival injection @ 2000 IU/kg. Decreased weight gain, food consumption @ 2000 IU/kg. Anaphylactic response on Day 14.	Increased RBC, Hct, Hgb, reticulocytes, LDH, total protein, triglycerides, bilirubin, potassium, cholesterol, CPK, alpha-2 globulin and beta globulin. Prolongation of APTT @ 200 IU/kg in males. Decreased MCH in males @ 200, 2000 IU/kg, MCHC @ 2000 IU/kg in females and males. Glucose and A/G ratios @ 200 or 2000 IU/kg.	Enlarged spleens. Extra-medullary erythropoiesis. Decreased lymphocytes in cortex of thymus, partial atrophy of seminiferous tubules @ 2000 IU/kg.
Dogs i.v. 3x/week/3 weeks 3 week Recovery	None	Red, swollen lips hypoactivity, pale mucous membranes and labored respiration in females @ 2800 IU/kg from Day 11 to 17 then decreased.	Increased RBC, Hgb, PCV, MCHC, reticulocytes, total protein, cholesterol, potassium and globulin. Decreased Glucose, A/G ratio, BUN, MCV and M:E ratios.	Enlarged spleens. Extra-medullary hematopoiesis.
Dogs i.v. 13 weeks/5 week recovery	None	Emesis, mucous stool. Decreased spontaneous activity. Prostration and tachypnea. Conjunctival injection. Redness of oral mucosa and auricle. Circumoral and circumpalebral swelling. Reversible.	Increased Urine volume, RBC, Hct, Hgb, reticulocytes, LDH, potassium, total protein and urinary occult blood. Prolongation of APTT and prothrombin. Decreased MCV, MCHC, MCH, glucose, albumin, A/G ratio, urine spec. Grav. And erythrocyte sedimentation rates. Reversible except MCV and MCH.	Enlarged spleens, kidneys, myelofibrosis, extramedullary erythropoietin. Reversible except fibrosis.

Table 2.11: Multidose Studies Results (Cont'd)

Study	Lethality	Toxic Signs	Clinical Path	Gross/Micro
Dogs i.v. 52 weeks	5 @ 100 IU/kg 6 @ 5000 IU/kg	Collapse, laboured respiration, salivation, tremors in dogs prior to death. Conjectival hyperemia. Increased water consumption and decreased body weight gain in 500 IU/kg males.	Increased RBC, Hgb, Hct platelet, reticulocyte, urine volume, urine occult blood, SGOT, LDH, BUN, TL, TCHO, PL, CPK @ 100, 500 IU/kg. Decreased Glucose	Enlarged spleens, kidneys swollen and increased weight @ 100, 500 IU/kg. Extramedullary hematopoiesis and megakaryopoiesis in spleen. Moderate to marked congestion of kidneys associated with glomerular dilation and slight to moderate round-cell infiltration. Dilation and thickening of Bowman's capsule with or without fibrosis. Slight to marked fibrosis of the femoral and sternal marrow cavities @ 100, 500 IU/kg.
Dogs (Neonates) i.v. 4 weeks/ 4 week recovery	No dose-related deaths.	None	Increased Hct in females. Slight RBC through Day 28. During withdrawal phase, RBC decreased @ 500 IU/kg but by Day 55 comparable to controls.	Enlarged spleens. Extra-medullary hematopoiesis. Erythroid hyperplasia of bone marrow.
Cynomolgus monkeys i.v. and s.c. (@ 1000 IU/kg only) 13 week/10 week recovery	1 @ 0 IU/kg 1 @ 500 IU/kg 1 @ 1000 IU/kg	Reddening of facial skin in females @ 100, 500, 1000 IU/kg. Minimal reduction in body weight and food consumption in females @ 1000 IU/kg (i.v.). Dilation of eye vessels @ 500, 1000 IU/kg (i.v. and s.c.).	Increased RBC, Hgb, PCV and reticulocytes.	Necropsy report not included in interim report.
Rhesus Monkeys (Adults Neonates) i.v. 6 week/10 week recovery	None	None	Increased RBC - adults only. Reversible.	Necropsy not performed.

The carcinogenic potential of epoetin alfa has not been evaluated.

There was no indication of teratogenicity in rats or rabbits and no toxicity in F1 and F2 generations at doses up to 500 IU/kg. In male and female rats treated intravenously with epoetin alfa, there was a trend for slightly increased fetal wastage at doses of 100 and 500 IU/kg/day. Fertility, teratology and reproductive performance studies are summarized in Tables 2.12 and 2.13

Table 2.12: Fertility and Reproductive Performance and Teratology Studies Protocol Summary/Results

Study	Toxicity	Embryo/Fetal Toxicity	Teratogenicity
Segment I Intravenous Fertility and Reproductive Performance in Sprague-Dawley Rats 0 (vehicle), 20, 100, 500 IU/kg/day. Treated animals mated to treated animals	Yes - Lethality in 1 male @ 100 IU/kg and 8 males @ 500 IU/kg. Mild redness of pinna and limbs, reduced food consumption and body weight gain, gastric erosion @ 100, 500 IU/kg Increased weight of heart, lungs, kidneys, spleen and adrenals due to pharmacologic effect of epoetin alfa @ 100 and 500 IU/kg. Decrease in thymus weights in males @ 500 IU/kg.	Reduced body weights and delays in fetal ossification @ 20, 100, 500 IU/kg were associated with reductions in maternal weight gain. Increase in resorptions @ 500 IU/kg and placental remnants @ 100, 500 IU/kg and dead implantations @ 500 IU/kg.	No - No external, visceral or skeletal abnormalities.
Segment II Intravenous Teratogenicity in Sprague-Dawley rats, 0 (vehicle), 20, 100, 500 IU/kg	No - Increased spleen, liver, left adrenal weights, @ 500 IU/kg due to pharmacologic effect epoetin alfa.	Yes - Fetal body weights and delayed ossification @ 500 IU/kg.	No - No increase in anomalies.
Intravenous Teratogenicity in NZW rabbits, 0 (vehicle), 20, 100, 500 IU/kg	Yes - Slight decrease in body weight and food consumption @ 500 IU/kg.	No	No - No increase in anomalies.

Table 2.13: Perinatal and Postnatal Studies Protocol Summary/Results

Study	Maternal/Toxicity	Embryo/Fetal Toxicity	Parturition/Neonatal Growth and Survival
Segment III Intravenous Peri- and Postnatal in Slc:SD rats. 0 (Vehicle), 20, 100, 500 IU/kg	Yes Redness of limbs and pinnae. Slight increase in body weight @ 100 and 500 IU/kg during lactation. Decrease in food consumption @ 500 IU/kg. Increased spleen and lung weights @ 100 and 500 IU/kg and dark red spots in stomach and increased heart weight @ 500 IU/kg.	Yes Reduced body weights and delayed ossification, appearance of abdominal hair, eyelid opening and decrease in the number of caudal vertebrae (day 22 postpartum) @ 500 IU/kg.	All F_1, F_2 generation normal.

In a series of mutagenicity studies, epoetin alfa failed to induce bacterial gene mutations (Ames Test), chromosomal aberrations in mammalian cells, gene mutation at the HGPRT locus or micronuclei in mice (see Table 2.14). Epoetin alfa was not pyrogenic when tested in rabbits.

Table 2.14

Test Type	Study	Dose Levels	Response
Ames	*Escherichia coli* (WP2, Hcr$^-$) *Salmonella typhimurium* (TA1535, TA100, TA1537, TA98)	312.5, 625, 1250, 5000 IU/plate in presence and absence of S-9 mix.	Negative
Chromosomal Aberration	Chinese Hamster Lung Cells	1136, 2273, 4545 IU/mL in the absence of, and 947, 1894, 3788 IU/mL in the presence of S-9 mix.	Negative
in vivo Micro-nucleus	Slc:ddY male Mice	1.25×10^5, 2.5×10^5, 5×10^5 IU/kg	
Gene Mutation at the HGPRT locus	Chinese Hamster Ovary Cells	625, 1250, 2500, 5000 IU/mL with and without S-9 mix.	Negative

Results of antigenicity studies indicated weak to strong evidence of antibody formation in rabbits and guinea pigs, but not in mice. The reason for this difference in the mouse is not clear, but anaphylaxis is not anticipated when administered to humans since the test material is of human origin. Seizure threshold potential in mice, water content of brain tissue and electrolyte distribution in rats were unaffected by intraperitoneal doses of epoetin alfa. The results of these and other special studies are summarized in Table 2.15.

Table 2.15: Special Studies

Key to Abbreviations

RBC	Red blood cells	SGOT	Serum glutamic-oxaloacetic transaminase
Hct	Hematocrit	LDH	Lactic acid dehydrogenase
Hgb	Hemoglobin	CPK	Creatinine phosphokinase
MCH	Mean corpuscular hemoglobin	A/G Ratio	Albumin/Globulin Ratio
MCV	Mean corpuscular volume	M:E Ratio	Myeloid:Erythrocytes Ratio
MCHC	Mean corpuscular hemoglobin concentration	TL	Total lipids
APTT	Activated partial thromboplastin time	TCHO	Total cholesterol
		PL	Phospholipid
		PT	Prothrombin time

Test Type	Study	Dose Levels	Average Response
Seizure Threshold	CF1 mice 20/group ip 3x/week for 3 weeks. Once a week after the third dose, i.v. infusion with 0.5% metrazole.	0 (saline), 0 (vehicle + saline), 450 or 1500 IU/kg	No changes in seizure threshold.
Electrolyte and Brain Water Distribution	Sprague Dawley Male Rats 15/group i.p. 3x/week for 3 weeks 5/group sacrificed after 3, 6, and 9 doses.	0 (saline), 0 (vehicle + saline), 450 or 1500 IU/kg.	No effect in electrolyte or water content of brain tissue, plasma or spinal fluid. Increased spleen and liver weight and Hct @ 1500 IU/kg. Increased Hct @ 450 IU/kg.
Antigenicity 72-Hr Passive Cutaneous Anaphylaxis (PCA) Test	C_3H/He and BALB/C mice 10/group i.p. 1x/week for 2 weeks	100, 1000 IU/kg animals + 2 mg alum/animal	Only one mouse (C_3H/He) in 1000 IU/animal gave positive response.
4-Hr Passive Cutaneous Anaphylaxis (PCA) Test	Hartley Guinea Pigs 5/group, i.v. 2x/week for 2 weeks 5/group s.c. 2x/week for 4 weeks.	100, 1000 IU/kg 14000 IU/kg + Freund's Complete Adjuvant (FCA)	Negative PCA test for 100 and 1000 IU/kg but 50 positive for 14000 IU/kg + FCA.
Active Systemic Anaphylaxis test	Hartley Guinea Pigs 5/group i.v. 2x/week for 2 weeks s.c. 2x/week for 4 weeks then challenged 27 (100, 1000 IU/kg groups) or 20 (14000 IU/kg + Freund's Complete Adjuvant [FCA] group) later with 50,000 IU/animal.	100, 1000 IU/kg 14000 IU/kg + FCA	Remarkable anaphylactic reaction at 1000 IU/kg and 14000 IU/kg.
Cutaneous Reaction	Hartley Guinea Pigs from PCA test were challenged 19 (100, 1000 IU/kg groups) or 26 (14000 IU/kg + FCA group) days later with intradermal doses of 1000 or 10,000 IU/animal.	100, 1000 IU/kg 14000 IU/kg + FCA	Positive reaction at 1000 IU/kg and 14000 IU/kg + FCA
Antigenicity study Passive Hemagglutination (PHA) + 4-Hr Passive Cutaneous Anaphylaxis (PCA) tests	New Zealand White Female Rabbits; 4/group i.m. and s.c. 2x/week for 4 weeks i.m. and s.c. 1x week for 4 weeks	100, 1000 IU/kg 2000 IU/kg + FCA	Hemagglutinating antibodies were detected in sera of 2000 IU/kg + FCA. Antibodies detected 4-Hr PCA in sera of almost all epoetin alfa-treated rabbits.

Table 2.15: Special Studies (cont'd)

Test Type	Study	Dose Levels	Average Response
Pyrogenicity Study	New Zealand White Rabbits i.v. 3/group single dose Pyrogenicity measured by temperature and limulus amoebocyte lysate test.	0 (saline), 0 (vehicle), 200, 2000, or 20000 IU/kg Positive control *E. coli*, LPS.	Negative for both temperature and endotoxin.
Primary Eye Irritation	New Zealand White Rabbits 3/group single ocular dose followed by irrigation 6/group single ocular dose no irrigation.	12,100 U/animal	Classified as non-irritating.
Hematologic	Dogs Beagle 3/sex/group, i.v. administration for 4 weeks then 15 week recovery.	0 (vehicle), 28, 2800 IU/kg 3x week/4 weeks Group 4 pretreated with 40 mg/kg iron dextran for 2 weeks prior to first dose of epoetin alfa @ 2800 IU/kg	No drug-related deaths. Increased RBC, PCV, Hgb, reticulocytes, and platelets. Decreased MCV/MCHC/ MCH, serum glucose and BUN @ 2800 IU/kg with and without iron supplement. Low dose only slight increase RBC, PCV, and Hgb. No other dose-related effects.

Treatment with 1000 IU/kg/day epoetin alfa for 90 days did not cause myelofibrosis in Cynomolgus monkeys. Gastric erosion of the glandular stomach has been observed in the rat and in one high-dose (1000 IU/kg/day) monkey. Kidney changes involving the Bowman's capsule were also observed in dogs after daily injection for a year. Anaphylaxis noted in dogs, rabbits and guinea pigs is thought to be due to a natural reaction to any foreign protein in these animals.

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PART III: CONSUMER INFORMATION

PrEPREX®
epoetin alfa

Sterile Solution

This leaflet is Part III of a three-part "Product Monograph" published when EPREX® was approved for sale in Canada and is designed specifically for Consumers. Please read this carefully before you start to take your medicine. This leaflet is a summary and will not tell you everything about EPREX®. Contact your doctor or pharmacist if you have any questions about the drug.

INFORMATION ABOUT ANEMIA

What is anemia:
Anemia is a condition where your blood contains a lower than normal number of red blood cells. Red blood cells contain a substance called hemoglobin that is responsible for transporting oxygen in your blood. As the number of red blood cells in your blood decreases, so does the amount of oxygen delivered to your body. Development of anemia is characterized by several symptoms, such as weakness, fatigue, shortness of breath, dizziness, poor concentration and chills. These symptoms over time can negatively impact your overall quality of life.

What causes anemia:
Anemia may be the result of several causes, including blood loss or nutritional deficiencies. Anemia due to blood loss must be investigated and treated by a physician. Nutritional anemia caused by a deficiency of iron, vitamin B_{12} or folic acid can be treated with dietary supplements. Anemia can also be caused by chronic disease, such as cancer or kidney (renal) disease.

Anemia in Chronic Kidney Disease:
In chronic kidney disease, anemia results when the kidneys are unable to manufacture enough natural erythropoietin to stimulate the bone marrow to produce more red blood cells.

Anemia in Cancer:
Anemia in cancer can be caused by the chemotherapy regimens used to treat the cancer. The toxic effects of chemotherapy reduce the body's ability to produce erythropoietin as well as the bone marrow's ability to respond and make more red blood cells. As a result, not enough red blood cells are produced and the patient becomes anemic.

ABOUT THIS MEDICATION

What the medication is used for:
EPREX® is used to increase the production of red blood cells and to decrease the need for red blood cell transfusion. The dose should be gradually adjusted to achieve this goal. EPREX® may be used in adults and children with chronic kidney disease; adults who have HIV-infection and are receiving a drug called zidovudine; adult cancer patients receiving chemotherapy; and adults scheduled to undergo major elective surgery.

What it does:
EPREX® is a protein made in the laboratory which acts like a substance naturally made in the human body called erythropoietin. Erythropoietin controls the production of red blood cells in the body.

When it should not be used:
You should not use EPREX® if:

- you are allergic to any of the ingredients in the product;
- you have been diagnosed with Pure Red Cell Aplasia (the bone marrow cannot produce enough red blood cells) after previous treatment with any product that stimulates red blood cell production (including EPREX®). See **Serious Warnings and Precautions**;
- you have uncontrolled high blood pressure;
- you are due to have major orthopedic surgery (such as hip or knee surgery), and you
  - have severe heart disease;
  - have severe disorders of the veins and arteries;
  - have recently had a heart attack or stroke;
- while on EPREX®, some people may need medicines to reduce the risk of blood clots. You should not take EPREX® if you cannot for any reason take medicines that prevent blood clotting.

What the medicinal ingredient is:
epoetin alfa

What the nonmedicinal ingredients are:
Glycine and polysorbate 80 as stabilizers, sodium chloride, water for injection and sodium phosphate

Pre-filled syringes do not contain preservatives.

The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which should not be handled by persons sensitive to this substance.

What dosage forms it comes in:
Single-use pre-filled syringes with PROTECS® needle guard: 1,000 IU/0.5 mL, 2,000 IU/0.5 mL, 3,000 IU/0.3 mL, 4,000 IU/0.4 mL, 5,000 IU/0.5 mL, 6,000 IU/0.6 mL, 8,000 IU/0.8 mL, 10,000 IU/mL, 20,000 IU/0.5 mL, 30,000 IU/0.75 mL, 40,000 IU/mL

To reduce the risk of accidental needle sticks to users, each pre-filled syringe is equipped with the PROTECS® needle guard that is automatically activated to cover the needle after complete delivery of the syringe content.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

ALL PATIENTS

- To minimize the risks for death and serious cardiovascular (heart and blood vessel-related) side effects, your doctor will follow the recommended dosage for each indication.
- Patients with uncontrolled hypertension should not be treated with EPREX®; blood pressure should be controlled adequately before initiation of therapy.
- EPREX® should be used with caution in patients with a history of seizures.
- During hemodialysis, patients treated with EPREX® may require increased anticoagulation with heparin to prevent clotting of the artificial kidney. Patients with pre-existing vascular disease should be monitored closely.
- Hemoglobin levels during EPREX® treatment should not be higher than 120 g/L (may not apply to surgery patients).
- If you undergo surgery while taking EPREX®, your physician may prescribe a blood thinner, as appropriate for the surgical procedure, to prevent blood clots.
- Antibody-mediated pure red cell aplasia (PRCA) has been reported after months to years of treatment with recombinant erythropoietins. If you develop PRCA, you may suddenly become severely anemic and this could result in a dependency on blood transfusions.

CHRONIC RENAL 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 will try to keep your hemoglobin between 100 and 115 g/L, not exceeding 120 g/L.

CANCER PATIENTS

- If you are a cancer patient and your hemoglobin is kept too high (over 120 g/L),
  - your tumor may grow faster,
  - you have an increased chance of heart attack, stroke, blood clots and death.
- Your doctor should use the lowest dose of EPREX® needed to avoid red blood cell transfusions.
- In some instances, red blood cell transfusion should be the preferred treatment option.
- Once you have finished your chemotherapy course, EPREX® should be discontinued.

BEFORE taking EPREX®:

- Tell your doctor about any medical problems and about any allergies you have or have had in the past.
- Tell your doctor if you have or have had high blood pressure, seizures, blood clots, liver disease, porphyria (a rare blood disorder), or gout.
- While you are treated with EPREX® your doctor will need to check your blood pressure. Your blood pressure will be monitored carefully and any changes outside of the guidelines that your doctor has given you must be reported. If your blood pressure increases, you may need medication to lower it. If you already take blood pressure medication, your doctor may increase the amount.
- Your doctor will also measure your serum iron levels, red blood cell levels and other factors in your blood, prior to starting and during treatment with EPREX®, as deemed appropriate.
- If you are on dialysis, your dialysis prescription may need to be changed while you are being treated with EPREX®. Your doctor will take blood tests to determine if any change is needed. Your doctor may also need to adjust any medication you receive to prevent blood clotting.
- Tell your doctor if you are pregnant, if you think you might be pregnant, or if you are trying to become pregnant.
- Tell your doctor if you are breast-feeding.
- In many women with severe kidney failure, the monthly period may stop. When these women take EPREX® they may restart their monthly cycle. If you are a woman with kidney disease, you should discuss contraception with your doctor.
- In patients with kidney disease, due to the possibility of an increase in blood pressure, there is a small chance of having a seizure when therapy starts. During the initial phase of treatment, your doctor may advise you to avoid driving, using machines or doing anything else that could be dangerous if you are not alert.
- If you are a home dialysis patient, you should continue to check your access, as your doctor or nurse has shown you, to make sure it is working. Be sure to let your healthcare professional know right away if there is a problem.
- If you are a cancer patient you should be aware that EPREX® is a red blood cell growth factor and in some circumstances your cancer may grow faster. You should discuss treatment options for your anemia with your doctor.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all medications you are using, including those obtained without a prescription and any other remedies or dietary supplements. It is especially important that your doctor know if you are taking high blood pressure medication.

PROPER USE OF THIS MEDICATION

EPREX® may be given by injection:
Either into a vein or a tube that goes into a vein (intravenously) by healthcare professional
Or under the skin (subcutaneously) into the arms, legs or abdomen

While you are receiving EPREX®, your doctor will measure your red blood cells. Your doctor will use this information to adjust the dose to the amount right for you.

Follow your doctor's instructions about when and how to take this medication.

Do not shake EPREX® Sterile Solution. The solution in pre-filled syringe should always be clear and colourless. Do not use EPREX® Sterile Solution if the contents of the pre-filled syringe appear discoloured or cloudy, or if pre-filled syringe appears to contain lumps, flakes, or particles. If the pre-filled syringe has been shaken vigorously, the solution may appear to be frothy and should not be used.

Pre-filled syringes of EPREX® Sterile Solution do not contain preservatives and therefore are to be used once and discarded. Any unused portion of a pre-filled syringe should not be used.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

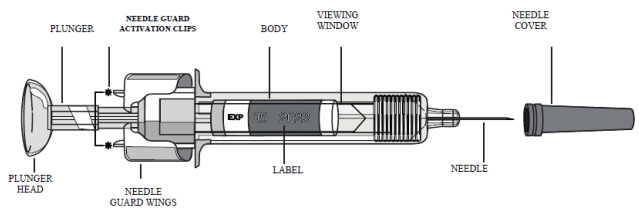
Missed Dose:
If you miss a dose, contact your doctor for instructions.

Subcutaneous Injection: Preparing and Injecting the Dose

Important: To help avoid contamination and possible infection, follow these instructions exactly.

Single-Use Pre-filled Syringe with PROTECS® needle guard

Figure 1



To reduce the risk of accidental needle sticks to users, each pre-filled syringe is equipped with the PROTECS® needle guard that is automatically activated to cover the needle after complete delivery of the syringe content.

1. **Take a syringe out of the refrigerator.** The liquid needs to come to room temperature. This usually takes between 15 to 30 minutes. Do not remove the syringe's needle cover while allowing it to reach room temperature.
2. **Check the syringe** to make sure it is the right dose, has not passed its expiry date, is not damaged, and the liquid is clear and not frozen.
3. **Choose an injection site.** Good sites are the top of the thigh and around the tummy (abdomen) but away from the navel. Vary the site from day to day.

4. **Wash your hands. Use an antiseptic swab on the injection site,** to disinfect it.
5. **Hold the pre-filled syringe by the body of the syringe with the covered needle pointing upward.**
6. **Do not hold by the plunger head, plunger, needle guard wings, or needle cover.**
7. **Do not pull back on the plunger at any time.**
8. **Do not remove the needle cover from the pre-filled syringe until you are ready to inject your EPREX®.**
9. **Take the cover off the syringe** by holding the barrel and pulling the cover off carefully without twisting it. Don't push the plunger, touch the needle or shake the syringe.
10. **Do not touch the needle activation clips (as indicated by asterisks * in Figure 1, to prevent prematurely covering the needle with the needle guard.**
11. **Pinch a fold of skin** between your thumb and index finger. Don't squeeze it.

12. **Push the needle in fully.** Your doctor or nurse may have shown you how to do this.

13. **Push the plunger with your thumb as far as it will go to inject all of the liquid.** Push it slowly and evenly, keeping the skinfold pinched. The PROTECS® needle guard will not activate unless the entire dose is given. **You may hear a click when the PROTECS® needle guard has been activated.**
14. **When the plunger is pushed as far as it will go,** take out the needle and let go of the skin.

15. **Slowly take your thumb off the**

plunger. Allow the syringe to move up until the entire needle is covered by the needle guard.

16. **When the needle is pulled out of your skin, there may be a little bleeding at the injection site. This is normal. Press an antiseptic swab** over the injection site for a few seconds after the injection.
17. **Dispose of your used syringe** in a safe container (see **Disposal of Syringes**).
18. **Only take one dose of EPREX® from each syringe.** If any liquid remains in the syringe after an injection, the syringe should be properly disposed of, not reused (see **Disposal of Syringes**).

Disposal of Syringes

1. Place all used needles and syringes in a hard plastic container with a screw-on cap, or a metal container with a plastic lid, such as a coffee can properly labelled 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.
2. Do not use glass or clear plastic containers (or any other container) that will be recycled or returned to a store.
3. Always store the container out of the reach of children.
4. Please check with your doctor, nurse, or pharmacist for other suggestions.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Any medicine may have unwanted effects. The side effects you might experience may vary depending on the reason you are taking EPREX®. Tell your doctor or pharmacist about any unusual sign or symptom whether listed or not. The side effects reported most often in all patients receiving EPREX® are high blood pressure and flu-like symptoms such as dizziness, drowsiness, fever, headache, muscle and joint pain and weakness, and gastrointestinal disturbances such as nausea, vomiting and diarrhea. Redness, burning and pain at the place where EPREX® is given have also been reported.

Call your doctor right away if you have an increase in headaches or develop unusual headaches, such as sudden stabbing migraine like headache as this may be a sign of very high blood pressure.

There is a possible association of a worsening of increased blood pressure if red blood cell production occurs too rapidly. Your doctor may need to reduce your dose of EPREX® and initiate or increase blood pressure medication. Signs and symptoms of serious cardiovascular events may include but are not limited to: chest pain, leg pain and swelling, shortness of breath, sudden weakness, numbing or tingling of face, arm or leg, an increase in headaches or severe sudden headaches, loss of vision or loss of speech, lightheadedness.

Patients experiencing these signs or symptoms should contact their doctor immediately.

Patients should NOT discontinue their medication without consulting their doctor first.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Additional side effects which have been reported more often in chronic renal failure patients than other patients include increases in blood pressure, clotted access, seizures and pure red cell aplasia (PRCA). PRCA is a condition in which severe and sudden anemia (characterized by symptoms such as severe tiredness/fatigue, and shortness of breath on mild exertion) develops due to failure of the bone marrow to produce red blood cells. PRCA could result in a dependency on blood transfusions. Should you be diagnosed with PRCA, your doctor will stop your EPREX® therapy and may initiate treatment with drugs and/or blood transfusions to help increase your red blood cell count.

If you develop signs of allergy such as difficulty breathing, hives, itching, rash, or swelling of the throat, face, eyelids, mouth or tongue, discontinue the use of EPREX® and contact your doctor or obtain medical help immediately.

If you experience a severe skin reaction, a rash, which may be severe, may cover your whole body and can also include blisters or areas of skin coming off, stop using EPREX® and call your doctor or get medical help right away.

This is not a complete list of side effects. For any unexpected effects while taking EPREX®, contact your doctor or pharmacist.

HOW TO STORE IT

- Store unopened in a refrigerator between 2 and 8 degrees centigrade. Do not freeze. Protect from light.
- Do not use this product after the expiry date written on the package.
- Keep this and all medicines in a safe place away from children.
- If you are using EPREX® at home, it is important that the syringe be stored in your refrigerator although not in the freezer compartment. EPREX® should not be frozen. Do not use EPREX® if it has been frozen.

Leave the EPREX® syringe to stand for about 15 to 30 minutes until it reaches room temperature prior to using it.

- When the pre-filled syringe is about to be used, it may be removed from the refrigerator and stored at room temperature (not above 25°C) for one single period of maximum 7 days.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting

NOTE: *Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

MORE INFORMATION

For questions, concerns, or the full Product Monograph go to: www.janssen.com/canada or contact the manufacturer, Janssen Inc., at: 1-800-567-3331 or 1-800-387-8781.

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