PROFESSIONAL INFORMATION

WARNING: ERYTHROPOIESIS STIMULATING MEDICINES (ESMs) INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOUR PROGRESSION OR RECURRENCE

Chronic Renal Failure:

In controlled trials, patients experienced higher risks for death, serious cardiovascular reactions and stroke when administered erythropoiesis-stimulating medicines (ESMs) to target a haemoglobin level of greater than 11g/dL.

No trial has identified a haemoglobin target level, dose, or dosing strategy that does not increase these risks

Use the lowest dose of the ESM that is sufficient to reduce the need for red blood cell (RBC) transfusions.

Cancer

ESMs shorten 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.

To decrease these risks, as well as the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid RBC transfusions.

Use ESMs only for anaemia due to myelosuppressive chemotherapy.

ESMs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure.

Discontinue ESMs following the completion of a chemotherapy course.

Peri-surgery

Due to the increased risk of deep venous thrombosis (DVT) with the use of ESMs, DVT prophylaxis is recommended.

SCHEDULING STATUS

Schedule 4

PROPRIETARY NAME AND DOSAGE FORM

Pre-filled syringes (Solution for injection):

EPREX® 2 000 IU/0,5 mL

EPREX® 4 000 IU/0,4 mL

EPREX® 6 000 IU/0,6 mL

EPREX® 10 000 IU/1,0 mL

EPREX® 40 000 IU/1,0 mL

COMPOSITION

Recombinant human erythropoietin (r-HuEPO) is a sterile phosphate-buffered solution for parenteral administration available in pre-filled syringes.

PRE-FILLED SYRINGE COMPONENTS	**CONCENTRATION PER PRE-FILLED SYRINGE**				
Active ingredient	2 000 IU/0,5 mL	4 000 IU/0,4 mL	6 000 IU/0,6 mL	10 000 IU/1,0 mL	40 000 IU/1,0 mL
r-HuEPO	16,8 µg/0,5 mL	33,6 µg/0,4 mL	50,4 µg/0,6 mL	84 µg/1,0 mL	336 µg/1,0 mL
Inactives: Disodium phosphate dihydrate, glycine, polysorbate 80, sodium chloride, sodium dihydrogen phosphate dihydrate, water for injections. Contains no preservatives.					

PHARMACOLOGICAL CLASSIFICATION

A. 8.3 Erythropoietics (haematinics)

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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), has an amino acid sequence identical to that of human urinary EPO; they are indistinguishable on the basis of functional assays.

Response to r-HuEPO may be reduced due to backlog iron, folate, vitamin B12 and other resources for erythropoietin.

Pharmacokinetic properties:

Intravenous administration

After multiple intravenous (IV) administration, the half-life of r-HuEPO was 4 hours in normal healthy volunteers, versus 5 hours in renal failure patients. In studies with longer sampling duration, the half-life estimates range from 20,1 to 33,0 h in cancer patients receiving 667 and 1500 IU/kg IV doses of Epoetin alfa.

Subcutaneous administration

After subcutaneous administration, serum levels are much lower than after intravenous administration, and the bioavailability is only 20 %. The levels increase slowly and reach a peak between 12 and 18 hours.

The half-life is about 24 hours.

There was no difference in half-life between patients who were older than 65 years and those below 65 years.

INDICATIONS

EPREX is indicated for the following:

- EPREX can be used for the treatment of anaemia with chronic renal failure in patients on haemodialysis and peritoneal dialysis.
- The treatment of anaemia and reduction of transfusion requirements in adult cancer patients with non-myeloid malignancies receiving chemotherapy.

  EPREX is not indicated for the treatment of anaemia in cancer patients due to other factors such as iron folate deficiencies, haemolysis or gastrointestinal bleeding, which should be managed appropriately.
- To increase the yield of autologous blood from patients in a pre-donation programme initiated to reduce the risk of exposure to homologous blood transfusions. Treatment is indicated in patients with moderate anaemia (PCV approximately 33 to 39 %, and no iron deficiency) if blood conserving procedures are not available or insufficient either:
  a) When the scheduled major elective surgery requires a large volume of blood (4 or more units blood for females or 5 or more units for males) or

b) When the period necessary to obtain the required volume of autologous blood is too short.

- To increase red cell production and hasten erythroid recovery in adult patients with a haemoglobin (Hb)> 10 g/dL to ≤ 13 g/dL scheduled for elective surgery and not participating in an autologous pre-donation programme.

CONTRAINDICATIONS

Patients who develop antibody-mediated pure red cell aplasia (PRCA) following treatment with any erythropoietin should not receive EPREX (See *WARNINGS and SPECIAL PRECAUTIONS – Pure Red Cell Aplasia*).

EPREX is contraindicated in patients with:

- uncontrolled hypertension.
- known hypersensitivity to mammalian-cell derived products.
- known hypersensitivity to the active substance or to any of the excipients.
- myeloid malignancies.
- surgery patients who for any reason cannot receive adequate anti-thrombotic prophylaxis.

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

All contraindications associated with autologous blood pre-donation programs should be respected in patients being supplemented with EPREX.

WARNINGS and SPECIAL PRECAUTIONS

Class related adverse events associated with Erythropoiesis Stimulating Medicines (ESMs)

ESMs increase the risk of death, myocardial infarction, stroke, venous thrombo-embolism, thrombosis of vascular access and tumour progression or recurrence.

Hypertension

Blood pressure should be adequately controlled prior to initiation of EPREX therapy.

In all patients receiving EPREX, blood pressure should be closely monitored and controlled as necessary. Particular attention should be paid to the development of unusual headaches or an increase in headaches as a possible warning signal.

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

Hypertensive crisis with encephalopathy and seizures have been reported during EPREX treatment in patients with previously normal blood pressure. (see *SIDE EFFECTS*).

Pure Red Cell Aplasia

Antibody-mediated pure Red Cell Aplasia (erythroblastopaenia) has been reported after months to years of EPREX treatment in chronic renal failure patients.

Cases also have been reported in patients with hepatitis C treated with interferon and ribavirin, when Erythropoiesis-stimulating agents (ESAs), such as EPREX, are used concomitantly. EPREX is 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, aluminium 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 (< 20 000/mm^3 or < 20 000 microlitre 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 EPREX should be discontinued immediately. No other erythropoietic therapy should be commenced because of the risk of cross-reaction. Appropriate therapy, such as blood transfusions, may be given to patients when indicated.

Seizures

EPREX should also 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.

Hepatic impairment

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

Thrombotic Vascular Events (TVEs)

An increased incidence of thrombotic vascular events (TVEs) has been observed in patients receiving ESAs such as EPREX (see *SIDE 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 risk of TVEs should be carefully weighed against the benefits from treatment with EPREX, 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.

Haematological issues

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

There may be a moderate dose-dependent rise in the platelet count, within the normal range, during treatment with EPREX. This regresses during the course of continued therapy. In addition, 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 EPREX 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 EPREX, 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 EPREX, adequate iron stores should be assured, and iron supplementation should be administered if necessary:

- For chronic renal failure patients, iron supplementation (elemental iron 200-300 mg/day orally for adults) is recommended if serum ferritin levels are below 100 ng/mL.
- For cancer patients, iron supplementation (elemental iron 200-300 mg/day orally) is recommended if transferring saturation is below 20 %.
- For patients in an autologous pre-donation programme, iron supplementation (elemental iron 200 mg/day orally) should be administered several weeks prior to initiating the autologous pre-deposit in order to achieve high iron stores prior to starting EPREX therapy, and throughout the course of EPREX therapy.
- For patients scheduled for major elective orthopaedic surgery, iron supplementation (elemental iron 200 mg/day orally) should be administered throughout the course of

EPREX therapy. If possible, iron supplementation should be initiated prior to starting EPREX therapy to achieve adequate iron stores.

Porphyria

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

Allergic reactions

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

Substitution

Erythropoiesis-stimulating agents (ESAs) are not necessarily equivalent nor interchangeable. 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 medical practitioner.

Chronic Renal Failure

In controlled trials, patients experienced increased risks for death, serious cardiovascular reactions and stroke when administered erythropoiesis-stimulating medicines (ESMs) to target a haemoglobin level of greater than 11g/dL.

No trial has identified a haemoglobin target level, dose, or dosing strategy that does not increase these risks.

Use the lowest dose sufficient to reduce the need for red blood cell (RBC) transfusions.

Treatment of symptomatic anaemia in adult chronic Renal Failure patients:

Chronic renal failure patients being treated with EPREX should have their 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 *DOSAGE AND DIRECTIONS FOR USE*.

Haemoglobin levels greater than 12 g/dL may be associated with a higher risk of cardiovascular events including death.

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

Based on information available to date, the use of EPREX in predialysis end stage renal insufficiency patients do not accelerate the rate of progression of renal insufficiency.

As a result of an increase in packed cell volume, haemodialysis patients receiving EPREX 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 EPREX therapy; the possibility of potential pregnancy should be discussed and the need for contraception evaluated.

Cancer

ESMs shorten 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.

To decrease these risks, as well as the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid RBC transfusions.

Use ESMs only for anaemia due to myelosuppressive chemotherapy.

ESMs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure.

Discontinue ESMs following the completion of a chemotherapy course.

As an increased incidence of thrombotic vascular events (TVEs) has been observed in cancer patients receiving erythropoiesis stimulating agents, this risk should be carefully weighed against the benefits derived from treatment (with EPREX) particularly in cancer patients with increased risk factors of thrombotic vascular events, such as obesity and patients with a prior history of TVEs (e.g. deep venous thrombosis or pulmonary embolism).

An investigational study (BEST study) in women with metastatic breast cancer was designed to determine whether EPREX treatment that extended beyond the correction of anaemia could improve treatment outcomes. In that study the incidence of fatal thromboembolic events was higher in patients receiving EPREX (epoetinum alfa) than in those receiving placebo.

Tumour progression and mortality

There is insufficient information to conclusively establish whether the use of erythropoietin products has an adverse effect on time to tumour progression or progression-free survival when used as recommended. In clinical studies erythropoiesis-stimulating agents shortened the time to tumour progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a haemoglobin of greater than 12 g/dL.

Controlled clinical studies in which erythropoiesis-stimulating agents were administered to patients with various cancers have shown an unexplained excess mortality.

In the BEST study EPREX shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to target a haemoglobin of greater than 12 g/dL.

A meta-analysis of 42 studies in patients with cancer treated with erythropoiesis - stimulating agents, within as well as beyond the recommended haemoglobin target, has shown an overall survival hazard ratio of 1,08 (95 % CI: 0,99; 1,18; 8167 patients) suggesting that erythropoietin has no negative effect on tumour progression.

In view of the above, the decision to administer EPREX 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.

In cancer patients receiving chemotherapy, the 2 – 3 week delay between ESA administration and the appearance of erythropoietin-induced red cells should be taken into account when determining the time of initiation of EPREX therapy (otherwise the patient is at risk of being transfused).

Adult surgery patients in an autologous pre-donation program

Patients scheduled for elective surgery should receive adequate anti-thrombotic prophylaxis, as thrombotic and vascular events may occur in surgical patients, especially in those with underlying cardiovascular disease.

Peri-surgery

Due to the increased risk of deep venous thrombosis (DVT) with the use of ESMs, DVT prophylaxis is recommended.

Effects on Ability to Drive and Use Machines

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

INTERACTIONS

There are no known clinically significant interactions, but the effect of EPREX may be potentiated by the simultaneous therapeutic administration of a haematinic agent such as ferrous sulphate when a deficiency state exists.

No evidence exists that indicates that treatment with EPREX alters the metabolism of other medicines. Medicines that decrease erythropoiesis may decrease the response to EPREX.

Since ciclosporin is bound by red blood cells there is potential for a medicine interaction. If EPREX is given concomitantly with ciclosporin blood levels of ciclosporin should be monitored and the dose of ciclosporin adjusted as the haematocrit rises.

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

Subcutaneous co-administration of 40 000 IU/mL EPREX with trastuzumab (6 mg/kg) had no effect on the pharmacokinetics of trastuzumab in subjects with metastatic breast cancer.

HUMAN REPRODUCTION

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

Erythropoietin is present in human milk. EPREX should be used with caution in breastfeeding women. In pregnant or lactating surgical patients participating in an autologous blood pre-donation program, the use of EPREX is not recommended.

DOSAGE AND DIRECTIONS FOR USE

Method of administration

EPREX may be administered by intravenous or subcutaneous injection.

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

EPREX in single use syringes contain no preservatives. Do not re-use syringe. Discard unused portion.

Incompatibilities – Do not dilute or transfer to any container. Do not administer by intravenous infusions or in conjunction with other medicine solutions.

- *Intravenous injection*

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

  EPREX should not be administered by intravenous infusion or mixed with other medicines.

- *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), EPREX may be administered subcutaneously.

In patients with chronic renal failure maintenance haemoglobin concentration should not exceed 10 - 12 g/dL (6,2 – 7,5 mmol/L). The maintenance haemoglobin concentration should not exceed the upper limit of the haemoglobin concentration range (see *WARNINGS and SPECIAL PRECAUTIONS – Chronic Renal Failure*).

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 EPREX should be increased if the haemoglobin does not increase by 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 target 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 suggest 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).

Adult Peritoneal Dialysis Patients

In peritoneal dialysis patients, where intravenous access is not readily available, administration may be 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, administration may be 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 target haemoglobin 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

The subcutaneous route of administration should be used. EPREX therapy may be administered three times a week or once per week.

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.

EPREX therapy should be administered to patients with anaemia (≤ 10,5 g/dL [6,5 mmol/L]).

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

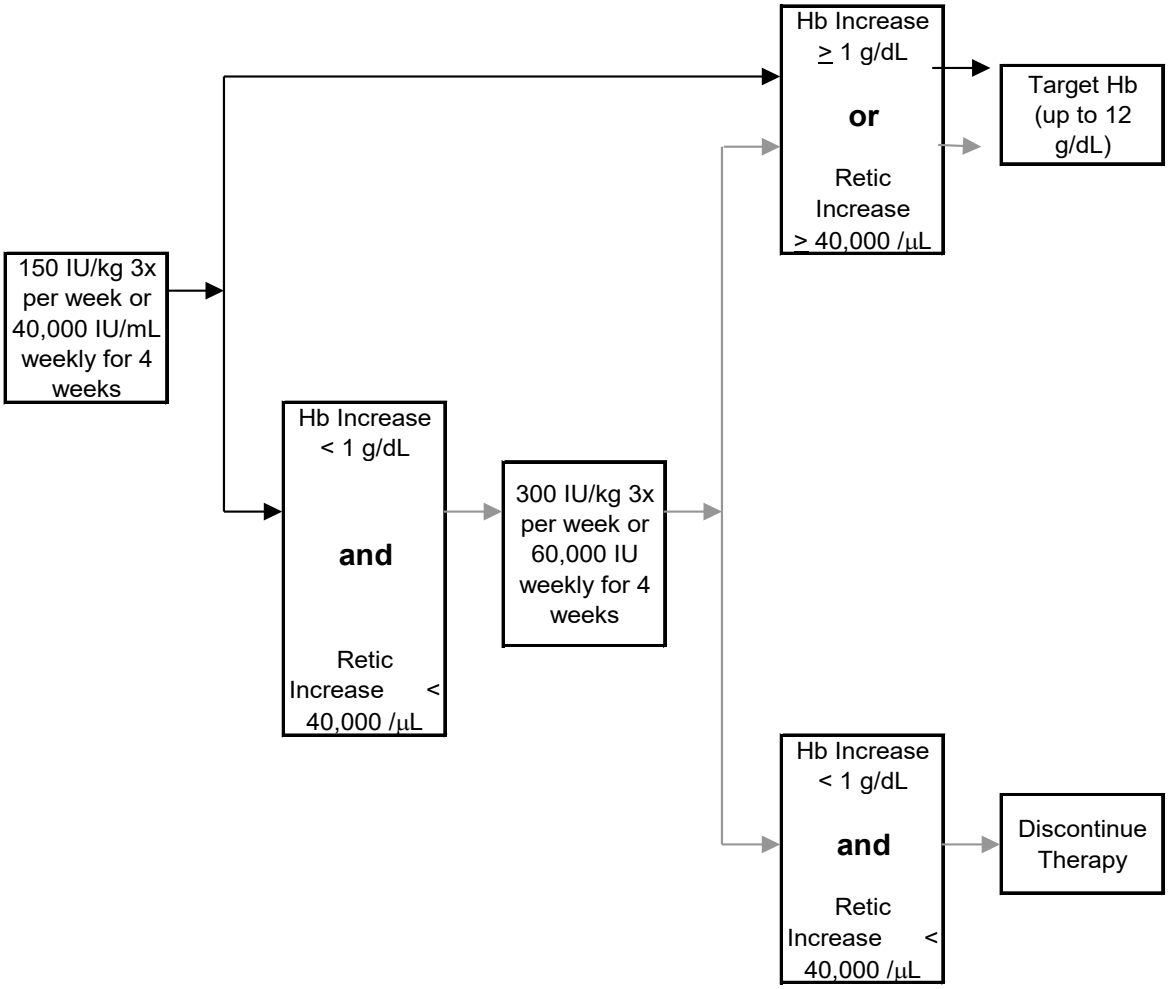
The initial dose for the treatment of anaemia is 150 IU/kg given subcutaneously 3 times per week or 40 000 IU once weekly.

If after 4 weeks of treatment at the initial dose, the haemoglobin has increased by at least 1 g/dL (0,6 mmol/L), 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), the dose may be increased to 300 IU/kg 3 times a week or 60 000 IU weekly, in the absence of red cell transfusion.

If after 4 weeks of additional therapy with 300 IU/kg 3 times per week or 60 000 IU weekly, the haemoglobin has increased by ≥ 1 g/dL the dose should remain unchanged.

If after 4 weeks of additional therapy with 300 IU/kg 3 times per week or 60 000 IU weekly, the haemoglobin has increased by < 1 g/dL response is unlikely, and treatment should be discontinued.



Dose adjustment

A rate of rise in haemoglobin of greater than 1 g/dL (0,6 mmol/L) per 2 weeks or 2 g/dL (1,25 mmol/L) per month or haemoglobin levels of > 12 g/dL (> 7,5 mmol/L) should be avoided. If the haemoglobin is rising by more than 1 g/dL (0,6 mmol/L) per 2 weeks or 2 g/dL (1,25 mmol/L) per month, or haemoglobin is approaching 12 g/dL (7,5 mmol/L), reduce the EPREX dose by 25 % to 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 EPREX therapy at a dose 25 % below the previous dose.

- ***Adult surgery patients in an autologous pre-donation programme****:*

  The intravenous route of administration should be used. EPREX should be administered after the completion of each blood donation procedure.

  Mildly anaemic patients (haematocrit of 33 - 39 % and/or haemoglobin 10 to 13 g/dL [6,2 – 8,1 mmol/L]) requiring a pre-deposit of ≥ 4 units of blood should be treated with EPREX at 600 IU/kg two 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 elective surgery patients not participating in an autologous pre-donation programme****:*

  The subcutaneous route of administration should be used.

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

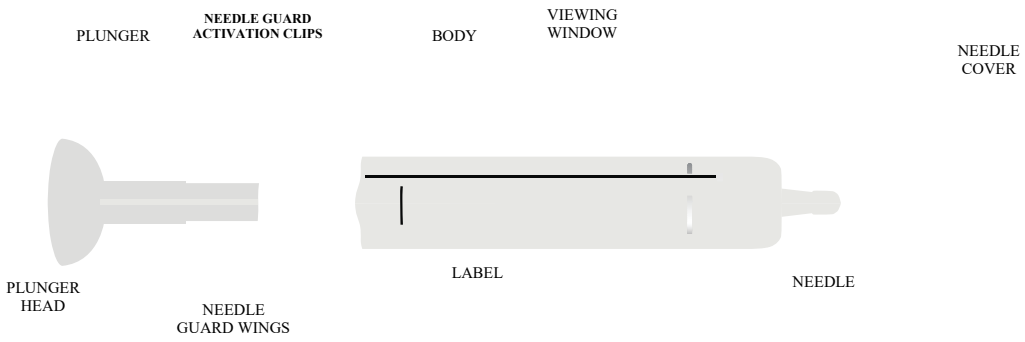
  In cases where there is a medical need to reduce the time before surgery to less than 3 weeks, 300 IU/kg EPREX should be given for 10 consecutive days prior to surgery, on the day of surgery, and for four days immediately thereafter. 300 IU/kg is recommended for haemoglobin levels ≤ 13 g/dL (8,1 mmol/L). If the haemoglobin levels reach 15 g/dL, or higher, administration of EPREX should be stopped and further dosages should not be given.

Instructions for Use and Handling and Disposal

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.

Figure 1



- **Take a syringe out of the refrigerator.** The liquid needs to come to room temperature. This usually takes between 15 to 30 minutes. Do not remove the syringe's needle cover while allowing it to reach room temperature.

- **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.

- **Hold the pre-filled syringe by the body of the syringe with the covered needle pointing upward.**

- **Do not hold by the plunger head, plunger, needle guard wings, or needle cover.**

- **Do not pull back on the plunger at any time.**

- **Do not remove the needle cover from the pre-filled syringe until you are ready to inject your EPREX.**

- **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.

- **Do not touch the needle activation clips (as indicated by asterisks ❋ in Figure 1) to prevent prematurely covering the needle with the needle guard.**

- **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.

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

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

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

- **When the needle is pulled out of your skin, there may be a little bleeding at the injection site. This is normal. You can 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 from each syringe. If any liquid remains in the syringe after an injection, the syringe should be properly disposed of, not reused.

SIDE EFFECTS

Clinical Trial Data

The most frequent adverse drug reaction during treatment with EPREX 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 the therapy.

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

An increased incidence of TVEs, has been observed in patients receiving ESAs (see *WARNINGS and SPECIAL PRECAUTIONS*).

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

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

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).

Table 1: Summary of Adverse Reactions Reported by ≥ 1 % of subjects in Clinical Studies with EPREX

System Organ Classification	Adverse reaction	Frequency
Blood and lymphatic system disorders	Thrombocythanaemia	Rare
Metabolism and nutrition disorders	Hyperkalaemia [1]	Uncommon
Immune system disorders	Hypersensitivity Anaphylactic reaction	Uncommon Rare
Nervous system disorders	Headache Convulsion	Common Uncommon
Vascular disorders	Hypertension, venous and arterial thromboses[2] Hypertensive crisis	Common Not known
Respiratory, thoracic and mediastinal disorders	Cough Respiratory tract congestion	Common Uncommon
Gastrointestinal disorders	Diarrhoea, nausea, vomiting	Very common
Skin and subcutaneous tissue disorders	Rash Urticaria Angioneurotic oedema	Common Uncommon Not known
Musculoskeletal and connective tissue disorders	Arthralgia, bone pain, myalgia, pain in extremity	Common

Congenital, familial and genetic disorders	Acute porphyria	Rare
General disorders and administration site conditions	Pyrexia Chills, influenza like illness, injection site reaction, peripheral oedema Medicine ineffective	Very common Common Not known
Investigations	Anti-erythropoietin 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 ischaemic attacks, and shunt thrombosis (including dialysis equipment) and thrombosis within arteriovenous shunt aneurisms

Postmarketing data

Adverse drug reactions identified during postmarketing experience with EPREX are included in Table 2.

Antibody-mediated pure red cell aplasia has been very rarely reported after months to years of treatment with EPREX.

Table 2: Adverse Drug Reactions Identified During Postmarketing Experience with EPREX

Blood and Lymphatic System Disorders
Erythropoietin antibody-mediated pure red cell aplasia; thrombocythaemia.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Response to EPREX is dose related and individualised. Therapeutic response to excessive doses may lead to hypertension. Phlebotomy may be performed if excessively high haemoglobin levels occur. Treatment is symptomatic and supportive.

IDENTIFICATION

A clear, colourless solution, free from visible foreign material.

PRESENTATION

Packs of six 0,4 mL; 0,5 mL; 0,6 mL, or 1 mL pre-filled syringes. These presentations (i.e. different fill volumes) are presented in 1 mL colourless glass syringe with a fixed needle for single-dose use.

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

STORAGE INSTRUCTIONS

STORE AT 2 TO 8 °C. DO NOT FREEZE OR SHAKE. PROTECT FROM LIGHT.

KEEP OUT OF REACH OF CHILDREN.

EPREX 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 3 days.

REGISTRATION NUMBERS

Pre-filled syringes

EPREX 2 000 IU/0,5 mL: 29/8.3/0769

EPREX 4 000 IU/0,4 mL: 29/8.3/0770

EPREX 6 000 IU/0,6 mL: 35/8.3/0415

EPREX 10 000 IU/1,0 mL: W/8.3/221

EPREX 40 000 IU/1,0 mL: 35/8.3/003

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



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DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION

- Date of registration of EPREX pre-filled syringes range:
    - EPREX 2 000 IU/0,5 mL: 26 June 1995
    - EPREX 4 000 IU/0,4 mL: 26 June 1995
    - EPREX 6 000 IU/0,6 mL: 20 September 2002
    - EPREX 10 000 IU/1,0 mL: 30 October 1991
    - EPREX 40 000 IU/1,0 mL: 10 August 2002

- Date of the most recently revised Professional Information as approved by SAHPRA:

  02 June 2021