PACKAGE INSERT

SCHEDULING STATUS

Schedule 4

PROPRIETARY NAMES AND DOSAGE FORMS

Pre-filled syringes	*Single-dose vials*	*Multi-dose vials*
EPREX® 1 000	EPREX® 1 000	EPREX® 10 000 / 2,5
EPREX® 2 000 / 0,5 ml	EPREX® 2 000	EPREX® 25 000 / 2,5
EPREX® 3 000 IU/ 0,3 ml	EPREX® 4 000	EPREX® 40 000 / 2,0
EPREX® 4 000 / 0,4 ml	EPREX® 10 000	
EPREX® 10 000/ml	EPREX® 40 000	
EPREX® 20 000/ 0,5 ml	EPREX® 40 000/ ml	
EPREX® 40 000/ ml		
EPREX® 5 000 IU/0,5 ml		
EPREX® 6 000 IU /0,6 ml		
EPREX® 7 000 IU /0,7 ml		
EPREX® 8 000 IU /0,8 ml		
EPREX® 9 000 IU /0,9 ml		

COMPOSITION

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

PRE-FILLED SYRINGE COMPONENTS	**CONCENTRATION PER SYRINGE**				
Active ingredient	1000 IU/0,5 ml	2 000 IU/0,5 ml	3 000 IU/0,3 ml	4 000 IU/0,4 ml	5 000 IU/0,5ml
r-HuEPO	8,4 µg/0,5 ml	16,8 µg/0,5 ml	25,2 µg/0,3 ml	33,6 µg/0,4 ml	42 µg/0,5 ml
Inactives: Sodium chloride, sodium phosphate (monobasic dihydrate and dibasic dihydrate), polysorbate 80, glycine (stabiliser) and water for injection. Contains no preservatives.					

PRE-FILLED SYRINGE COMPONENTS	**CONCENTRATION PER SYRINGE**				
Active ingredient	6 000 IU/0,6 ml	7 000 IU/0,7 ml	8 000 IU/0,8 ml	9 000 IU/0,9 ml	10 000 IU/1ml
r-HuEPO	50,4 µg/0,6 ml	58,8 µg/0,7 ml	67,2 µg/0,8 ml	75,6 µg/0,9 ml	84 µg/1,0 ml
Inactives: Sodium chloride, sodium phosphate (monobasic dihydrate and dibasic dihydrate), polysorbate 80, glycine (stabiliser) and water for injection. Contains no preservatives.					

PRE-FILLED SYRINGE COMPONENTS	**CONCENTRATION PER SYRINGE**		
Active ingredient	20 000 IU/0,5 ml	40 000 IU/ml	
r-HuEPO	168 µg/0,5 ml	336 µg/1,0 ml	
Inactives: Sodium chloride, sodium phosphate (monobasic dihydrate and dibasic dihydrate), polysorbate 80, glycine (stabiliser) and water for injection. Contains no preservatives.			

SINGLE – DOSE	**CONCENTRATION PER SINGLE-DOSE VIAL**

VIAL COMPONENTS					
Active ingredient	1000 IU/0,5 ml	2 000 IU/1 ml	4 000 IU/1ml	10 000 IU/1 ml	40 000 IU/ml
r-HuEPO	8,4 µg/0,5 ml	16,8 µg /1,0 ml	33,6 µg/ 1,0 ml	84 µg / 1,0 ml	336 µg /1,0 ml
Inactives: Sodium chloride, sodium phosphate (monobasic dihydrate and dibasic dihydrate), polysorbate 80, glycine (stabiliser) and water for injection. Contains no preservatives.					

MULTI-DOSE VIAL COMPONENTS.	CONCENTRATION PER MULTI-DOSE VIAL		
Active ingredient	10 000 IU/2,5ml	25 000 IU/2,5 ml	40 000 IU/ 2 ml
r-HuEPO	8,4 µg/2,5 ml	210 µg/2,5 ml	268,8 µg/2,0 ml
Inactive ingredients			
Albumin (human)	1,25 mg/2,5 ml	2,50 mg/2,5 ml	2,5 mg/2,0 ml
Others: Sodium phosphate (monobasic dihydrate and dibasic dihydrate), m-Cresol 0,3 % w/v (*preservative*), glycine (stabiliser) and water for injection.			

PHARMACOLOGICAL CLASSIFICATION

A. 8.3 Erythropoietics (haematinics)

PHARMACOLOGICAL ACTION OF THE MEDICINE

Erythropoietin (EPO) is a sialylglycoprotein hormone, which is the primary regulator of red blood cell formation in mammals. Recombinant human erythropoietin (r-HuEPO) is a purified glycoprotein which stimulates erythropoiesis. It is produced from mammalian cells into which the gene coding for human erythropoietin has been inserted. r-HuEPO is indistinguishable from human urinary erythropoietin by biological activity and immunological reactivity. r-HuEPO has a molecular mass of about 30 000 daltons. The protein moiety, a single chain polypeptide with

165 amino acids, has a sequence molecular mass of 18 244 daltons. The carbohydrate moiety with three N-linked and one O-linked carbohydrate groups corresponds to a mass fraction of approximately 40 %.

Pharmacokinetics:

Intravenous route

Measurement of the r-HuEPO following multiple dose intravenous administration revealed a half-life of approximately 4 hours in normal healthy volunteers and a more prolonged half-life in renal failure patients, approximately 5 hours.

Subcutaneous route

Following subcutaneous injection, serum levels are much lower than those achieved following intravenous injection, the levels increase slowly and reach a peak between 12 and 18 hours post-dose. The peak is always well below that achieved using the intravenous route.

There is no accumulation. The half-life is difficult to evaluate for the subcutaneous route and is estimated to be about 24 hours. The bioavailability of subcutaneous injectable erythropoietin is much lower than that of the intravenously administered EPREX i.e. approximately 20 %.

Anaemic cancer patients receiving chemotherapy after subcutaneous administration of epoetinum alfa 40 000 IU once per week, had a higher C_{max}, higher exposure of erythropoietin in serum (in terms of $AUC_{0\text{-}168h}$) and a lower CL/F, than patients receiving epoetinum alfa 150 IU/kg three times per week. However, similar responses, in terms of Hb levels and related haematocrit, red blood cell counts, absolute reticulocyte counts, and initial % reticulocytes, were observed with both dosing regimens.

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 predonation 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.

CONTRA-INDICATIONS

Patients who develop antibody-mediated pure red cell aplasia (PRCA) following treatment with any erythropoietin should not receive EPREX or any other erythropoietin (See SIDE EFFECTS AND SPECIAL PRECAUTIONS – Pure Red Cell Aplasia).

EPREX is contra-indicated 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 contra-indicated in patients with severe coronary, peripheral arterial, carotid, or cerebral vascular disease, including patients with recent myocardial infarction or cerebral vascular accident.

WARNINGS

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. EPREX should be used with caution in the presence of untreated, inadequately treated or poorly controlled hypertension. 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.

EPREX should be used with caution in patients with a history of seizures.

EPREX should also be used with caution in patients with epilepsy and chronic liver failure.

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 target for the indication of use.

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

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.

There may be a moderate dose-dependent rise in the platelet count, within the normal range, during treatment with EPREX. This usually 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 EPREX therapy.

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

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

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.

PREGNANCY AND LACTATION

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

Erythropoietin is present in human milk. However, it is not known whether EPREX is distributed into human milk. EPREX should be used with caution in breastfeeding women. In pregnant or lactating surgical patients participating in an autologous blood predonation programme, the use of EPREX is not recommended.

DOSAGE AND DIRECTIONS FOR USE

Method of administration

EPREX may be administered by intravenous or subcutaneous injection.

When changing from one route of administration to the other, the same dose should be used, and the haemoglobin should be monitored carefully (e.g. weekly) so that appropriate changes in EPREX dose can be made to keep the haemoglobin within target range.

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 vials and syringes contains no preservatives. Do not re-enter vial or 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.

Epoetinum alfa in multidose vials contains preservatives. Store at 2° to 8° C after initial entry and between doses. Discard unused portion 30 days after initial entry.

- *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 (hemodialysis 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).

Iron status should be evaluated for all patients prior to and during treatment. Iron supplementation should be administered if necessary. A reduced response may be observed in patients with aluminium intoxication or infection.

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.

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

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 (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).

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 target haemoglobin concentration (10-12 g/dL [6,2-7,5 mmol/L]) is achieved.

Maintenance phase:

The usual dose to maintain the target haemoglobin (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 target haemoglobin concentration (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 receiving chemotherapy***

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

The target haemoglobin concentration should be up 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.

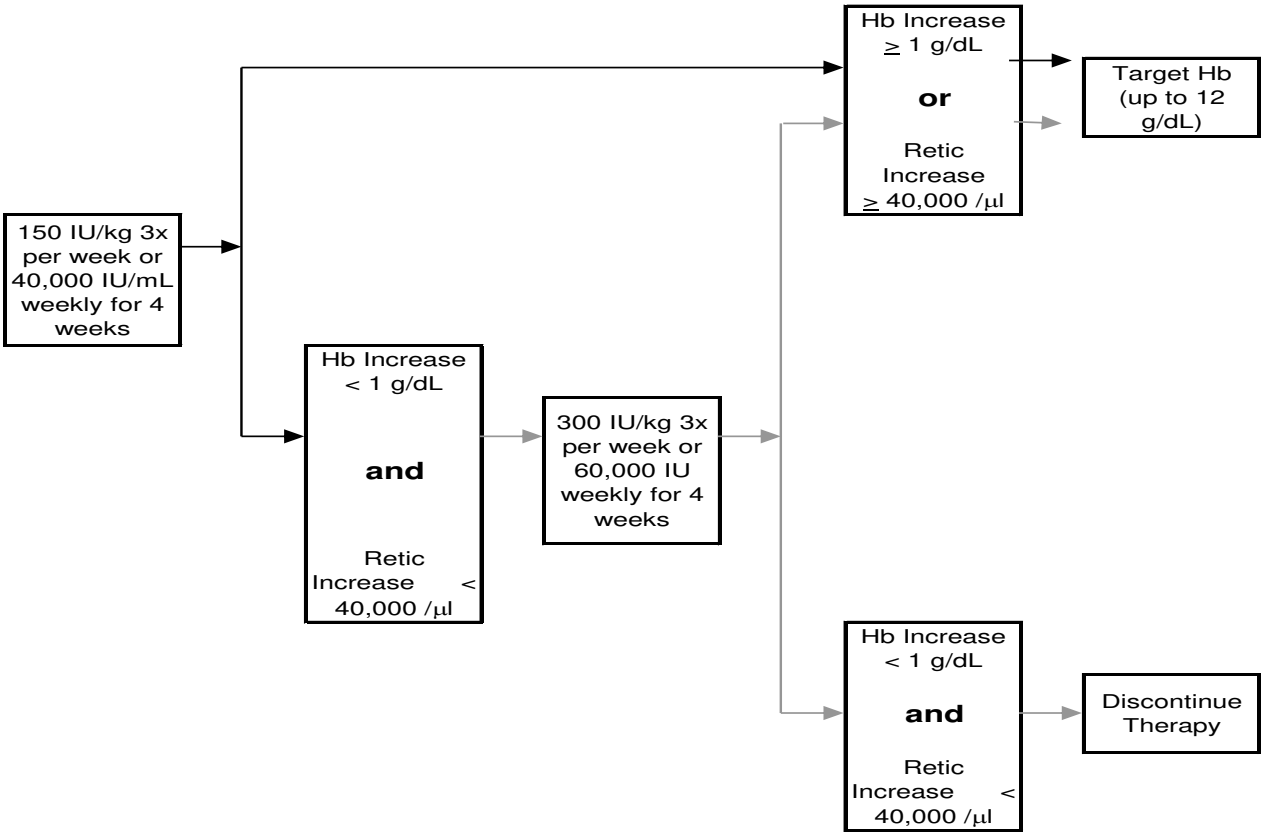
The initial dose is 150 IU/kg given subcutaneously 3 times per week or 40 000 IU once weekly.

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 150 to 600 IU/kg two times weekly for 3 weeks prior to surgery.

All patients being treated with EPREX should receive adequate iron supplementation (e.g. 200 mg oral elemental iron daily) throughout the course of EPREX treatment.

Iron supplementation should be started as soon as possible, even several weeks prior to initiating the autologous pre-deposit, in order to achieve high iron stores prior to starting therapy with EPREX.

- ***Adult elective surgery patients not participating in an autologous pre-donation programme:***

The subcutaneous route of administration should be used.

The recommended dosage 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 shorten the lead 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). When performing haematologic assessments during the preoperative period, if the haemoglobin levels reach 15 g/dL, or higher, administration of EPREX should be stopped and further dosages should not be given.

All patients being treated with EPREX should receive adequate iron supplementation (e.g. 200 mg oral elemental iron daily) throughout the course of EPREX treatment. If possible, iron supplementation should start prior to EPREX therapy, to achieve adequate iron stores.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

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. Other common adverse drug reactions observed in clinical trials of EPREX are diarrhoea, nausea, headache, influenza-like illness, pyrexia, rash, and vomiting. Influenza-like illness including headaches, joint pains, myalgia, and pyrexia may occur especially at the start of treatment.

Serious adverse drug reactions include venous and arterial thromboses and embolism (including some with fatal outcomes), such as deep venous thrombosis, pulmonary emboli, arterial thrombosis, retinal thrombosis, and shunt thrombosis (including dialysis equipment). In a cumulative analysis of 10 double-blind, randomised, placebo-controlled trials in subjects with cancer receiving chemotherapy, deep venous thrombosis was reported in 2,1 % and pulmonary embolism in 1,2 % of the 1 564 subjects exposed to EPREX, compared to 1,2 % and 1,2 %, respectively, of the 1 207 subjects exposed to placebo. Additionally, cerebrovascular accidents (including cerebral infarction and cerebral haemorrhage) and transient ischaemic attacks have been reported in clinical trials of EPREX.

Hypersensitivity reactions, including cases of rash, urticaria, anaphylactic reaction, and angioneurotic 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 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.

The overall safety profile of EPREX was evaluated in 142 subjects with chronic renal failure and in 765 subjects with cancer who participated in placebo-controlled, double-blind clinical registration trials. Adverse drug reactions reported by ≥ 0.2 % of EPREX-treated subjects in these trials are shown in Table 1.

Table 1: Adverse Drug Reactions Reported by ≥ 0.2 % of Subjects in Clinical Registration Trials with EPREX

System/Organ Class Adverse Drug Reaction	EPREX Clinical Trial Data			
	CRF (EP86-001, EP86-003, EP86-004)		Cancer (INT-2, INT-3, INT-10, P-174)	
	EPREX N=96 (%)	Placebo N=46 (%)	EPREX N=488 (%)	Placebo N=277 (%)
Blood & Lymphatic System Disorders				
Thrombocythaemia	NR	NR	0,2	NR
Nervous System Disorders				
Cerebral haemorrhage *	NR	NR	0,41	NR
Seizures	2,1	2,2	0,2	NR

Headache	33	46	3,7	3,6
Vascular Disorders				
Deep vein thrombosis*	NR	NR	1,6	0,36
Hypertension	4,1	NR	2,5	1,1
Gastrointestinal Disorders				
Nausea	10,7	7,6	17	32
Diarrhoea	1	NR	5,7	4,4
Vomiting	2,1	NR	4,9	5,4
Skin and Subcutaneous Tissue Disorders				
Rash	1	NR	1,2	1,1
Musculoskeletal, Connective Tissue and Bone Disorders				
Arthralgia	23	20	1,4	1,8
Myalgia	NR	NR	1	1,4
General Disorders and Administrative Site Condition				
Influenza-like illness	19	26	4,9	3,3
Pyrexia	NR	NR	12	11
Injury, Poisoning and Procedural Complications				
Shunt thromboses (including dialysis equipment)	1,1	2,2	NA	NA

KEY: NR = Not Reported; NA – Not Applicable; * Including cases with fatal outcome.

Additional adverse drug reactions with unknown incidence rates identified through other controlled and non-controlled clinical trials with EPREX are shown in Table 2.

Table 2: Additional Adverse Drug Reactions with Unknown Incidence Rate Identified in Other Clinical Trials of EPREX

Immune System Disorders

Anaphylactic reaction

Hypersensitivity

Nervous System Disorders

Cerebrovascular accident [ab]

Hypertensive encephalopathy

Transient ischaemic attacks [b]

Eye Disorders

Retinal thrombosis [b]

Vascular Disorders

Hypertensive crisis

Arterial thrombosis [b]

Respiratory, Thoracic and Mediastinal Disorders

Pulmonary embolism [a,b]

Skin and Subcutaneous Tissue Disorders

Urticaria

Angioneurotic oedema

Congenital and Familial/Genetic Disorders

Porphyria

General Disorders and Administration Site Conditions

Drug ineffective

Peripheral oedema

Injection site reaction

a Including cases with fatal outcomes;

b Venous and arterial thromboembolic events have been reported in patients receiving EPREX (see section above – Clinical Trial data)

Renal Failure Patients

In chronic renal failure patients, haemoglobin levels greater than 12 g/dL may be associated with a higher risk of cardiovascular events, including death. (See Special Precautions).

Shunt thromboses have occurred in haemodialysis patients, especially in those who have a tendency to hypotension or whose arteriovenous fistulae exhibit complications.

Cancer patients

An increased incidence of thromboembolic events (see Special Precautions) have been reported in cancer patients receiving erythropoiesis stimulating agents, including EPREX.

Post-marketing data

Adverse drug reactions identified during post-marketing experience with EPREX are included in Table 3.

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

Table 3: Adverse Drug Reactions Identified During Post-marketing Experience with EPREX

Blood and Lymphatic System Disorders

Erythropoietin antibody-mediated pure red cell aplasia

Investigations

Anti-erythropoietin antibody positive

Special Precautions:

EPREX should be used with caution in those patients with uncontrolled hypertension, ischaemic vascular disease, history of seizures, or suspected allergy to the product.

Pure Red Cell Aplasia

Antibody-mediated pure Red Cell Aplasia (erythroblastopenia) has been very rarely reported after months to years of subcutaneous 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, and haemolysis) 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 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.

- *Renal Failure Patients*

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 target haemoglobin concentration as recommended under DOSAGE AND DIRECTIONS FOR USE.

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

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

In order to ensure optimum response to EPREX, adequate iron stores should be assured, and folic acid and vitamin B_{12} deficiencies should be excluded prior to initiating therapy. In most cases, the ferritin values in the serum fall simultaneously with the rise in packed cell volume. Therefore, iron supplementation, e.g., 200-300 mg/day orally, (100-200 mg/day for paediatric patients) is recommended for chronic renal failure patients whose serum ferritin levels are below 100 ng/mL.

Based on information available to date, the use of EPREX in predialysis [end stage renal insufficiency] patients does 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.

Rarely, exacerbation of porphyria has been observed in epoetinum alfa-treated patients with chronic renal failure. EPREX should be used with caution in patients with known porphyria.

- *Cancer Patients*

The target haemoglobin concentration should be up to 12 g/dL (7,5 mmol/L) in men and women and it should not be exceeded.

In cancer patients receiving chemotherapy; should the rate of increase in haemoglobin exceed 2 g/dL (1,25 mmol/L) per month, or the haemoglobin concentration is approaching 12 g/dL or the

haemoglobin level exceeds 12 g/dL (7,5 mmol/L), the dose adjustment detailed in DOSAGE AND DIRECTIONS FOR USE should be thoroughly performed to minimise potential risk factors of thrombotic events.

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.

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.

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.

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

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

Another erythropoiesis-stimulating agent (darbepoietin alfa) increased the risk of death when administered to target a haemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. EPREX (Epoetinum alfa) is not indicated for this population.

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 order to ensure optimum response to EPREX, adequate iron stores should be assured, and folic acid and vitamin B_{12} deficiencies should be excluded prior to initiating therapy. In most cases, the ferritin values in the serum fall simultaneously with the rise in packed cell volume. Therefore, iron supplementation, *e.g.*, 200-300 mg/day orally is recommended for cancer patients whose serum ferritin levels are below 100 ng/ml.

All of these additive factors of anaemia should also be carefully considered when deciding to increase the dose of EPREX in cancer patients.

In cancer patients receiving chemotherapy, the delay (about 2 weeks) between erythropoietin administration and the appearance of erythropoietin-induced red cells should be taken into

account when determining time of initiation of EPREX therapy (otherwise patient is at risk of being transfused).

- *Surgery patients in autologous pre-donation programs*

Independent of EPREX treatment, routine volume replacements should be performed in surgical patients with underlying cardiovascular disease following phlebotomy, as thrombotic and vascular events may occur.

- *Elective surgery patients not participating in an autologous pre-donation programme*

Patients scheduled for elective surgery should receive adequate anti-thrombotic prophylaxis as appropriate for the surgical procedure, as thrombotic and vascular events may occur in surgical patients, especially in those with underlying cardiovascular disease. This can be a risk and should be carefully weighed against the benefit to be derived from the treatment in this patient group.

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 EPREX 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 (8,1mmol/l).

The use of EPREX is not recommended in perisurgery patients with a baseline haemoglobin of > 13 g/dL (8,1 mmol/l).

In patients scheduled for major elective orthopaedic surgery the cause of anaemia should be established and treated, if possible, before the start of EPREX treatment.

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 one or six 0,3 ml; 0,4 ml; 0,5 ml; 0,6 ml, 0,7 ml, 0,8 ml, 0,9 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.

Packs of one or six 0,5 or 1 ml single-dose vials.

Packs of one or six 2 or 2,5 ml multi-dose vials

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® 1 000 IU: 29/8.3/0001

EPREX® 2 000 IU/0,5 ml: 29/8.3/0769

EPREX® 3 000 IU/0,3 ml: 33/8.3/0318

EPREX® 4 000 IU/0,4 ml: 29/8.3/0770

EPREX® 10 000 IU/ml: W/8.3/221

EPREX® 20 000 IU/0,5 ml: 35/8.3/0035

EPREX® 40 000 IU/ ml: 35/8.3/0036

EPREX® 5 000 IU/0,5 ml: 35/8.3/0414

EPREX® 6 000 IU/0,6 ml: 35/8.3/0415

EPREX® 7 000 IU/0,7 ml: 35/8.3/0416

EPREX® 8 000 IU/0,8 ml: 35/8.3/0417

EPREX® 9 000 IU/0,9 ml: 35/8.3/0418

Single-dose vials

EPREX® 1 000: 29/8.3/0001

EPREX® 2 000: W/8.3/219

EPREX® 4 000: W/8.3/220

EPREX® 10 000: W/8.3/221

EPREX® 40 000: 33/8.3/0446

EPREX® 40 000/ml: 35/8.3/0036

Multi-dose vials:

EPREX® 10 000 / 2,5: 31/8.3/0209

EPREX® 25 000/2,5: 31/8.3/0210

EPREX® 40 000/2,0: 31/8.3/0211

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

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