NP-POETIN
(Epoetin alpha)

2000IU, 4000IU and 10000IU

For S.C. or I.V. use

WARNING

ERYTHROPOIESIS-STIMULATING AGENTS INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE

Chronic Kidney Disease:

- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a haemoglobin level of greater than 11 g/dL.
- No trial has identified a haemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.
- Use the lowest Epoetin alpha dose sufficient to reduce the need for red blood cell (RBC) transfusions.

Cancer:

- ESAs shortened overall survival and/or increased the risk of tumour progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.
- Use the lowest dose to avoid RBC transfusions.
- Use ESAs only for anaemia from myelosuppressive chemotherapy.
- ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- Discontinue following the completion of a chemotherapy course.

Perisurgery:

- Due to increased risk of deep venous thrombosis (DVT), DVT prophylaxis is recommended.

COMPOSITION

Each prefilled syringe contains:
Erythropoietin…….. 2000 IU
Mfg. B.P. Specifications
Each prefilled syringe contains:
Erythropoietin ……...4000 IU
Mfg. B.P. Specifications
Each prefilled syringe contains:
Erythropoietin…… 10000 IU
Mfg. B.P. Specifications

THERAPEUTIC INDICATIONS

Anemia Due to Chronic Kidney Disease

Epoetin alpha is indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion.

Anemia Due to Zidovudine in Patients with HIV-infection

Epoetin alpha is indicated for the treatment of anemia due to zidovudine administered at ≤ 4200 mg/week in patients with HIV-infection with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL.

Anemia Due to Chemotherapy in Patients With Cancer

Epoetin alpha is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

Reduction of Allogeneic Red Blood Cell Transfusions in Patients Undergoing Elective, Noncardiac, Nonvascular Surgery

Epoetin alpha is indicated to reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery. Epoetin alpha is not indicated for patients who are willing to donate autologous blood pre-operatively.

Limitations of Use

Epoetin alpha has not been shown to improve quality of life, fatigue, or patient well-being.

Epoetin alpha is not indicated for use:

- In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion.
- In patients scheduled for surgery who are willing to donate autologous blood.
- In patients undergoing cardiac or vascular surgery.
- As a substitute for RBC transfusions in patients who require immediate correction of anemia.

DOSAGE AND ADMINISTRATION

Important Dosing Information

Evaluation of Iron Stores and Nutritional Factors

Evaluate the iron status in all patients before and during treatment. Administer supplemental iron therapy when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20%. The majority of patients with CKD will require supplemental iron during the course of ESA therapy.

Monitoring of Response to Therapy

Correct or exclude other causes of anemia (e.g., vitamin deficiency, metabolic or chronic inflammatory conditions, bleeding, etc.) before initiating Epoetin alpha. Following initiation of therapy and after each dose adjustment, monitor hemoglobin weekly until the hemoglobin level is stable and sufficient to minimize the need for RBC transfusion.

Selection of Formulation

In pregnant women, lactating women, neonates, and infants use only single-dose vials (the benzyl alcohol-free formulation)

Patients with Chronic Kidney Disease

In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL. No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks. Individualize dosing and use the lowest dose of Epoetin alpha sufficient to reduce the need for RBC transfusions. Physicians and patients should weigh the possible

benefits of decreasing transfusions against the increased risks of death and other serious cardiovascular adverse reactions.

For all patients with CKD:

When initiating or adjusting therapy, monitor hemoglobin levels at least weekly until stable, then monitor at least monthly. When adjusting therapy consider hemoglobin rate of rise, rate of decline, ESA responsiveness and hemoglobin variability. A single hemoglobin excursion may not require a dosing change.

- Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently. Avoid frequent dose adjustments.
- If the hemoglobin rises rapidly (e.g., more than 1 g/dL in any 2-week period), reduce the dose of Epoetin alpha by 25% or more as needed to reduce rapid responses.
- For patients who do not respond adequately, if the hemoglobin has not increased by more than 1 g/dL after 4 weeks of therapy, increase the dose by 25%.
- For patients who do not respond adequately over a 12-week escalation period, increasing the Epoetin alpha dose further is unlikely to improve response and may increase risks. Use the lowest dose that will maintain a hemoglobin level sufficient to reduce the need for RBC transfusions. Evaluate other causes of anemia. Discontinue Epoetin alpha if responsiveness does not improve.

For adult patients with CKD on dialysis:

- Initiate Epoetin alpha treatment when the hemoglobin level is less than 10 g/dL.
- If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of Epoetin alpha.
- The recommended starting dose for adult patients is 50 to 100 Units/kg 3 times weekly intravenously or subcutaneously. The intravenous route is recommended for patients on hemodialysis.

For adult patients with CKD not on dialysis:

- Consider initiating Epoetin alpha treatment only when the hemoglobin level is less than 10 g/dL and the following considerations apply:
  ○ The rate of hemoglobin decline indicates the likelihood of requiring a RBC transfusion and,
  ○ Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal
- If the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of Epoetin alpha, and use the lowest dose of Epoetin alpha sufficient to reduce the need for RBC transfusions.
- The recommended starting dose for adult patients is 50 to 100 Units/kg 3 times weekly intravenously or subcutaneously.

For pediatric patients with CKD:

• Initiate Epoetin alpha treatment only when the hemoglobin level is less than 10 g/dL.

• If the hemoglobin level approaches or exceeds 12 g/dL, reduce or interrupt the dose of Epoetin alpha.

• The recommended starting dose for pediatric patients (ages 1 month or older) is 50 Units/kg 3 times weekly intravenously or subcutaneously.

Zidovudine-treated Patients with HIV-infection

Starting Dose

The recommended starting dose in adults is 100 Units/kg as an intravenous or subcutaneous injection 3 times per week.

Dose Adjustment

- If hemoglobin does not increase after 8 weeks of therapy, increase Epoetin alpha dose by approximately 50 to 100 Units/kg at 4- to 8-week intervals until hemoglobin reaches a level needed to avoid RBC transfusions or 300 Units/kg.
- Withhold Epoetin alpha if hemoglobin exceeds 12 g/dL. Resume therapy at a dose 25% below the previous dose when hemoglobin declines to less than 11 g/dL.

Discontinue Epoetin alpha if an increase in hemoglobin is not achieved at a dose of 300 Units/kg for 8 weeks.

Patients on Cancer Chemotherapy

Initiate Epoetin alpha in patients on cancer chemotherapy only if the hemoglobin is less than 10 g/dL, and if there is a minimum of two additional months of planned chemotherapy.

Use the lowest dose of Epoetin alpha necessary to avoid RBC transfusions.

Recommended Starting Dose

Adults:

- 150 Units/kg subcutaneously 3 times per week until completion of a chemotherapy course or
- 40,000 Units subcutaneously weekly until completion of a chemotherapy course.

Pediatric Patients (5 to 18 years):

- 600 Units/kg intravenously weekly until completion of a chemotherapy course.

Dose Reduction

Reduce dose by 25% if:

- Hemoglobin increases greater than 1 g/dL in any 2-week period or
- Hemoglobin reaches a level needed to avoid RBC transfusion.

Withhold dose if hemoglobin exceeds a level needed to avoid RBC transfusion. Reinitiate at a dose 25% below the previous dose when hemoglobin approaches a level where RBC transfusions may be required.

Dose Increase

After the initial 4 weeks of Epoetin alpha therapy, if hemoglobin increases by less than 1 g/dL and remains below 10 g/dL, increase dose to:

- 300 Units/kg three times per week in adults or
- 60,000 Units weekly in adults
- 900 Units/kg (maximum 60,000 Units) weekly in pediatric patients

After 8 weeks of therapy, if there is no response as measured by hemoglobin levels or if RBC transfusions are still required, discontinue Epoetin alpha.

Surgery Patients

The recommended Epoetin alpha regimens are:

- 300 Units/kg per day subcutaneously for 15 days total: administered daily for 10 days before surgery, on the day of surgery, and for 4 days after surgery.
- 600 Units/kg subcutaneously in 4 doses administered 21, 14, and 7 days before surgery and on the day of surgery.

Deep venous thrombosis prophylaxis is recommended during Epoetin alpha therapy

Method of Administration

Intravenous administration

Administer over at least one to five minutes, depending on the total dose. In hemodialyzed patients, a bolus injection may be given during the dialysis session through a suitable venous port in the dialysis line. Alternatively, the injection can be given at the end of the dialysis session via the fistula needle tubing, followed by 10 mL of isotonic saline to rinse the tubing and ensure satisfactory injection of the product into the circulation.

A slower administration is preferable in patients who react to the treatment with “flu-like” symptoms

Do not administer Epoetin alpha by intravenous infusion or in conjunction with other drug solutions.

Subcutaneous administration

A maximum volume of 1 mL at one injection site should generally not be exceeded. In case of larger volumes, more than one site should be chosen for the injection.

The injections should be given in the limbs or the anterior abdominal wall.

In those situations, in which the physician determines that a patient or caregiver can safely and effectively administer Epoetin alpha subcutaneously themselves, instruction as to the proper dosage and administration should be provided.

As with any other injectable product, check that there are no particles in the solution or change in colour.

Graduation marks

The syringe label contains numbered graduation marks to provide for the administration of a part of the dose. However the product is for single use only. Only one dose of Epoetin alpha from each syringe should be taken.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Patients who develop pure red cell aplasia (PRCA) following treatment with any erythropoietin should not receive Erythropoietin or any other erythropoietin.

Uncontrolled hypertension.

All contraindications associated with autologous blood predonation programmes should be respected in patients being supplemented with Erythropoietin.

The use of Erythropoietin in patients scheduled for major elective orthopaedic surgery and not participating in an autologous blood predonation programme is contraindicated in patients with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including patients with recent myocardial infarction or cerebral vascular accident.

Surgery patients who for any reason cannot receive adequate antithrombotic prophylaxis.

WARNINGS AND PRECAUTIONS

General

In all patients receiving erythropoietin, blood pressure should be closely monitored and controlled as necessary. Erythropoietin should be used with caution in the presence of untreated, inadequately treated or poorly controllable hypertension. It may be necessary to add or increase anti-hypertensive treatment. If blood pressure cannot be controlled, erythropoietin treatment should be discontinued.

Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have occurred also during erythropoietin treatment in patients with previously normal or low blood pressure. Particular attention should be paid to sudden stabbing migraine-like headaches as a possible warning signal

Erythropoietin should be used with caution in patients with epilepsy, history of seizures, or medical conditions associated with a predisposition to seizure activity such as CNS infections and brain metastases.

Erythropoietin should be used with caution in patients with chronic liver failure. The safety of erythropoietin has not been established in patients with hepatic dysfunction.

An increased incidence of thrombotic vascular events (TVEs) has been observed in patients receiving ESAs. These include venous and arterial thromboses and embolism (including some with fatal outcomes), such as deep venous thrombosis, pulmonary emboli, retinal thrombosis, and myocardial infarction. Additionally, cerebrovascular accidents (including cerebral infarction, cerebral haemorrhage and transient ischemic attacks) have been reported.

The reported risk of these TVEs should be carefully weighed against the benefits to be derived from treatment with erythropoietin particularly in patients with pre-existing risk factors for TVE, including obesity and prior history of TVEs (e.g., deep venous thrombosis, pulmonary embolism, and cerebral vascular accident).

In all patients, haemoglobin levels should be closely monitored due to a potential increased risk of thromboembolic events and fatal outcomes when patients are treated at haemoglobin levels above the concentration range for the indication of use.

There may be a moderate dose-dependent rise in the platelet count within the normal range during treatment with erythropoietin. This regresses during the course of continued therapy. In addition, thrombocythaemia above the normal range has been reported. It is recommended that the platelet count is regularly monitored during the first 8 weeks of therapy.

All other causes of anaemia (iron, folate or Vitamin B_{12} deficiency, aluminium intoxication, infection or inflammation, blood loss, haemolysis and bone marrow fibrosis of any origin) should be evaluated and treated prior to initiating therapy with erythropoietin, and when deciding to increase the dose. In most cases, the ferritin values in the serum fall simultaneously with the rise in packed cell volume. In order to ensure optimum response to erythropoietin, adequate iron stores should be assured and iron supplementation should be administered if necessary:

• For chronic renal failure patients, iron supplementation (elemental iron 200 to 300 mg/day orally for adults and 100 to 200 mg/day orally for paediatrics) is recommended if serum ferritin levels are below 100 ng/mL.

• For cancer patients, iron supplementation (elemental iron 200 to 300 mg/day orally) is recommended if transferrin saturation is below 20%.

• For patients in an autologous predonation programme, iron supplementation (elemental iron 200 mg/day orally) should be administered several weeks prior to initiating the autologous predeposit in order to achieve high iron stores prior to starting erythropoietin therapy, and throughout the course of erythropoietin therapy.

• For patients scheduled for major elective orthopaedic surgery, iron supplementation (elemental iron 200 mg/day orally) should be administered throughout the course of erythropoietin therapy. If possible, iron supplementation should be initiated prior to starting erythropoietin therapy to achieve adequate iron stores.

Very rarely, development of or exacerbation of porphyria has been observed in erythropoietin-treated patients. Erythropoietin should be used with caution in patients with porphyria.

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. More severe cases have been observed with long-acting epoetins.

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, Erythropoietin should be withdrawn immediately and an alternative treatment considered.

If the patient has developed a severe cutaneous skin reaction such as SJS or TEN due to the use of Erythropoietin, treatment with Erythropoietin must not be restarted in this patient at any time.

In order to improve the traceability of erythropoiesis-stimulating agents (ESAs), the trade name and the batch number 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.

Pure Red Cell Aplasia

Antibody-mediated pure red cell aplasia (PRCA) has been reported after months to years of erythropoietin treatment.

Cases have also been reported in patients with hepatitis C treated with interferon and ribavirin, when ESAs are used concomitantly. Erythropoietin is not approved in the management of anaemia associated with hepatitis C.

In patients developing sudden lack of efficacy defined by a decrease in haemoglobin (1 to 2 g/dL per month) with increased need for transfusions, a reticulocyte count should be obtained and typical causes of non-response (e.g. iron, folate or Vitamin B_{12} deficiency, aluminium intoxication, infection or inflammation, blood loss, haemolysis and bone marrow fibrosis of any origin) should be investigated.

A paradoxical decrease in haemoglobin and development of severe anaemia associated with low reticulocyte counts should prompt to discontinue treatment with erythropoietin and perform anti-erythropoietin antibody testing. A bone marrow examination should also be considered for diagnosis of PRCA.

No other ESA therapy should be commenced because of the risk of cross-reaction.

Treatment of symptomatic anaemia in adult and paediatric chronic renal failure patients

Chronic renal failure patients being treated with erythropoietin should have haemoglobin levels measured on a regular basis until a stable level is achieved, and periodically thereafter.

In chronic renal failure patients the rate of increase in haemoglobin should be approximately 1 g/dL (0.62 mmol/L) per month and should not exceed 2 g/dL (1.25 mmol/L) per month to minimise risks of an increase in hypertension.

In patients with chronic renal failure, maintenance haemoglobin concentration should not exceed the upper limit of the haemoglobin concentration. In clinical trials, an increased risk of death and serious cardiovascular events was observed when ESAs were administered to achieve a haemoglobin concentration level of greater than 12 g/dL (7.5 mmol/L).

Controlled clinical trials have not shown significant benefits attributable to the administration of epoetin when haemoglobin concentration is increased beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.

Caution should be exercised with escalation of Erythropoietin doses in patients with chronic renal failure since high cumulative epoetin doses may be associated with an increased risk of mortality, serious cardiovascular and cerebrovascular events. In patients with a poor haemoglobin response to epoetin, alternative explanations for the poor response should be considered.

Chronic renal failure patients treated with erythropoietin by the subcutaneous route should be monitored regularly for loss of efficacy, defined as absent or decreased response to erythropoietin treatment in patients who previously responded to such therapy. This is characterised by a sustained decrease in haemoglobin despite an increase in erythropoietin dosage.

Some patients with more extended dosing intervals (greater than once weekly) of erythropoietin may not maintain adequate haemoglobin levels and may require an increase in erythropoietin dose. Haemoglobin levels should be monitored regularly.

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

Hyperkalaemia has been observed in isolated cases though causality has not been established. Serum electrolytes should be monitored in chronic renal failure patients. If an elevated or rising serum potassium level is detected, then in addition to appropriate treatment of the hyperkalaemia**,** consideration should be given to ceasing erythropoietin administration until the serum potassium level has been corrected.

An increase in heparin dose during haemodialysis is frequently required during the course of therapy with erythropoietin as a result of the increased packed cell volume. Occlusion of the dialysis system is possible if heparinisation is not optimum.

Based on information available to date, correction of anaemia with erythropoietin in adult patients with renal insufficiency not yet undergoing dialysis does not accelerate the rate of progression of renal insufficiency.

Treatment of patients with chemotherapy-induced anaemia

Cancer patients being treated with erythropoietin should have haemoglobin levels measured on a regular basis until a stable level is achieved, and periodically thereafter.

Erythropoietins are growth factors that primarily stimulate red blood cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells. As with all growth factors, there is a concern that epoetin could stimulate the growth of tumours.

The role of ESAs on tumour progression or reduced progression-free survival cannot be excluded. In controlled clinical studies, use of erythropoietin and other ESAs have been associated with decreased locoregional tumour control or decreased overall survival:

• Decreased locoregional control in patients with advanced head and neck cancer receiving radiation therapy when administered to achieve a haemoglobin concentration level of greater than 14 g/dL (8.7 mmol/L),

• Shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to achieve a haemoglobin concentration range of 12 to 14 g/dL (7.5 to 8.7 mmol/L),

• Increased risk of death when administered to achieve a haemoglobin concentration level of 12 g/dL (7.5 mmol/L) in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for use in this patient population,

• An observed 9% increase in risk for PD or death in the erythropoietin plus SOC group from a primary analysis and a 15% increased risk that cannot be statistically ruled out in patients with metastatic breast cancer receiving chemotherapy when administered to achieve a haemoglobin concentration range of 10 to 12 g/dL (6.2 to 7.5 mmol/L).

In view of the above, in some clinical situations blood transfusion should be the preferred treatment for the management of anaemia in patients with cancer. The decision to administer recombinant erythropoietin treatment should be based on a benefit-risk assessment with the participation of the individual patient, which should take into account the specific clinical context. Factors that should be considered in this assessment should include the type of tumour and its stage; the degree of anaemia; life-expectancy; the environment in which the patient is being treated; and patient preference.

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 erythropoietin therapy is appropriate (patient at risk of being transfused).

Surgery patients in autologous predonation programmes

All special warnings and special precautions associated with autologous predonation programmes, especially routine volume replacement, should be respected.

Patients scheduled for major elective orthopaedic surgery

Good blood management practices should always be used in the perisurgical setting.

Patients scheduled for major elective orthopaedic surgery should receive adequate antithrombotic prophylaxis, as thrombotic and vascular events may

occur in surgical patients, especially in those with underlying cardiovascular disease. In addition, special precaution should be taken in patients with predisposition for development of DVTs. Moreover, in patients with baseline haemoglobin of > 13 g/dL, the possibility that erythropoietin treatment may be associated with an increased risk of postoperative thrombotic/vascular events cannot be excluded. Therefore, erythropoietin should not be used in patients with baseline haemoglobin > 13 g/dL.

DRUG INTERACTIONS

No evidence exists that indicates that treatment with erythropoietin alters the metabolism of other drugs.

Drugs that decrease erythropoiesis may decrease the response to erythropoietin.

Since cyclosporin is bound by RBCs there is potential for a drug interaction. If erythropoietin is given concomitantly with cyclosporin, blood levels of cyclosporin should be monitored and the dose of cyclosporin adjusted as the haematocrit rises.

No evidence exists that indicates an interaction between erythropoietin and G-CSF or GM-CSF with regard to haematological differentiation or proliferation of tumour biopsy specimens *in vitro*.

In female adult patients with metastatic breast cancer, subcutaneous co-administration of 40,000 IU/mL erythropoietin with trastuzumab 6 mg/kg had no effect on the pharmacokinetics of trastuzumab.

PREGNANCY, LACTATION AND FERTILITY

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Studies in animals have shown reproduction toxicity. Consequently, erythropoietin should be used in pregnancy only if the potential benefit outweighs the potential risk to the foetus. The use of erythropoietin is not recommended in pregnant surgical patients participating in an autologous blood predonation.

Breastfeeding

It is not known whether exogenous erythropoietin is excreted in human milk. Erythropoietin should be used with caution in nursing women. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with erythropoietin should be made taking into account the benefit of breast-feeding to the child and the benefit of erythropoietin therapy to the woman.

The use of erythropoietin is not recommended in lactating surgical patients participating in an autologous blood predonation programme.

Fertility

There are no studies assessing the potential effect of erythropoietin on male or female fertility.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

ADVERSE REACTIONS

Summary of Safety Profile

The most frequent adverse drug reaction during treatment with erythropoietin is a dose-dependent increase in blood pressure or aggravation of existing hypertension. Monitoring of the blood pressure should be performed, particularly at the start of therapy.

The most frequently occurring adverse drug reactions observed in clinical trials of erythropoietin are diarrhoea, nausea, vomiting, pyrexia and headache. Influenza-like illness may occur especially at the start of treatment.

Respiratory tract congestion, which includes events of upper respiratory tract congestion, nasal congestion and nasopharyngitis, have been reported in studies with extended interval dosing in adult patients with renal insufficiency not yet undergoing dialysis.

An increased incidence of thrombotic vascular events (TVEs) has been observed in patients receiving ESAs.

Tabulated List of Adverse Reactions

Of a total 3,417 subjects in 25 randomized, double-blinded, placebo or standard of care-controlled studies, the overall safety profile of Erythropoietin was evaluated in 2,094 anaemic subjects. Included were 228 erythropoietin-treated CRF subjects in 4 chronic renal failure studies (2 studies in predialysis [N = 131 exposed CRF subjects] and 2 in dialysis [N = 97 exposed CRF subjects]; 1,404 exposed cancer subjects in 16 studies of anaemia due to chemotherapy; 147 exposed subjects in 2 studies for autologous blood donation; 213 exposed subjects in 1 study in the perisurgical period, and 102 exposed subjects in 2 MDS studies. Adverse drug reactions reported by ≥1% of subjects treated with erythropoietin in these trials are shown in the table below.

Frequency estimate: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very Rare (< 1/10,000), Not known (cannot be estimated from the available data).

MedDRA System Organ Classification (SOC)	**Adverse Reaction (Preferred Term Level)**	**Frequency**
Blood and lymphatic system disorders	Pure red cell aplasia[3], Thrombocythaemia	Rare
Metabolism and nutrition disorders	Hyperkalaemia[1]	Uncommon
Immune system disorders	Hypersensitivity[3]	Uncommon
	Anaphylactic reaction[3]	Rare
Nervous system disorders	Headache	Common
	Convulsion	Uncommon
Vascular disorders	Hypertension, Venous and arterial thromboses[2]	Common
	Hypertensive crisis[3]	Not known
Respiratory, thoracic and mediastinal disorders	Cough	Common
	Respiratory tract congestion	Uncommon
Gastrointestinal disorders	Diarrhoea, Nausea, Vomiting	Very common
Skin and subcutaneous tissue disorders	Rash	Common
	Urticaria[3]	Uncommon
	Angioneurotic oedema[3]	Not known
Musculoskeletal and connective tissue disorders	Arthralgia, Bone pain, Myalgia, Pain in extremity	Common
Congenital, familial and genetic disorders	Porphyria acute[3]	Rare

General disorders and administration site conditions	Pyrexia	Very common
	Chills, Influenza like illness, Injection site reaction, Oedema peripheral	Common
	Drug ineffective[3]	Not known
Investigations	Anti-erythropoeitin antibody positive	Rare

[1] Common in dialysis

[2] Includes arterial and venous, fatal and non fatal events, such as deep venous thrombosis, pulmonary emboli, retinal thrombosis, arterial thrombosis (including myocardial infarction), cerebrovascular accidents (including cerebral infarction and cerebral haemorrhage) transient ischemic attacks, and shunt thrombosis (including dialysis equipment) and thrombosis within arteriovenous shunt aneurisms

[3] Addressed in the subsection below

Description of selected adverse reactions

Hypersensitivity reactions, including cases of rash (including urticaria), anaphylactic reactions, and angioneurotic oedema have been reported.

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.

Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have occurred also during erythropoietin treatment in patients with previously normal or low blood pressure. Particular attention should be paid to sudden stabbing migraine-like headaches as a possible warning signal.

Antibody-mediated pure red cell aplasia has been very rarely reported in < 1/10,000 cases per patient year after months to years of treatment with Erythropoietin. More cases have been reported with subcutaneous (SC) route of administration, compared with the IV route.

Adult patients with low- or intermediate-1-risk MDS

In the randomized, double-blind, placebo-controlled, multicenter study 4 (4.7%) subjects experienced TVEs (sudden death, ischemic stroke, embolism, and phlebitis). All TVEs occurred in the erythropoietin group and in the first 24 weeks of the study. Three were confirmed TVE and in the remaining case (sudden death), the thromboembolic event was not confirmed. Two subjects had significant risk factors (atrial fibrillation, heart failure and thrombophlebitis).

Paediatric population with chronic renal failure on haemodialysis

The exposure of paediatric patients with chronic renal failure on haemodialysis in clinical trials and post-marketing experience is limited. No paediatric-specific adverse reactions, not mentioned previously in the table above or any that were not consistent with the underlying disease were reported in this population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com.

OVERDOSE

The therapeutic margin of erythropoietin is very wide. Over dosage of erythropoietin may produce effects that are extensions of the pharmacological effects of the hormone. Phlebotomy may be performed if excessively high haemoglobin levels occur. Additional supportive care should be provided as necessary.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: anti-anaemic, ATC code: B03XA01.

Mechanism of action

Erythropoietin (EPO) is a glycoprotein hormone produced primarily by the kidney in response to hypoxia and is the key regulator of red blood cell (RBC) production. EPO is involved in all phases of erythroid development, and has its principal effect at the level of erythroid precursors. After EPO binds to its cell surface receptor, it activates signal transduction pathways that interfere with apoptosis and stimulates erythroid cell proliferation. Recombinant human EPO (erythropoietin), expressed in Chinese hamster ovary cells, has a 165 amino acid sequence identical to that of human urinary EPO; the 2 are indistinguishable on the basis of functional assays. The apparent molecular weight of erythropoietin is 32,000 to 40,000 Dalton.

Erythropoietin is a growth factor that primarily stimulates red cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells.

Pharmacodynamic effects

Healthy volunteers

After single doses (20,000 to 160,000 IU subcutaneously) of erythropoietin, a dose-dependent response was observed for the pharmacodynamic markers investigated including: reticulocytes, RBCs, and haemoglobin. A defined concentration-time profile with peak and return to baseline was observed for changes in percent reticulocytes. A less defined profile was observed for RBCs and haemoglobin. In general, all pharmacodynamic markers increased in a linear manner with dose reaching a maximum response at the highest dose levels.

Further pharmacodynamic studies explored 40,000 IU once weekly versus 150 IU/kg 3 times per week. Despite differences in concentration-time profiles the pharmacodynamic response (as measured by changes in percent reticulocytes, haemoglobin, and total RBCs) was similar between these regimens. Additional studies compared the 40,000 IU once-weekly regimen of erythropoietin with biweekly doses ranging from 80,000 to 120,000 IU subcutaneously. Overall, based on the results of these pharmacodynamic studies in healthy subjects, the 40,000 IU once-weekly dosing regimen seems to be more efficient in producing RBCs than the biweekly regimens despite an observed similarity in reticulocyte production in the once-weekly and biweekly regimens.

Chronic renal failure

Erythropoietin has been shown to stimulate erythropoiesis in anaemic patients with CRF, including dialysis and pre-dialysis patients. The first evidence of a response to erythropoietin is an increase in the reticulocyte count within 10 days, followed by increases in the red cell count, haemoglobin and haematocrit, usually within 2 to 6 weeks. The haemoglobin response varies between patients and may be impacted by iron stores and the presence of concurrent medical problems.

Chemotherapy-induced anaemia

Erythropoietin administered 3 times per week or once weekly has been shown to increase haemoglobin and decrease transfusion requirements after the first month of therapy in anaemic cancer patients receiving chemotherapy.

Adult surgery patients in an autologous predonation programme

Erythropoietin has been shown to stimulate red blood cell production in order to augment autologous blood collection, and to limit the decline in haemoglobin in adult patients scheduled for major elective surgery who are not expected to predeposit their complete preoperative blood needs. The greatest effects are observed in patients with low haemoglobin (≤ 13 g/dL).

Treatment of adult patients scheduled for major elective orthopaedic surgery

In patients scheduled for major elective orthopaedic surgery with pre-treatment haemoglobin of > 10 to ≤ 13 g/dL, erythropoietin has been shown to decrease the risk of receiving allogeneic transfusions and hasten erythroid

recovery (increased haemoglobin levels, haematocrit levels, and reticulocyte counts).

Clinical efficacy and safety

Chronic renal failure

Erythropoietin has been studied in clinical trials in adult anaemic CRF patients, including haemodialysis and pre-dialysis patients, to treat anaemia and maintain haematocrit within a target concentration range of 30 to 36%.

In clinical trials at starting doses of 50 to 150 IU/kg, three times per week, approximately 95% of all patients responded with a clinically significant increase in haematocrit. After approximately two months of therapy, virtually all patients were transfusion-independent. Once the target haematocrit was achieved, the maintenance dose was individualised for each patient.

In the three largest clinical trials conducted in adult patients on dialysis, the median maintenance dose necessary to maintain the haematocrit between 30 to 36% was approximately 75 IU/kg given 3 times per week.

In a double-blind, placebo-controlled, multicentre, quality of life study in CRF patients on haemodialysis, clinically and statistically significant improvement was shown in the patients treated with erythropoietin compared to the placebo group when measuring fatigue, physical symptoms, relationships and depression (Kidney Disease Questionnaire) after six months of therapy. Patients from the group treated with erythropoietin were also enrolled in an open-label extension study which demonstrated improvements in their quality of life that were maintained for an additional 12 months.

Adult patients with renal insufficiency not yet undergoing dialysis

In clinical trials conducted in patients with CRF not on dialysis treated with erythropoietin, the average duration of therapy was nearly five months. These patients responded to erythropoietin 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 haematocrit when erythropoietin was administered by either an intravenous or subcutaneous route. Similar rates of rise of haematocrit were noted when erythropoietin was administered by either route. Moreover, erythropoietin doses of 75 to 150 IU/kg per week have been shown to maintain haematocrits of 36 to 38% for up to six months.

In 2 studies with extended interval dosing of Erythropoietin (3 times per week, once weekly, once every 2 weeks, and once every 4 weeks) some patients with longer dosing intervals did not maintain adequate haemoglobin levels and reached protocol-defined haemoglobin withdrawal criteria (0% in once weekly, 3.7% in once-every-2-weeks, and 3.3% in the once-every-4-weeks groups).

A randomized prospective trial (CHOIR) evaluated 1,432 anaemic chronic renal failure patients who were not undergoing dialysis. Patients were assigned to erythropoietin treatment targeting a maintenance haemoglobin level of 13.5 g/dL (higher than the recommended haemoglobin concentration level) or 11.3 g/dL. A major cardiovascular event (death, myocardial infarction, stroke or hospitalization for congestive heart failure) occurred among 125 (18%) of the 715 patients in the higher haemoglobin group compared to 97 (14%) among the 717 patients in the lower haemoglobin group (hazard ratio [HR] 1.3, 95% CI: 1.0, 1.7, p = 0.03).

Pooled post-hoc analyses of clinical studies of ESAs have been performed in chronic renal failure patients (on dialysis, not on dialysis, in diabetic and non-diabetic patients). A tendency towards increased risk estimates for all-cause mortality, cardiovascular and cerebrovascular events associated with higher cumulative ESA doses independent of the diabetes or dialysis status was observed.

Treatment of patients with chemotherapy-induced anaemia

Erythropoietin has been studied in clinical trials in adult anaemic cancer patients with lymphoid and solid tumors, and patients on various chemotherapy regimens, including platinum and non-platinum-containing regimens. In these trials, erythropoietin administered 3 times per week and once weekly has been shown to increase haemoglobin and decrease transfusion requirements after the first month of therapy in anaemic cancer patients. In some studies, the double-blind phase was followed by an open-label phase during which all patients received erythropoietin and maintenance of effect was observed.

Available evidence suggests patients with haematological malignancies and solid tumours respond equivalently to erythropoietin therapy, and those patients with or without tumour infiltration of the bone marrow respond equivalently to erythropoietin therapy. Comparable intensity of chemotherapy in the erythropoietin and placebo groups in the chemotherapy trials was demonstrated by a similar area under the neutrophil time curve in patients treated with erythropoietin and placebo-treated patients, as well as by a similar proportion of patients in groups treated with erythropoietin and placebo-treated groups whose absolute neutrophil counts fell below 1,000 and 500 cells/µL.

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

Survival and tumour progression have been examined in five large controlled studies involving a total of 2,833 patients, of which four were double-blind placebo-controlled studies and one was an open-label study. The studies either recruited patients who were being treated with chemotherapy (two studies) or used patient populations in which ESAs are not indicated: anaemia in patients with cancer not receiving chemotherapy, and head and neck cancer patients receiving radiotherapy. The desired haemoglobin concentration level in two studies was > 13 g/dL; in the remaining three studies it was 12 to 14 g/dL. In the open-label study there was no difference in overall survival between patients treated with recombinant human erythropoietin and controls. In the four placebo-controlled studies the hazard ratios for overall survival ranged between 1.25 and 2.47 in favour of controls. These studies have shown a consistent unexplained statistically significant excess mortality in patients who have anaemia associated with various common cancers who received recombinant human erythropoietin compared to controls. Overall survival outcome in the trials could not be satisfactorily explained by differences in the incidence of thrombosis and related complications between those given recombinant human erythropoietin and those in the control group.

A patient-level data analysis has also been performed on more than 13,900 cancer patients (chemo-, radio-, chemoradio-, or no therapy) participating in 53 controlled clinical trials involving several epoetins. Meta-analysis of overall survival data produced a hazard ratio point estimate of 1.06 in favour of controls (95% CI: 1.00, 1.12; 53 trials and 13,933 patients) and for the cancer patients receiving chemotherapy, the overall survival hazard ratio was 1.04 (95% CI: 0.97, 1.11; 38 trials and 10,441 patients). Meta-analyses also indicate consistently a significantly increased relative risk of thromboembolic events in cancer patients receiving recombinant human erythropoietin.

A randomised, open-label, multicentre study was conducted in 2,098 anaemic women with metastatic breast cancer, who received first line or second line chemotherapy. This was a non inferiority study designed to rule out a 15% risk increase in tumour progression or death of erythropoietin plus standard of care (SOC) as compared with SOC alone. At the time of clinical data cut-off, the median progression free survival (PFS) per investigator assessment of disease progression was 7.4 months in each arm (HR 1.09, 95% CI: 0.99, 1.20), indicating the study objective was not met. Significantly fewer patients received RBC transfusions in the erythropoietin plus SOC arm (5.8% versus 11.4%); however, significantly more patients had thrombotic vascular events in the erythropoietin plus SOC arm (2.8% versus 1.4%). At

the final analysis, 1653 deaths were reported. Median overall survival in the erythropoietin plus SOC group was 17.8 months compared with 18.0 months in the SOC alone group (HR 1.07, 95% CI: 0.97, 1.18). The median time to progression (TTP) based on investigator-determined progressive disease (PD) was 7.5 months in the erythropoietin plus SOC group and 7.5 months in the SOC group (HR 1.099, 95% CI: 0.998, 1.210). The median TTP based on IRC-determined PD was 8.0 months in the erythropoietin plus SOC group and 8.3 months in the SOC group (HR 1.033, 95% CI: 0.924, 1.156).

Autologous predonation programme

The effect of erythropoietin in facilitating autologous blood donation in patients with low haematocrits (≤ 39% and no underlying anaemia due to iron deficiency) scheduled for major orthopaedic surgery was evaluated in a

double-blind, placebo-controlled study conducted in 204 patients, and a single-blind placebo controlled study in 55 patients.

In the double-blind study, patients were treated with erythropoietin600 IU/kg or placebo intravenously once daily every 3 to 4 days over 3 weeks (total 6 doses). On average, patients treated with erythropoietin were able to predeposit significantly more units of blood (4.5 units) than placebo-treated patients (3.0 units).

In the single-blind study, patients were treated with erythropoietin300 IU/kg or 600 IU/kg or placebo intravenously once daily every 3 to 4 days over 3 weeks (total 6 doses). Patients treated with erythropoietin were also able to predeposit significantly more units of blood (erythropoietin300 IU/kg = 4.4 units; erythropoietin600 IU/kg = 4.7 units) than placebo-treated patients (2.9 units).

Erythropoietin therapy reduced the risk of exposure to allogeneic blood by 50% compared to patients not receiving erythropoietin.

Major elective orthopaedic surgery

The effect of erythropoietin (300 IU/kg or 100 IU/kg) on the exposure to allogeneic blood transfusion has been evaluated in a placebo-controlled, double-blind clinical trial in non-iron deficient adult patients scheduled for major elective orthopaedic hip or knee surgery. Erythropoietin was administered subcutaneously for 10 days prior to surgery, on the day of surgery, and for four days after surgery. Patients were stratified according to their baseline haemoglobin (≤ 10 g/dL, > 10 to ≤ 13 g/dL and > 13 g/dL).

Erythropoietin300 IU/kg significantly reduced the risk of allogeneic transfusion in patients with a pre-treatment haemoglobin of > 10 to ≤ 13 g/dL. Sixteen percent of erythropoietin300 IU/kg, 23% of erythropoietin100 IU/kg and 45% of placebo-treated patients required transfusion.

An open-label, parallel-group trial in non-iron deficient adult subjects with a pre-treatment haemoglobin of ≥ 10 to ≤ 13 g/dL who were scheduled for major orthopaedic hip or knee surgery compared erythropoietin300 IU/kg subcutaneously daily for 10 days prior to surgery, on the day of surgery and for four days after surgery to erythropoietin600 IU/kg subcutaneously once weekly for 3 weeks prior to surgery and on the day of surgery.

From pre-treatment to presurgery, the mean increase in haemoglobin in the 600 IU/kg weekly group (1.44 g/dL) was twice than that observed in the 300 IU/kg daily group (0.73 g/dL). Mean haemoglobin 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).

Treatment of adult patients with low- or intermediate-1-risk MDS

A randomized, double-blind, placebo-controlled, multicentre study evaluated the efficacy and safety of erythropoietin in adult anaemic subjects with low- or intermediate-1-risk MDS.

Subjects were stratified by serum erythropoietin (sEPO) level and prior transfusion status at screening. Key baseline characteristics for the <200 mU/mL stratum are shown in the table below.

Baseline Characteristics for Subjects with sEPO<200mU/mL at Screening		
	Randomized	
	Erythropoietin	Placebo
Total (N)[b]	85[a]	45
Screening sEPO <200 mU/mL (N)	71	39
Hemoglobin (g/L)		
N	71	39
Mean	92.1 (8.57)	92.1 (8.51)
Median	94.0	96.0
Range	(71, 109)	(69, 105)
95% CI for mean	(90.1, 94.1)	(89.3, 94.9)
Prior Transfusions		
N	71	39
Yes	31 (43.7%)	17 (43.6%)
≤ 2 RBC Units	16 (51.6%)	9 (52.9%)
>2 and ≤4 RBC Units	14 (45.2%)	8 (47.1%)
>4 RBC Units	1 (3.2%)	0
No	40 (56.3%)	22 (56.4%)

[a] one subject did not have sEPO data
[b] in the ≥200 mU/mL stratum there were 13 subjects in the erythropoietin group and 6 subjects in the placebo group

Erythroid response was defined according to International Working Group (IWG) 2006 criteria as a haemoglobin increase ≥ 1.5 g/dL from baseline or a reduction of RBC units transfused by an absolute number of at least 4 units every 8 weeks compared to the 8 weeks prior to baseline, and a response duration of at least 8 weeks.

Erythroid response during the first 24 weeks of the study was demonstrated by 27/85 (31.8%) of the subjects in the erythropoietin group compared to 2/45 (4.4%) of the subjects in the placebo group (p<0.001). All of the responding subjects were in the stratum with sEPO <200 mU/mL during screening. In that stratum, 20/40 (50%) subjects without prior transfusions demonstrated erythroid response during the first 24 weeks, compared with 7/31 (22.6%) subjects with prior transfusions (two subjects with prior transfusion reached primary endpoint based on reduction of RBC units transfused by an absolute number of at least 4 units every 8 weeks compared to the 8 weeks prior to baseline).

Median time from baseline to first transfusion was statistically significantly longer in the erythropoietin group compared to placebo (49 vs. 37 days; p=0.046). After 4 weeks of treatment the time to first transfusion was further increased in the erythropoietin group (142 vs. 50 days, p=0.007). The percentage of subjects who were transfused in the erythropoietin group decreased from 51.8% in the 8 weeks prior to baseline to 24.7% between weeks 16 and 24, compared to the placebo group which had an increase in transfusion rate from 48.9% to 54.1% over the same time periods.

Paediatric population

Chronic Renal Failure

Erythropoietin was evaluated in an open-label, non-randomised, open dose-range, 52-week clinical study in paediatric CRF patients undergoing haemodialysis. The median age of patients enrolled in the study was 11.6 years (range 0.5 to 20.1 years).

Erythropoietin was administered at 75 IU/kg/week intravenously in 2 or 3 divided doses post-dialysis, titrated by 75 IU/kg/week at intervals of 4 weeks (up to a maximum of 300 IU/kg/week), to achieve a 1 g/dL/month increase in haemoglobin. The desired haemoglobin concentration range was 9.6 to 11.2 g/dL. Eighty-one percent of patients achieved the haemoglobin concentration level. The median time to target was 11 weeks and the median dose at target was 150 IU/kg/week. Of the patients who achieved the target, 90% did so on a 3 times-per-week dosing regimen.

After 52 weeks, 57% of patients remained in the study, receiving a median dose of 200 IU/kg/week.

Clinical data with subcutaneous administration in children are limited. In 5 small, open label, uncontrolled studies (number of patients ranged from 9-22, total N=72), Erythropoietin has been administered subcutaneously in children at starting doses of 100 IU/kg/week to 150 IU/kg/week with the possibility to increase up to 300 IU/kg/week. In these studies, most were predialysis patients (N=44), 27 patients were on peritoneal dialysis and 2 were on haemodialysis with age ranging from 4 months to 17 years. Overall, these studies have methodological limitations but treatment was associated with positive trends towards higher haemoglobin levels. No unexpected adverse events were reported.

Chemotherapy-induced anaemia

Erythropoietin600 IU/kg (administered intravenously or subcutaneously once weekly) has been evaluated in a randomised, double-blind, placebo-controlled, 16-week study and in a randomised, controlled, open-label, 20-

week study in anaemic paediatric patients receiving myelosuppressive chemotherapy for the treatment of various childhood non-myeloid malignancies.

In the 16-week study (n=222), in the erythropoietin-treated patients there was no statistically significant effect on patient-reported or parent-reported Paediatric Quality of Life Inventory or Cancer Module scores compared with placebo (primary efficacy endpoint). In addition, there was no statistical difference between the proportion of patients requiring pRBC transfusions between the Erythropoietin group and placebo.

In the 20-week study (n=225), no significant difference was observed in the primary efficacy endpoint, i.e. the proportion of patients who required a RBC transfusion after Day 28 (62% of erythropoietin patients versus 69% of standard therapy patients).

Pharmacokinetic properties

Absorption

Following subcutaneous injection, serum levels of erythropoietin reach a peak between 12 and 18 hours post-dose. There was no accumulation after multiple dose administration of 600 IU/kg administered subcutaneously weekly.

The absolute bioavailability of subcutaneous injectable erythropoietin is approximately 20% in healthy subjects.

Distribution

The mean volume of distribution was 49.3 mL/kg after intravenous doses of 50 and 100 IU/kg in healthy subjects. Following intravenous administration of erythropoietin in subjects with chronic renal failure, the volume of distribution ranged from 57-107 mL/kg after single dosing (12 IU/kg) to 42-64 mL/kg after multiple dosing (48-192 IU/kg), respectively. Thus, the volume of distribution is slightly greater than the plasma space.

Elimination

The half-life of erythropoietin following multiple dose intravenous administration is approximately 4 hours in healthy subjects. The half-life for the subcutaneous route is estimated to be approximately 24 hours in healthy subjects.

The mean CL/F for the 150 IU/kg 3 times-per-week and 40,000 IU once-weekly regimens in healthy subjects were 31.2 and 12.6 mL/h/kg, respectively. The mean CL/F for the 150 IU/kg, 3-times-per-week and 40,000 IU, once-weekly regimens in the anaemic cancer subjects were 45.8 and 11.3 mL/h/kg, respectively. In most anaemic subjects with cancer receiving cyclic chemotherapy CL/F was lower after subcutaneous doses of 40,000 IU once weekly and 150 IU/kg, 3 times per week compared with the values for healthy subjects.

Linearity/non-linearity

In healthy subjects, a dose-proportional increase in serum erythropoietin concentrations was observed after intravenous administration of 150 and 300 IU/kg, 3 times per week. Administration of single doses of 300 to 2,400 IU/kg subcutaneous erythropoietin resulted in a linear relationship between mean C_{max} and dose and between mean AUC and dose. An inverse relationship between apparent clearance and dose was noted in healthy subjects.

Pharmacokinetic/ pharmacodynamic relationships

Erythropoietin exhibits a dose-related effect on haematological parameters which is independent of route of administration.

Paediatric population

A half-life of approximately 6.2 to 8.7 hours has been reported in paediatric subjects with chronic renal failure following multiple dose intravenous administration of erythropoietin. The pharmacokinetic profile of erythropoietin in children and adolescents appears to be similar to that of adults.

Pharmacokinetic data in neonates is limited.

A study of 7 preterm very low birth weight neonates and 10 healthy adults given i.v. erythropoietin suggested that distribution volume was approximately 1.5 to 2 times higher in the preterm neonates than in the healthy adults, and clearance was approximately 3 times higher in the preterm neonates than in healthy adults.

Renal impairment

In chronic renal failure patients, the half-life of intravenously administered erythropoietin is slightly prolonged, approximately 5 hours, compared to healthy subjects.

PRECLINICAL SAFETY DATA

In repeated dose toxicological studies in dogs and rats, but not in monkeys, erythropoietin therapy was associated with subclinical bone marrow fibrosis. Bone marrow fibrosis is a known complication of chronic renal failure in humans and may be related to secondary hyperparathyroidism or unknown factors. The incidence of bone marrow fibrosis was not increased in a study of haemodialysis patients who were treated with erythropoietin for 3 years compared to a matched control group of dialysis patients who had not been treated with erythropoietin.

Erythropoietin does not induce bacterial gene mutation (Ames test), chromosomal aberrations in mammalian cells, micronuclei in mice, or gene mutation at the HGPRT locus.

Long-term carcinogenicity studies have not been carried out. Conflicting reports in the literature, based on *in vitro* findings from human tumour samples, suggest erythropoietin may play a role as tumour proliferators. This is of uncertain significance in the clinical situation.

In cell cultures of human bone marrow cells, erythropoietin stimulates erythropoiesis specifically and does not affect leucopoiesis. Cytotoxic actions of erythropoietin on bone marrow cells could not be detected.

In animal studies, erythropoietin has been shown to decrease foetal body weight, delay ossification and increase foetal mortality when given in weekly doses of approximately 20 times the recommended human weekly dose. These changes are interpreted as being secondary to decreased maternal body weight gain, and the significance to humans is unknown given therapeutic dose levels.

PRESENTATION

NP-Poetin 2000IU Injection: Is available in 1ml x 1 PFS.

NP-Poetin 4000IU Injection: Is available in 1ml x 1 PFS.

NP-Poetin 10000IU Injection: Is available in 1ml x 1 PFS.

INSTRUCTIONS

The product should not be used, and discarded

• if the seal is broken,

• if the liquid is colored or you can see particles floating in it,

• if you know, or think that it may have been accidentally frozen, or

• if there has been a refrigerator failure.

The product is for single use only. Only take one dose of Epoetin alpha from each syringe. In case only a partial dose of the syringe is required, the cover should be removed before the plunger is pushed up to the desired numbered graduation mark to remove unwanted solution before injection

● Keep all medicines out of the sight & reach of children.

REGISTRATION NUMBER

NP-Poetin 2000IU : 077536

NP-Poetin 4000IU : 077537

NP-Poetin 10000IU : 095293

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Manufactured by:

Nextar Pharma (Pvt.) Ltd.

E-58, North Western Industrial Zone, Port Qasim, Karachi - Pakistan.

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