NAME OF THE MEDICINAL PRODUCT

Trade Name: EPREX
Pre-Filled Syringes with needle guard (PROTECS™)
International Non Proprietary Name: Epoetinum alfa
Chemical name: Recombinant human erythropoietin

QUALITATIVE AND QUANTITATIVE COMPOSITION

Epoetinum alfa, a glycoprotein produced by recombinant DNA technology, is the active ingredient.

Epoetinum alfa in pre-filled syringes with needle guard (PROTECS™)

Concentration of Epoetinum alfa International Units	µg	Volume per syringe (mL)
1000	8.4	0.5
2000	16.8	0.5
3000	25.2	0.3
4000	33.6	0.4
5000	42.0	0.5
6000	50.4	0.6
8000	67.2	0.8
10000	84.0	1.0
20000	168.0	0.5
30000	252	0.75
40000	336.0	1.0

For excipients, see List of Excipients.

PHARMACEUTICAL FORM

Epoetinum alfa is a sterile, clear, colourless, buffered parenteral solution for intravenous or subcutaneous injection.

CLINICAL PARTICULARS

Therapeutic Indications

Epoetinum alfa is indicated for the treatment of anaemia associated with chronic renal failure in adult patients on haemodialysis and peritoneal dialysis, and in pediatric patients on haemodialysis.

Epoetinum alfa is indicated for the treatment of severe anaemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing dialysis.

Epoetinum alfa is indicated for the treatment of anaemia and reduction of transfusion requirements in adult cancer patients with non-myeloid malignancies receiving chemotherapy.

Epoetinum alfa is indicated for the treatment of anaemia in adult HIV-infected patients being treated with zidovudine having endogenous erythropoietin levels ≤500 mU/ml.

Epoetinum alfa is indicated in adults to facilitate autologous blood collection within a predeposit programme and decrease the risk of receiving allogeneic blood transfusions in patients with moderate anaemia (haematocrits of 33-39%, haemoglobin of 10-13 g/dL, [6.2-8.1 mmol/l], no iron deficiency), 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 Epoetinum alfa. Treatment should only be given to patients if blood saving procedures are not available or insufficient when the scheduled major elective surgery requires a large volume of blood (4 or more units of blood for females or 5 or more units for males).

Epoetinum alfa is indicated to augment erythropoiesis in the perisurgical period in order to reduce allogeneic blood transfusions and correct postoperative anaemia in adult non-iron deficient patients undergoing major elective orthopaedic surgery. Use should be restricted to patients with moderate anaemia (*eg* Hb 10-13 g/dL) who do not have an autologous predonation programme available and with expected moderate blood loss (900 to 1800 ml).

Posology and Method of Administration

Method of Administration

Epoetinum alfa may be administered by intravenous or subcutaneous injection.

As for any parenterally administered drug, the injection solution should be inspected for particles and discolouration prior to administration. Do not shake, shaking may denature the glycoprotein, rendering it inactive.

Epoetinum alfa in syringes contains no preservatives. Do not re-use syringe. Discard unused portion.

Intravenous Injection

Epoetinum alfa should be administered over at least one to five minutes, depending on the total dose.

A slower injection may be preferable in patients who react to the treatment with flu-like symptoms.

In haemodialysis patients, a bolus injection may be given during dialysis via a suitable venous port in the dialysis line. Alternatively, at the completion of a haemodialysis session, the injection can be given via the fistula needle tubing, followed by 10 ml of isotonic saline to rinse the tubing and to ensure satisfactory injection of the product into the circulation.

Epoetinum alfa should not be administered by intravenous infusion or mixed with other drugs.

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.

Chronic Renal Failure Patients

In patients with chronic renal failure where intravenous access is routinely available (haemodialysis patients), administration by the intravenous route is preferable. Where intravenous access is not readily available (patients not yet undergoing dialysis and peritoneal dialysis patients), Epoetinum alfa may be administered subcutaneously.

The haemoglobin concentration aimed for should be between 10 to 12 g/dL (6.2-7.5 mmol/l) in adults and 9.5 to 11 g/dL (5.9-6.8 mmol/l) in children.

In patients with chronic renal failure, maintenance haemoglobin concentration should not exceed the upper limit of the haemoglobin concentration range (see Special Warnings and Special Precautions for Use - Renal Failure Patients).

When changing the route of administration, the same dose should be used initially and then titrated to keep haemoglobin in the haemoglobin concentration range.

In the correction phase, the dose of Epoetinum alfa should be increased if the haemoglobin does not increase at least 1 g/dL (0.62 mmol/l) per month.

A clinically significant increase in haemoglobin is usually not observed in less than 2 weeks and may require up to 6-10 weeks in some patients.

When the haemoglobin concentration is within range, the dose should be decreased by 25 IU/kg/dose in order to avoid exceeding the haemoglobin concentration range. Dose should be reduced when haemoglobin approaches 12 g/dL.

Dose reductions may be made by omitting one of the weekly doses or by decreasing the amount of each dose.

Adult Haemodialysis Patients

In patients on haemodialysis, where intravenous access is readily available, administration by the intravenous route is preferable.

The treatment is divided into two stages:

Correction phase

50 IU/kg three times per week.

When necessary, dose adjustments should be made in increments of 25 IU/kg three times per week at intervals of at least 4 weeks until the haemoglobin concentration range (10-12 g/dL [6.2-7.5 mmol/l]) is achieved.

Maintenance phase

Adjust dosage in order to maintain haemoglobin values at the desired level: Hb between 10 and 12 g/dL (6.2 – 7.5 mmol/l).

The maintenance dose should be individualised for each chronic renal failure patient. The recommended total weekly dose is between 75 and 300 IU/kg.

Available data suggests that patients with a baseline haemoglobin (<6 g/dL or <3.7 mmol/l) may require higher maintenance doses than patients with a baseline haemoglobin (> 8 g/dL or > 5 mmol/l).

Paediatric Haemodialysis Patients

The treatment is divided into two stages:

Correction phase

50 IU/kg three times per week by the intravenous route.

When necessary, dose adjustments should be made in increments of 25 IU/kg three times per week at intervals of at least 4 weeks until the haemoglobin concentration range (9.5-11 g/dL [5.9-6.8 mmol/l]) is achieved.

Maintenance phase

Appropriate adjustment of the dose should be made in order to maintain the haemoglobin concentration within the desired range between 9.5 g/dl to 11 g/dl (5.9 to 6.8 mmol/l).

Generally, children under 30 kg require higher maintenance doses than children over 30 kg and adults. For example, the following maintenance doses were observed in clinical trials after 6 months of treatment.

Weight (kg)	Dose (IU/kg given 3x week)	
	Median	Usual maintenance dose
<10	100	75-150
10-30	75	60-150
>30	33	30-100

Available data suggest that patients whose initial haemoglobin is very low (haemoglobin <6.8 g/dL [4.2 mmol/l]) may require higher maintenance doses than patients whose initial haemoglobin is higher (haemoglobin >6.8 g/dL [4.2 mmol/l]).

Adult Peritoneal Dialysis Patients

In peritoneal dialysis patients, where intravenous access is not readily available, Epoetinum alfa may be administered subcutaneously

The treatment is divided into two stages:

Correction phase

50 IU/kg twice per week.

When necessary, dose adjustments should be made in increments of 25 IU/kg twice per week at intervals of at least 4 weeks until the haemoglobin concentration range (10-12 g/dL [6.2-7.5 mmol/l]) is achieved.

Maintenance phase
The usual dose to maintain the haemoglobin concentration range (10-12 g/dL [6.2-7.5 mmol/l]) is between 25 and 50 IU/kg twice per week in two equal injections.

Adult Predialysis Patients [Adult Patients With End Stage Renal Insufficiency]

In patients with renal insufficiency not yet undergoing dialysis, where intravenous access is not readily available, Epoetinum alfa may be administered subcutaneously. The treatment is divided into two stages:

Correction phase
50 IU/kg three times per week.

When necessary, dose adjustments should be made in increments of 25 IU/kg three times per week at intervals of at least 4 weeks until the haemoglobin concentration range (10-12 g/dL [6.2-7.5 mmol/l]) is achieved.

Maintenance phase
The usual dose to maintain the haemoglobin concentration range is between 17 and 33 IU/kg three times per week.

The maximum dosage should not exceed 200 IU/kg 3 times per week.

Cancer Patients

Adult Cancer Patients

The subcutaneous route of administration should be used.

The haemoglobin concentration range should be 10 to 12 g/dL (7.5 mmol/l) in men and women and it should not be exceeded.

Epoetinum alfa therapy should continue until one month after the end of chemotherapy. However, the need to continue Epoetinum alfa therapy should be re-evaluated periodically.

The initial dose for the treatment of anaemia should be 150 IU/kg 3 times per week.

Alternatively, Epoetinum alfa can be administered at an initial dose of 40000 IU subcutaneously once weekly.

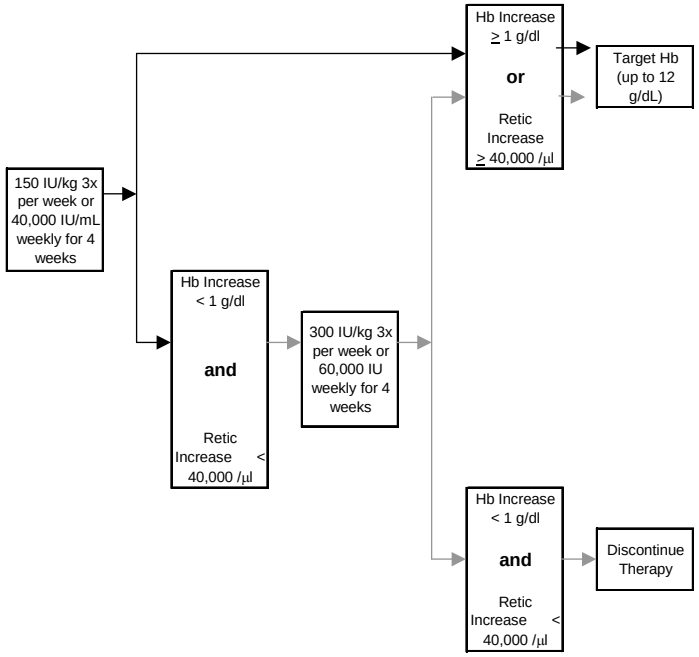
If after 4 weeks of treatment at the initial dose, the haemoglobin has increased by at least 1 g/dL (0.6 mmol/L) [or the reticulocyte count has increased ≥ 40000 cells/µl above baseline] the dose should remain unchanged.

If after 4 weeks of treatment at the initial dose, the haemoglobin has not increased by ≥1 g/dL (0.6 mmol/l) [and the reticulocyte count has not increased by ≥ 40000 cells/µl above baseline], in the absence of red blood cell transfusion, the dose should be increased to 300 IU/kg 3 times per week or 60000 IU weekly.

If after 4 weeks of additional therapy with 300 IU/kg 3 times per week or 60000 IU weekly, the haemoglobin has increased ≥1 g/dL (≥ 0.6 mmol/l), [or the reticulocyte count has increased ≥ 40000 cells/μl] the dose should remain unchanged.

If after 4 weeks of additional therapy with 300 IU/kg three times per week or 60000 IU per week, the haemoglobin has increased <1 g/dL (0.6 mmol/l) [and the reticulocyte count has increased < 40000 cells/μl above baseline], response is unlikely and treatment should be discontinued.

[The recommended dosing regimen is described in the following diagram:]



A rate of rise in haemoglobin of greater than 1 g/dL (0.6 mmol/L) per 2 week or 2 g/dL (1.25 mmol/L) per month or haemoglobin levels of >12 g/dL (>8.1 mmol/L) should be avoided. If the haemoglobin is rising by more than 1 g/dL (0.6 mmol/l) per two week or 2 g/dL (1.25 mmol/L) per month or haemoglobin is approaching 12 g/dL (7.5 mmol/l), reduce the Epoetinum alfa dose by about 25-50% depending upon the rate of rise of haemoglobin. If the haemoglobin exceeds 12 g/dL (7.5 mmol/l), withhold therapy until it falls below 12 g/dL (7.5 mmol/l) and then reinitiate Epoetinum alfa therapy at a dose 25% below the previous dose.

Zidovudine Treated HIV-Infected Patients

Adult Zidovudine Treated HIV-Infected Patients

Prior to beginning Epoetinum alfa, it is recommended that the endogenous serum erythropoietin level be determined prior to transfusion. Available data suggests that patients with endogenous serum erythropoietin levels >500 mU/ml are unlikely to respond to therapy with Epoetinum alfa.

The treatment is divided into two stages:

Correction phase
100 IU/kg three times per week by the subcutaneous or intravenous route for 8 weeks.

If the response is not satisfactory (*ie*, reduced transfusion requirements or increased haemoglobin) after 8 weeks of therapy, the dose of Epoetinum alfa can be increased. Dose increases should be made in increments of 50 to 100 IU/kg three times per week at intervals of at least 4 weeks. If patients have not responded satisfactorily to an Epoetinum alfa dose of 300 IU/kg three times per week, it is unlikely that they will respond to higher doses.

Maintenance phase
After the desired response is attained, the dose should be titrated to maintain the haematocrit between 30-35%, based on factors such as variations in zidovudine dose and the presence of intercurrent infections or inflammatory episodes. If the haematocrit exceeds 40%, the dose should be discontinued until the haematocrit decreases to 36%. When treatment is resumed, the dose should be reduced by 25% and then titrated to maintain the desired haematocrit.

In zidovudine-treated HIV-infected patients the haemoglobin concentration should not exceed 12g/dL (7.5mmol/l).

Adult Surgery Patients in an Autologous Pre-Donation Programme
The intravenous route of administration should be used. Epoetinum alfa should be administered after the completion of each blood donation procedure

Mildly anaemic patients (haematocrit of 33 to 39% and/or haemoglobin 10 to 13 g/dL [6.2-8.1 mmol/l]) requiring predeposit [of ≥ 4 units] of blood should be treated with Epoetinum alfa at 600 IU/kg 2 times weekly for 3 weeks prior to surgery.

For those patients who require a lesser degree of erythropoietic stimulation, a dose regimen of 150-300 IU/kg administered twice weekly has been shown to augment autologous pre-donation and to decrease the subsequent decline in haematocrit.

Adult Perisurgery Patients (Without Autologous Blood Donation)
The subcutaneous route of administration should be used.

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

In cases where there is a medical need to reduce the time before surgery to less than three weeks, the recommended dose regimen is 300 IU/kg for 10 consecutive days before surgery, on the day of surgery and up to 4 days after surgery. 300 IU/kg/day is recommended for haemoglobin levels ≤ 13 g/dL (8.1 mmol/l). If the haemoglobin level reaches 15 g/dL, or higher, administration of Epoetinum alfa should be stopped and further dose should not be given.

Contraindications
Patients who develop antibody-mediated Pure Red Cell Aplasia (PRCA) following treatment with any erythropoietin should not receive Epoetinum alfa or any other

erythropoietin (see Special Warnings and Special Precautions for Use - Pure Red Cell Aplasia).

Uncontrolled hypertension.

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

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

The use of Epoetinum alfa 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.

Special Warnings and Special Precautions for Use

General

In all patients receiving Epoetinum alfa, blood pressure should be closely monitored and controlled as necessary. Epoetinum alfa should be used with caution in the presence of untreated, inadequately treated or poorly controllable hypertension.

It may be necessary to initiate or increase anti-hypertensive treatment during Epoetinum alfa therapy. If blood pressure cannot be controlled, Epoetinum alfa treatment should be discontinued.

Epoetinum alfa 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.

Epoetinum alfa should be used with caution in patients with chronic liver failure. The safety of Epoetinum alfa has not been established in patients with hepatic dysfunction. Due to decreased metabolism, patients with hepatic dysfunction may have increased erythropoiesis with Epoetinum alfa.

An increased incidence of thrombotic vascular events (TVEs) has been observed in patients receiving ESAs (see Undesirable Effects) 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 ischaemic attacks) have been reported.

The reported risk of TVEs should be carefully weighed against the benefits to be derived from treatment with Epoetinum alfa particularly in patients with pre-existing risk factors.

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

The safety and efficacy of Epoetinum alfa therapy have not been established in patients with underlying haematologic diseases (e.g. haemolytic anaemia, sickle cell anaemia, thalassemia

There may be a moderate dose-dependent rise in the platelet count, within the normal range, during treatment with Epoetinum alfa. 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 should be regularly monitored during the first 8 weeks of therapy.

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 Epoetinum alfa, 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 Epoetinum alfa, adequate iron stores should be assured and iron supplementation should be administered if necessary:

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

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

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

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

Very rarely, the initial presentation or exacerbation of porphyria has been observed in Epoetinum alfa-treated patients. Epoetinum alfa should be used with caution in patients with porphyria.

Erythropoiesis-stimulating agents (ESAs) are not necessarily equivalent. Therefore, it should be emphasised that patients should only be switched from one ESA (such as EPREX) to another ESA with the authorisation of the treating physician.

Pure Red Cell Aplasia

Antibody-mediated pure red cell aplasia (PRCA) has been very rarely reported after months to years of subcutaneous Epoetin treatment in chronic renal failure patients.

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

In chronic renal failure 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, aluminum intoxication, infection or inflammation, blood loss, haemolysis and bone marrow fibrosis of any origin) should be investigated. If the reticulocyte count corrected for anaemia (i.e., the reticulocyte "index") is low (<20000/mm^3 or <20000/uL or <0.5%) platelet and white blood cell counts are normal, and if no other cause of loss of effect has been found, anti-erythropoietin antibodies should be determined and a bone marrow examination should be considered for diagnosis of PRCA.

If anti-erythropoietin, antibody-mediated PRCA is suspected, therapy with Epoetinum alfa should be discontinued immediately. No other ESA therapy should be commenced because of the risk of cross-reaction.Appropriate therapy, such as blood transfusions, may be given to patients when indicated.

Renal Failure Patients

Chronic renal failure patients being treated with Epoetinum alfa 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 (1.2 mmol/l)/per month to minimise risks of an increase in hypertension. Dose should be reduced when haemoglobin approaches 12 g/dL.

In patients with chronic renal failure, maintenance haemoglobin concentration should not exceed the upper limit of the haemoglobin concentration range as recommended under 4.2 Posology and Method of Administration. Haemoglobin levels targeted to 13 g/dL or higher may be associated with a higher risk of cardiovascular events, including death.

Patients with chronic renal failure and insufficient haemogloblin response to ESA therapy may be at even greater risk for cardiovascular events and mortality than other patients.

Based on information available to date, the use of Epoetinum alfa in predialysis [end stage renal insufficiency] patients does not accelerate the rate of progression of renal insufficiency.

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, aneurisms, 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 the appropriate treatment of the hyperkalaemia, consideration should be given to ceasing Epoetinum alfa administration until the serum potassium level has been corrected.

As a result of an increase in packed cell volume, haemodialysis patients receiving Epoetinum alfa frequently require an increase in heparin dose during dialysis. If heparinisation is not optimal, occlusion of the dialysis system is possible.

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

Cancer Patients

Cancer patients on Epoetinum alfa should have haemoglobin levels measured on a regular basis until a stable level is achieved and periodically thereafter.

ESAs 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 ESAs could stimulate the growth of tumours.

In controlled clinical studies, use of Epoetinum alfa and other ESAs have shown:

- decreased locoregional control in patients with advanced head and neck cancer receiving radiation therapy when administered to a haemoglobin target 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 a haemoglobin target of 12-14 g/dl (7.5-8.7 mmol/l),

- Another ESA (darbepoietin alfa) increased risk of death when administered to target a haemoglobin 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.

In view of the above, 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 to consider in this assessment 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 (see Pharmacodynamic Properties).

In cancer patients receiving chemotherapy, the 2-3 week delay between ESA administration and the appearance of erythropoietin-induced red cells should be

considered when assessing whether or not Epoetinum alfa therapy is appropriate (in particular for patients at risk of transfusion).

HIV-Infected Patients

If HIV-infected patients fail to respond or maintain a response to Epoetinum alfa, other etiologies including iron deficiency anaemia should be considered and evaluated.

Adult Surgery Patients in an Autologous Pre-Donation Programme

All special warnings and special precautions associated with autologous blood donation programmes, especially routine volume replacement, should be respected in patients being supplemented with Epoetinum alfa.

Adult Perisurgery Patients (Without Autologous Blood Donation)

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 a baseline haemoglobin of >13 g/dL (8.1 mmol/l), the possibility that Epoetinum alfa treatment may be associated with an increased risk of postoperative thrombotic/vascular events cannot be excluded. Therefore, it should not be used in patients with baseline haemoglobin >13 g/dL (8.1 mmol/l).

The use of Epoetinum alfa is not recommended in perisurgery patients with a baseline haemoglobin of >13 g/dL (8.1 mmol/l).

Interactions with Other Medicinal Products and Other Forms of Interaction

No evidence exists that indicates that treatment with Epoetinum alfa alters the metabolism of other drugs. Drugs that decrease erythropoiesis may decrease the response to Epoetinum alfa.

Since cyclosporin is bound by red blood cells there is potential for a drug interaction. If Epoetinum alfa 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 Epoetinum alfa and G-CSF or GM-CSF with regard to haematological differentiation or proliferation of tumour cells from biopsy specimens *in vitro*.

In patients with metastatic breast cancer, subcutaneous co-administration of 40000 IU/mL Epoetinum alfa with trastuzumab (6 mg/kg) had no effect on the pharmacokinetics of trastuzumab.

Pregnancy and Lactation

Use During Pregnancy

In animal studies, Epoetinum alfa has been shown to decrease fetal body weight, delay ossification and increase fetal 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.

There are no adequate and well-controlled studies in pregnant women.

Epoetinum alfa should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (See Reproduction Toxicology).

Use During Lactation

Erythropoietin is present in human milk. However, it is not known whether Epoetinum alfa is distributed into human milk. Epoetinum alfa should be used with caution in nursing women.

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

Effects on Ability to Drive and Use Machines

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

Undesirable Effects

Summary of the Safety Profile

The most frequent adverse drug reaction during treatment with Epoetinum alfa 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 Epoetinum alfa are diarrhoea, nausea, vomiting, pyrexia, and headache. Influenza-like illness may occur especially at the start of treatment.

An increased incidence of thrombotic vascular events (TVEs), has been observed in patients receiving ESAs (See Special Warnings and Special Precautions for Use).

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

Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have occurred also during Epoetinum alfa 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.

Clinical Trial Experience

Of a total 3559 subjects in 27 randomized, double-blinded, placebo or standard of care controlled studies, the overall safety profile of Epoetinum alfa was evaluated in 2136 anemic subjects. Included were 228 Epoetinum alfa-treated CRF subjects in 4 chronic renal failure studies (2 studies in predialysis [N=131 exposed CRF subjects not yet on dialysis] and 2 in dialysis [N=97 exposed CRF subjects on dialysis]; 1404 exposed cancer subjects in 16 studies of anaemia due to chemotherapy; 144 exposed

subjects in 4 HIV-infection studies; 147 exposed subjects in 2 studies for autologous blood donation; and 213 exposed subjects in 1 study in the perisurgical setting. Adverse drug reactions reported by ≥1% of subjects treated with Epoetinum alfa in these trials are shown in the table below:

Summary of Adverse Drug Reactions Reported by ≥1% of Subjects in Clinical Studies With Epoetinum Alfa

	CRF											
	Predialysis		Dialysis		Oncology		HIV		ABD		Surgery	
	EPO	Placebo	EPO	Placebo	EPO	Non-ESA	EPO	Placebo	EPO	Non-ESA	EPO	Placebo
System/Organ Class	N=131	N=79	N=97	N=46	N=1404	N=930	N=144	N=153	N=147	N=112	N=213	N=103
Adverse Drug Reaction	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gastrointestinal disorders												
Nausea	14 (11)	10 (13)	23 (24)	13 (28)	265 (19)	193 (21)	36 (25)	39 (25)	26 (18)	11(10)	96 (45)	46 (45)
Diarrhea	16 (12)	8 (10)	7 (7)	4 (9)	168 (12)	102 (11)	43 (30)	51 (33)	5 (3)	7 (6)	18 (8)	12 (12)
Vomiting	12 (9)	6 (8)	9 (9)	8 (17)	173 (12)	134 (14)	21 (15)	24 (16)	7 (5)	1 (1)	36 (17)	14 (14)
General disorders and administration site conditions												
Chills	6 (5)	2 (3)	10 (10)	3 (7)	33 (2)	32 (3)	5 (3)	14 (9)	8 (5)	4 (4)	12 (6)	1 (1)
Influenza like illness	1 (1)	NR	9 (9)	6 (13)	23 (2)	10 (1)	3 (2)	1 (1)	4 (3)	1 (1)	1(<1)	NR
Injection site reaction	14 (11)	16 (20)	1 (1)	NR	42 (3)	31 (3)	14 (10)	13 (9)	NR	1 (1)	39 (18)	19 (18)
Pyrexia	4 (3)	4 (5)	9 (9)	6 (13)	189 (13)	130 (14)	61 (42)	52 (34)	7 (5)	3 (3)	37 (17)	27 (26)
Peripheral edema	9 (7)	10 (13)	NR	NR	72 (5)	34 (4)	7 (5)	5 (3)	2 (1)	2 (2)	14 (7)	4 (4)
Metabolism and nutrition disorders												
Hyperkalemia	3 (2)	3 (4)	10 (10)	2 (4)	2 (<1)	2 (<1)	NR	NR	NR	NR	NR	1 (1)
Musculoskeletal and connective tissue disorders												
Arthralgia	16 (12)	6 (8)	23 (24)	3 (7)	45 (3)	43 (5)	5 (3)	11 (7)	3 (2)	3 (3)	5 (2)	3 (3)
Bone pain	1 (1)	NR	6 (6)	1 (2)	47 (3)	26 (3)	3 (2)	NR	NR	1 (1)	1(<1)	NR
Myalgia	3 (2)	1 (1)	6 (6)	NR	46 (3)	25 (3)	8 (6)	9 (6)	2 (1)	3 (3)	2 (1)	NR
Pain in extremity	7 (5)	7 (9)	15 (15)	2 (4)	37 (3)	19 (2)	10 (7)	13 (8)	6 (4)	2 (2)	7 (3)	4 (4)
Nervous system disorders												
Convulsion	1 (1)	2 (3)	2 (2)	NR	12 (1)	4 (<1)	2 (1)	2 (1)	NR	NR	NR	NR
Headache	22 (17)	14 (18)	33 (34)	20 (43)	98 (7)	50 (5)	28 (19)	32 (21)	17 (12)	16 (14)	25 (12)	9 (9)

Footnotes appear at the end of the table.

Continued

Summary of Adverse Drug Reactions Reported by ≥1% of Subjects in Clinical Studies With Epoetinum Alfa (Continued)

	CRF											
	Predialysis		Dialysis		**Oncology**		**HIV**		**ABD**		**Surgery**	
	EPO	Placebo	EPO	Placebo	EPO	Non-ESA	EPO	Placebo	EPO	Non-ESA	EPO	Placebo
System/Organ Class	N=131	N=79	N=97	N=46	N=1404	N=930	N=144	N=153	N=147	N=112	N=213	N=103
Adverse Drug Reaction	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Respiratory, thoracic and mediastinal disorders												
ɔugh	5 (4)	1 (1)	9 (9)	8 (17)	98 (7)	66 (7)	37 (26)	22 (14)	2 (1)	2 (2)	10 (5)	NR
ɛsp tract congestion	NR	NR	9 (9)	2 (4)	NR	NR	1 (1)	NR	NR	NR	NR	NR
Skin and subcutaneous tissue disorders												
ɹash[a]	8 (6)	6(8)	11(11)	2(4)	93 (7)	47 (5)	36 (25)	19 (12)	3 (2)	2 (2)	8 (4)	2 (2)
Vascular disorders												
ɱbolism and thrombosis[b]	2 (2)	NR	15 (15)	2 (4)	76 (5)	33 (4)	7 (5)	1 (1)	6 (4)	3 (3)	18 (8)	6 (6)
ɛep vein thrombosis	NR	NR	NR	NR	24 (2)	6 (1)	NR	NR	2 (1)	2 (2)	10 (5)	3 (3)
ɹrombosis	NR	NR	4(4)	1 (2)	18 (1)	6 (1)	NR	NR	2 (1)	NR	3(1)	NR
ypertension[c]	35 (27)	20 (25)	32 (33)	5 (11)	43 (3)	24 (3)	3(2)	4 (3)	NR	2 (2)	23 (11)	9 (9)

ADB=autologous blood donation; NR=not reported;

[a]Rash includes urticaria and angioedema

[b]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 (i.e. stroke including cerebral infarction and cerebral haemorrhage) transient ischaemic attacks, and shunt thrombosis (including dialysis equipment) and thrombosis within arteriovenous shunt aneurisms

[c]Hypertension includes hypertensive crisis and hypertensive

Post-marketing Experience

Adverse drug reactions identified during the postmarketing experience with Epoetinum alfa are included in Table 3. In the table, the frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 and < 1/10
Uncommon	≥1/1000 and <1/100
Rare	≥1/10000, <1/1000
Very rare	<1/10000, including isolated reports

Antibody-mediated pure red cell aplasia has been very rarely reported (<1/10000 cases per patient-year) after months to years of treatment with EPREX.

Table 3. Adverse Drug Reactions Identified During Postmarketing Experience with Epoetinum Alfa by Frequency Category Estimated from Spontaneous Reporting Rates

Blood & Lymphatic System Disorders	
Very rare	Erythropoietin Antibody-Mediated Pure Red Cell Aplasia
Very rare	Thrombocythemia

Overdose

The therapeutic margin of Epoetinum alfa is very wide. Overdosage of Epoetinum alfa 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 (Epoetinum alfa), 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 32000 to 40000 dalton.

Pharmacodynamic responses to HSA-free Epoetinum alfa, change in percent reticulocytes, haemoglobin, and total red blood cell counts as well as the area under the curve (AUCs) of these pharmacodynamic parameters, were similar between two

dosing regimens (150 IU/kg SC three times per week to 40000 IU/mL SC once weekly).

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

Clinical efficacy and safety

Chronic renal failure
A randomized prospective trial (CHOIR) evaluated 1432 anaemic chronic renal failure patients who were not undergoing dialysis. Patients were assigned to Epoetinim alfa treatment targeting a maintenance haemoglobin level of 13.5 g/dL (higher than the recommended target haemoglobin 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).

Chemotherapy induced anaemia
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).

The totality of evidence, including results of meta-analyses and clinical experience from controlled studies of ESAs in patients with cancer, continues to support a favorable benefit-risk balance for the use of ESAs in patients with chemotherapy-induced anaemia, when used according to the prescribing information. In meta-analyses of studies in which patients were receiving chemotherapy there were no statistically significant increases in either mortality or tumour progression. Signals in individual studies conducted outside of the recommendations in the product labeling (haemoglobin targets above 12 g/dL and/or no chemotherapy treatment) have raised concerns (see Special Warnings and Special Precautions for Use - Cancer Patients).

Pharmacokinetic Properties
Intravenous Administration
Measurement of Epoetinum alfa following multiple dose intravenous (IV) administration of 50 to 100 IU/kg revealed a half-life of approximately 4 hours in healthy subjects and a longer half-life in renal failure patients of approximately 5 hours after doses of 50, 100 and 150 IU/kg. A half-life of approximately 6 hours has been reported in children. With at least 4 days of PK blood sampling, half-life estimates ranging from 20.1 to 33.0 hours were observed in cancer subjects receiving 667 and 1500 IU/kg IV doses of Epoetinum alfa.

Subcutaneous Administration

Serum concentrations following subcutaneous injection are lower than those following intravenous injection. Serum levels increase slowly and reach a peak 12 to 18 hours after subcutaneous dosing. The peak serum concentration is below the peak observed using the intravenous route (approximately 1/20th of the value).

There is no accumulation: serum levels remain the same, whether data are collected 24 hours after the first injection or 24 hours after the last injection. Concentration-time profiles of erythropoietin on Week 1 and Week 4 were similar during multiple dosing of 600 IU/kg/once weekly in healthy subjects.

The half-life for the subcutaneous route of administration is approximately 24 hours. Mean half-life values in healthy subjects were 19.4 ± 8.1 and 15.0 ± 6.1 with multiple dosing of 150 IU/kg three times per week and 40000 IU/mL once weekly, respectively.

In a study comparing 40000 IU SC once weekly to 150 IU/kg SC three times per week dosing regimens of HSA-containing Epoetinum alfa in healthy subjects, the following parameters were estimated using data corrected for predose endogenous erythropoietin concentration during Week 4:

	C_{max} (mIU/mL)	C_{min} (mIU/mL)	$t_{1/2}$ (h)
150 IU/kg TIW (n=24)	191(100.1)	39 (17.9	31.8
40000 IU QW (n=22)	785 (427.3)	13 (9.5)	39.3

TIW = three times per week
QW = once weekly
Data from Study EPO-PHI-370

Based on AUC comparison, relative bioavailability of Epoetinum alfa 40000 IU once weekly versus 150 IU/kg three times per week was 176%.

In a study comparing 40000 IU SC once weekly versus 150 IU/kg SC three times per week dosing of HSA-free Epoetinum alfa in healthy subjects, the following parameters were estimated using data corrected for predose endogenous erythropoietin concentration during Week 4:

	C_{max} (mIU/mL)	C_{min} (mIU/mL)	$t_{1/2}$ (h)
150 IU/kg TIW (n=17)	143 (54.2)	18 (9.3)	19.4
40000 IU QW (n=17)	861 (445.1)	3.8 (4.27)	15.0

TIW = three times per week
QW = once weekly
Data from Study EPO-PHI 373

Based on AUC comparision, relative bioavailability of Epoetinum alfa 40000 IU/mL once weekly versus 150 IU/kg three times per week was 239%.

The bioavailability of subcutaneous Epoetinum alfa after a dose of 120 IU/kg is much lower than that of the intravenous drug: approximately 20%.

Pharmacokinetic parameters were estimated in healthy subjects and anemic cancer subjects receiving cyclic chemotherapy and either 150 IU/kg three times per week or 40000 IU/mL once weekly of HSA-containing Epoetinum alfa. The pharmacokinetic parameters of anemic cancer subjects were different from those observed in healthy subjects during Week 1 (when the anemic cancer subjects were receiving chemotherapy) but were similar during Week 3 (when the anemic cancer subjects were not receiving chemotherapy).

	C_{max} (mIU/mL)	C_{min} [b] (mIU/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (mL/h/kg)
Healthy Subjects					
150 IU/kg TIW (n=6)[a]	163 (53.6)	28.6 (10.4)	9.00 (3.29)	25.0 (7.13) [n=4]	31.2 (11.5)
40000 IU QW (n=6)	1036 (238)	9.25 (5.74)	21.0 (7.10)	28.8 (8.10)	12.6 (3.05)
Anemic Cancer Subjects: Week 1 when subjects were receiving chemotherapy					
150 IU/kg TIW (n=14) [a]	414 (312)	90.4 (41.4)	13.3 (12.4)	43.7 (3.94) [n=3]	20.2 (15.9)
40000 IU QW (n=18) [a]	1077 (510)	116 (230)	38.5 (17.8)	35.3 (16.8) [n=11]	9.16 (4.69)
Anemic Cancer Subjects: Week 3 when subjects were not receiving chemotherapy					
150 IU/kg TIW (n=4) [a]	178 (57.5)	---	14.2 (6.67)	41.9 (14.8) [n=2]	23.6 (9.51)
40000 IU QW (n=7)	897 (322)	---	22.3 (4.54)	38.8 (11.0)	13.9 (7.55)

TIW = three times per week
QW = once weekly
Data from Study PHI 377

[a] n as indicated unless specifically stated
[b] C_{min} was estimated by averaging weekly predose serum concentrations during the study

Pharmacokinetics of HSA-free Epoetinum alfa were studied in anemic cancer subjects receiving cyclic chemotherapy after the 150 IU/kg three times per week and 40000 IU/mL once weekly dosing regimens. In general, there was a high degree of variability associated with the pharmacokinetic parameters in anemic cancer subjects. In general, the first pharmacokinetic profile of Epoetinum alfa during Week 1 (when the anemic cancer subjects were receiving chemotherapy) demonstrated higher C_{max}, increased half-life, and lower clearance than the second pharmacokinetic profile during Week 3 or 4 (when the anemic cancer subjects were not receiving chemotherapy).

	C_{max} (mIU/mL)	C_{min} [b] (mIU/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (mL/h/kg)
Week 1	when subjects were receiving chemotherapy				
150 IU/kg TIW (n=16)[a]	642 (402.7)	207 (301.4)	14.98 (8.8)	28.3 (19.2) [n=7]	12.1 (11.2)
40000 IU QW (n=19) [a]	1289 (431.0)	148 (144.2)	48.74 (283)	76.2 (45.8) [n=9]	5.6 (1.8)
Week 3 or 4	when subjects were not receiving chemotherapy				
150 IU/kg TIW (n=9) [a]	357 (246.2)	---	20.67 (20.1)	30.0 (10.0) [n=6]	17.2 (7.8)
40000 IU QW (n=11)	941 (372.7)	---	24.54 (10.8)	46.7 (22.3)	12.7 (7.5)

TIW = three times per week
QW = once weekly
Data from Study EPO-P01-108

[a] "n" as indicated unless specifically stated
[b] C_{min} was estimated by averaging weekly predose serum concentrations during the study

Preclinical Safety Data

Chronic Toxicity

In some pre-clinical toxicological studies in dogs and rats, but not in monkeys, Epoetinum alfa therapy was associated with subclinical bone marrow fibrosis. Bone marrow fibrosis is a known complication of chronic renal failure in humans; it may be related to secondary hyperparathyroidism or unknown factors. In one study, there was no difference in the incidence of bone marrow fibrosis in haemodialysis patients treated with Epoetinum alfa for 3 years and haemodialysis patients not treated with Epoetinum alfa.

Carcinogenicity

Long-term carcinogenicity studies have not been carried out. There are conflicting reports in the literature regarding ESAs as tumour proliferators. The clinical significance of these reports, based on *in vitro* findings from human tumour samples, are unknown.

Mutagenicity

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

Reproduction Toxicology

Preclinical studies have shown no evidence of teratogenicity in rats or rabbits at dosages up to 500 IU/kg/day administered intravenously. However, intravenous administration of Epoetinum alfa causes a slight but not statistically significant decrease in fertility at 500 IU/kg, increased pre- and post-implantation loss and decreased fetal body weight at 100 and 500 IU/kg/day and delayed ossification at 20, 100, and 500 IU/kg/day. The latter finding was associated with reduced maternal body weight. Intravenous administration to lactating rats resulted in decreases in body weight gain, delays in appearance of abdominal hair and eyelid opening, and decreases in the number of caudal vertebrae in the F_1 fetuses of the 500 IU/kg/day group. There were no Epoetinum alfa-related effects on the F_2 generation fetuses.

PHARMACEUTICAL PARTICULARS

List of Excipients

HSA-free, Phosphate-buffered, Pre-filled Syringes with needle guard (PROTECS™)

- Polysorbate 80, Pharm. Eur.
- Sodium chloride, Pharm. Eur.
- Disodium phosphate dihydrate, Pharm. Eur.
- Sodium dihydrogen phosphate dihydrate, Pharm. Eur.
- Glycine, Pharm. Eur.
- Water for injections, Pharm. Eur.

Incompatibilities

Do not dilute or transfer to any other container. Do not administer by intravenous infusion or in conjunction with other drug solutions.

Shelf Life

HSA-free, Phosphate-buffered pre-filled syringes with needle guard (PROTECS™)	1000 IU/0.5 ml	18 months
	2000 IU/0.5 ml	18 months
	3000 IU/0.3 ml	18 months
	4000 IU/0.4 ml	18 months
	5000 IU/0.5 ml	18 months
	6000 IU/0.6 ml	18 months
	8000 IU/0.8 ml	18 months
	10000 IU/1.0 ml	18 months
	20000 IU/0.5 ml	18 months
	30000 IU/0.75ml	18 months
	40000 IU/1.0 ml	18 months

Observe expiry date on the outer pack.

Special Precautions for Storage

EPREX/ERYPO syringes are to be stored between 2°C and 8°C [36°F to 46°F] in the refrigerator, away from the freezer compartment. Do not freeze or shake. Keep the syringes in the original carton to protect from light. EPREX/ERYPO syringes that are being used or about to be used can be kept at room temperature (not above 25°C) for a maximum single period of 7 days.

Keep out of reach of children.

Nature and Contents of Container
Epoetinum alfa is supplied in type I glass prefilled syringes with polystyrene Teflon-faced rubber stoppers.

The pre-filled syringes are fitted with the PROTECS™ needle guard device to help prevent needle stick injuries after use.

[Package of 6 syringes	1000 IU/0.5 mL of Epoetinum alfa
	2000 IU/0.5 mL of Epoetinum alfa
	3000 IU/0.3 mL of Epoetinum alfa
	4000 IU/0.4 mL of Epoetinum alfa
	5000 IU/0.5 mL of Epoetinum alfa
	6000 IU/0.6 mL of Epoetinum alfa
	8000 IU/0.8 mL of Epoetinum alfa
	10000 IU/1.0 mL of Epoetinum alfa
1 syringe per package	20000 IU/0.5 mL of Epoetinum alfa
	30000 IU/0.75 mL of Epoetinum alfa
	40000 IU/1.0 mL of Epoetinum alfa]

Instructions for Use and Handling <and Disposal>
[The product is for single use only.]

The product should not be used, and should be discarded if:

– the seal is broken,

– the liquid is coloured or

– particles are in it,

– it may have been frozen, or

– there has been a refrigeration failure.

Any waste material should be disposed of in accordance with local requirements.

Patient Instructions for Use and Handling and Disposal

<u>Injecting EPREX/ERYPO under the skin yourself</u>

At the start of your therapy, EPREX/ERYPO may be injected by medical or nursing staff. However, your doctor may decide that it is right for you to learn how to inject EPREX/ERYPO under the skin (subcutaneously) yourself. You will receive appropriate training for you to do this. Under no circumstances should you attempt to inject yourself unless you have been trained to do so.

If EPREX/ERYPO is injected under the skin (*subcutaneously*), the amount injected is not normally more than one millilitre (1 ml) in a single injection.

EPREX/ERYPO is given alone and not mixed with other liquids for injection.

Do not shake EPREX/ERYPO syringes. Prolonged vigorous shaking may damage the product. If the product has been shaken vigorously, don't use it.

How to inject yourself using a prefilled syringe

The pre-filled syringes are fitted with the PROTECS™ needle guard device to help prevent needle stick injuries after use. This is indicated on the packaging.

-**Take a syringe out of the refrigerator.** The liquid needs to come to room temperature. This usually takes between 15 to 30 minutes.

-**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.

-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.

-Wash your hands. Use an antiseptic swab on the injection site, to disinfect it.

-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.

-Pinch a fold of skin between your thumb and index finger. Don't squeeze it.

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

-Check that you haven't punctured a blood vessel. Pull back slightly on the plunger. If you see blood, take the syringe out and try somewhere else.

-**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 needle guard will not activate unless the entire dose is given.

-When the plunger is pushed as far as it will go, take out the needle and let go of the skin.

-Take your thumb off the plunger. Allow the syringe to move up until the entire needle is covered by the needle guard.

-Press an antiseptic swab over the injection site for a few seconds after the injection.

-Dispose of your used syringe in a safe container.

Only take one dose of EPREX/ERYPO from each syringe. If any liquid remains in the syringe after an injection, the syringe should be properly disposed of, not reused. See 'How to dispose of EPREX/ERYPO'.

What to do if you use too much EPREX/ERYPO?

Tell the doctor or nurse immediately if you think too much EPREX/ERYPRO has been injected.

What to do if you forget to use EPREX/ERYPO?

Make the next injection as soon as you remember. If you are within a day of your next injection, forget the missed one and carry on with your normal schedule. Do not double up the injections.

How should EPREX/ERYPO be stored?

In hospital, pre-filled syringes are stored unopened in a refrigerator between 2 and 8 degrees centigrade. If you are using EPREX/ERYPO at home, it is important that the pre-filled syringe is stored in your refrigerator although not in the freezer compartment. EPREX/ERYPO should not be frozen. Allow the pre-filled syringe to reach room temperature prior to using it. This usually takes between 15 and 30 minutes. EPREX/ERYPO pre-filled syringes that are being used or about to be used can be kept at room temperature (not above 25°C) for a maximum single period of 7 days.

Pre-filled syringes should be protected from light.

Other important points

EPREX/ERYPO should not be used:

- after the expiry date on the label;

- if the seal is broken,

- if the liquid is coloured or you can see particles floating in it;

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

- if there has been a refrigerator failure;

Always keep medicine out of the reach of children.

How to dispose of EPREX/ERYPO

Medicines should not be disposed of via waste water or in household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

MANUFACTURED BY
See outer carton.

DATE OF REVISION OF THE TEXT

October 2010