
EPREX[®]

INTRAVENOUS & SUBCUTANEOUS INJECTION

PRODUCT INFORMATION

NAME OF THE MEDICINE

Epoetin alfa (rch)

Its CAS Registry Number is 113427-24-0.

Most common abbreviation: r-HuEPO

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

DESCRIPTION

Epoetin alfa is recombinant human erythropoietin (EPO). It is expressed in Chinese hamster ovary cells (rch) and has a 165 amino acid sequence identical to that of human urinary EPO; the two are indistinguishable on the basis of functional assays. The apparent molecular weight of erythropoietin is about 30,400 daltons.

EPREX pre-filled syringes contain glycine, polysorbate 80, sodium chloride, sodium phosphate – dibasic dihydrate, sodium phosphate – monobasic, sodium citrate and water for injections.

Pharmacology

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.

Erythropoietin stimulates erythropoiesis in anaemic patients with chronic renal failure in whom the endogenous production of erythropoietin is impaired. Because of the length of time required for erythropoiesis – several days for erythroid progenitors to mature and be released into the circulation – a clinically significant increase in haemoglobin is usually not observed in less than two weeks and may require up to ten weeks in some patients.

Erythropoiesis-stimulating agents ESAs are growth factors that primarily stimulate red cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells (see PRECAUTIONS – Use in Cancer Patients).

Pharmacokinetics

Measurement of Epoetin alfa (rch) following intravenous administration showed 10% excretion by the kidneys with the major routes of elimination not determined. After intravenous administration the mean half lives in normal volunteers ranged from 4.0 to 6.1 hours and in patients with chronic renal failure from 6.5 to 9.3 hours. Following subcutaneous injection, serum levels are much lower than the levels achieved following IV injection; the levels increase slowly and reach a peak

between 12 and 18 hours post-dose. The peak is always well below the peak achieved using the IV route (approximately 1/20th of the value). Following subcutaneous injection, erythropoietin serum levels remain elevated above baseline for about 72 hours. There is no accumulation when thrice weekly dosing is used: the levels remain the same, whether they are determined 24 hours after the first injection or 24 hours after the last injection. The half-life is difficult to evaluate for the subcutaneous route and is estimated about 24 hours. The bioavailability of subcutaneous injectable erythropoietin is much lower than that of the intravenous drug: approximately 20-30%. No information is available in the young and in the elderly. Due to decreased metabolism patients with hepatic dysfunction may have increased erythropoiesis with EPREX.

CLINICAL TRIALS

EPREX has been studied in a series of placebo-controlled, double-blind trials in a total of 131 anaemic cancer patients. Within this group, 72 patients were treated with concomitant noncisplatin-containing chemotherapy regimens and 59 patients were treated with concomitant cisplatin-containing chemotherapy regimens. Patients were randomised to EPREX 150 IU/kg or placebo subcutaneously (three times a week) for 12 weeks.

EPREX therapy was associated with a significantly ($p < 0.008$) greater haematocrit response than in the corresponding placebo-treated patients (see TABLE 1).

Table 1. Haematocrit (%): Mean change from baseline to final value

STUDY	EPREX	PLACEBO
Chemotherapy	7.6	1.3
Cisplatin	6.9	0.6

* Significantly higher in EPREX patients than in placebo patients ($p < 0.008$)

In the two types of chemotherapy studies [utilising an EPREX dose of 150 IU/kg three times weekly] the mean number of units of blood transfused per patient after the first month of therapy was significantly ($p < 0.02$) lower in patients treated with EPREX (0.71 units in months 2, 3) than in corresponding placebo-treated patients (1.84 units in months 2, 3). Moreover, the proportion of patients transfused during months 2 and 3 of therapy combined was significantly ($p < 0.03$) lower in the patients treated with EPREX than in the corresponding placebo-treated patients (22% versus 43%).

Comparable intensity of chemotherapy in the EPREX and placebo groups in the chemotherapy trials was suggested by a similar area under the neutrophil time curve in patients treated with EPREX and placebo-treated patients as well as by a similar proportion of patients in groups treated with EPREX and placebo-treated groups whose absolute neutrophil counts fell below 1,000 cells/microlitre. Available evidence suggests that patients with lymphoid and solid cancers respond equivalently to EPREX therapy and that patients with or without tumour infiltration of the bone marrow respond equivalently to EPREX therapy.

* A randomized, open-label, multicenter study was conducted in 2098 anaemic women with metastatic breast cancer, who received first line or second line chemotherapy. This was a non-inferiority study designed to rule out a 15% risk increase in tumor progression or death of epoetin alfa plus standard of care (SOC) as compared with SOC alone. The median progression free survival (PFS) per investigator assessment of disease progression was 7.4 months in each arm (HR 1.09, 95% CI: 0.99, 1.20), indicating the study objective was not met. Median PFS with disease progression assessed by the Independent Review Committee was 7.6 months in each arm (HR 1.03, 95% CI: 0.92, 1.15). At clinical cutoff, 1337 deaths were reported. Median overall survival in the epoetin alfa plus SOC group was 17.2 months compared with 17.4 months in the SOC alone group (HR 1.06, 95% CI: 0.95, 1.18). Significantly fewer patients received RBC transfusions in the epoetin alfa plus SOC arm (5.8% versus 11.4%); however, significantly more patients had thrombotic vascular events in the epoetin alfa plus SOC arm (2.8% versus 1.4%).

Efficacy and safety of EPREX in the prevention and treatment of anaemia of cancer has not been demonstrated in children.

Epoetin alfa has been studied in a placebo-controlled, double-blind trial enrolling 316 patients scheduled for major, elective orthopaedic hip or knee surgery who were expected to require ≥ 2 units of blood. Patients were randomly assigned to receive 300 IU/kg epoetin alfa, 100 IU/kg epoetin alfa or placebo by subcutaneous injection for 10 days before surgery, on the day of surgery, and for four days after surgery. All patients received oral iron and a low dose postoperative warfarin regimen.

Treatment with epoetin alfa 300 IU/kg significantly ($p=0.024$) reduced the risk of allogeneic transfusion in patients with a pretreatment haemoglobin of > 100 to ≤ 130 g/L; 5/31 (16%) of Epoetin alfa 300 IU/kg, 6/26 (23%) of epoetin alfa 100 IU/kg and 13/29 (45%) of placebo-treated patients were transfused.

In the >100 to ≤ 130 g/L pre-treatment stratum, the mean number of units transfused per epoetin alfa treated patient (0.45 units blood for 300 IU/kg, 0.42 units blood for 100 IU/kg) was less than the mean transfused per placebo-treated patient (1.14 units) (overall $p=0.028$). In addition, mean haemoglobin, haematocrit and reticulocyte counts increased significantly during the pre-surgery period in epoetin alfa treated patients.

Epoetin alfa was also studied in an open label, parallel-group trial enrolling 145 subjects with a pretreatment haemoglobin level of ≥ 100 to ≤ 130 g/L who were scheduled for major orthopaedic hip or knee surgery and who were not participating in an autologous program.

Subjects were randomly assigned to receive one of two subcutaneous dosing regimens of epoetin alfa (600 IU/kg once weekly for three weeks prior to surgery and on the day of surgery or 300 IU/kg once daily for 10 days prior to surgery, on the day of surgery and for four days after surgery). All subjects received oral iron and appropriate pharmacologic anticoagulation therapy.

From pretreatment to pre-surgery, the mean increase in haemoglobin in 600 IU/kg weekly group (14.4 g/L) was greater than observed in the 300 IU/kg daily group.

The erythropoietic response observed in both treatment groups resulted in similar transfusion rates [11/169 (16%) in the 600 IU/kg weekly group and 14/71 (20%) in the 300 IU/kg daily group]. The mean number of units transfused per subject was approximately 0.3 units in both treatment groups.

Using linear logistic models it can be calculated that for a patient with an entry haemoglobin level of 100 g/L, use of 300 IU/kg daily or 600 IU/kg weekly would reduce the probability of transfusion to about 38%, compared to 58% in the same patient receiving a 100 IU/kg daily regimen, or 81% in a patient given no EPREX therapy.

Similarly, at a higher entry haemoglobin of 120 g/L, the 300 IU/kg daily or 600 IU/kg weekly regimens would reduce the probability of transfusion to about 18%, compared to 35% in the same patient receiving 100 IU/kg daily, or 61% in a patient receiving no EPREX.

In autologous blood donation, a double blind study was conducted in 204 patients scheduled to undergo elective orthopaedic surgery with haematocrits $\leq 39\%$ and no underlying anaemia due to iron deficiency. On average, patients treated with EPREX 600 IU/kg twice weekly for three weeks were able to pre-deposit significantly more units of blood (4.5 units) than placebo treated patients (3.0 units) ($p<0.001$). Also, significantly more patients treated with EPREX ($p<0.05$) were able to pre-deposit between 3 and 6 units, inclusively, of autologous blood than the corresponding placebo treated patients. Virtually all (98%) of EPREX treated patients pre-deposited 3 or more units, compared with 69% of placebo treated patients. While 37% of placebo patients were able to pre-deposit 4 or 5 units, 81% of EPREX patients pre-deposited 4 or more units. Among the

evaluable patients, fewer patients who received EPREX required allogeneic transfusions (19.8%) than placebo patients (31%).

In a second placebo controlled study, 55 patients with low haematocrits were enrolled 2:2:1 to receive EPREX 600 IU/kg, EPREX 300 IU/kg or placebo twice weekly for three weeks. A significantly greater amount of autologous blood ($p < 0.005$) was donated by the EPREX treated patients (4.68 vs 4.42 vs 2.89 units). Likewise 84, 79 and 11% of patients were able to donate four or more units over the three-week study.

INDICATIONS

EPREX is indicated for the treatment of patients with symptomatic or transfusion requiring anaemia associated with chronic renal failure to improve their quality of life by improving energy levels, exercise performance, fatigue and sleep patterns and by reducing the need for blood transfusions.

EPREX is also indicated for the treatment of anaemia and reduction of transfusion in patients with non-myeloid malignancies where anaemia develops as a result of concomitantly administered chemotherapy

EPREX is also indicated in adult patients with mild-to-moderate anaemia (haemoglobin > 100 to ≤ 130 g/L) scheduled for elective surgery with an expected moderate blood loss (2 – 4 units or 900 to 1800 mL) to reduce exposure to allogeneic blood transfusion and to facilitate erythropoietic recovery.

EPREX is also indicated to augment autologous blood collection and to limit the decline in haemoglobin in anaemic adult patients who are scheduled for major elective surgery and who are not expected to pre-deposit their complete peri-operative blood needs.

CONTRAINDICATIONS

EPREX is contraindicated in patients with:

1. Uncontrolled hypertension
2. Known sensitivity to mammalian cell derived products
3. Hypersensitivity to the active substance or to any of the excipients
4. Patients scheduled for elective surgery, who are not participating in an autologous blood pre-deposit programme and who have severe coronary, peripheral arterial, carotid or cerebral vascular disease, including patients with recent myocardial infarction or cerebral vascular accident.
5. ** All contraindications associated with autologous blood predonation programs should be respected in patients being supplemented with EPREX.*
6. Surgery patients who for any reason cannot receive adequate antithrombotic prophylaxis or treatment.
7. Patients who develop Pure Red Cell Aplasia (PRCA) following treatment with any erythropoietin should not receive EPREX or any other erythropoietin (see PRCA paragraph in Precautions)

PRECAUTIONS

Cardiovascular and Thrombotic Events / Increased Mortality

An increased incidence of thrombotic vascular events (TVEs) has been observed in patients receiving ESAs such as epoetin alfa (see ADVERSE 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 (see also PRECAUTIONS – Use in Chronic Renal Failure).

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

In all patients, haemoglobin concentrations 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.

Use in Cancer Patients

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

As with all growth factors, there is a concern that ESAs could stimulate the growth of tumours. In controlled clinical studies, use of EPREX 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 140 g/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 120-140 g/L,
- Another ESA (darbepoetin alfa) increased risk of death when administered to target a haemoglobin of 120 g/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.

EPREX should only be used to treat cancer patients with anaemia where the anaemia has arisen as a result of concomitantly administered chemotherapy. A haemoglobin concentration of 120g/L should not be exceeded.

Use in Chronic Renal Failure Patients

Chronic renal failure patients being treated with epoetin 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 10 g/L per month and should not exceed 20 g/L per month to minimise risks of an increase in hypertension. Dose should be reduced when haemoglobin approaches 120 g/L.

In patients with chronic renal failure, maintenance haemoglobin concentration should not exceed the upper limit of the target haemoglobin concentration range as recommended under Dosage and Administration. In controlled trials, haemoglobin levels targeted to 130 g/L were associated with a higher risk of cardiovascular events, including death.

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

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

Hyperkalaemia has been observed in isolated cases. 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 EPREX administration until the serum potassium level has been corrected.

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.

In some preclinical toxicological studies in dogs and rats, but not in monkeys, epoetin alfa (rch) therapy was associated with subclinical bone marrow fibrosis. Bone marrow fibrosis is a known complication of chronic renal failure in humans and may be related to secondary hyperparathyroidism or unknown factors. The incidence of bone marrow fibrosis was not increased in a study of dialysis patients who were treated with epoetin alfa for 12-19 months compared to the incidence of bone marrow fibrosis in a matched control group of dialysis patients who had not been treated with epoetin alfa. In a 13-week study, dogs were treated subcutaneously or intravenously with 80, 240, or 520 IU/kg/day. The majority of dogs treated subcutaneously and 50% of dogs treated intravenously developed anaemia with or without bone marrow hypoplasia. The cause of these observations is unknown, however, no cases of paradoxical anaemia have been reported in haematologically normal humans treated with EPREX, making the significance of the findings in dogs unclear.

Use in Patients Scheduled for Elective Surgery

In patients with a baseline haemoglobin of >130 g/L (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 a baseline haemoglobin >130 g/L (8.1 mmol/L).

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

Use in Surgery Patients in an Autologous Pre-Donation Programme (ABD)

All special precautions associated with autologous pre-donation programmes, especially routine volume replacement, should be respected.

Hypertension

Patients with uncontrolled hypertension should not be treated with EPREX; blood pressure should be controlled adequately before initiation of therapy. Blood pressure may rise during treatment of anaemia with EPREX. Hypertensive encephalopathy and seizures have been observed.

Special care should be taken to closely monitor and control blood pressure in patients treated with EPREX. During EPREX therapy, patients should be advised of the importance of compliance with antihypertensive therapy and dietary restrictions. If blood pressure is difficult to control after initiation of appropriate measures, the dose of EPREX should be reduced or temporarily withheld until haemoglobin begins to decrease (see DOSAGE AND ADMINISTRATION).

** Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have also occurred during EPREX 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 (see ADVERSE EFFECTS).*

Pure Red Cell Aplasia

In chronic renal failure patients, antibody-mediated pure red cell aplasia (PRCA) (erythroblastopaenia) has been rarely reported after months to years of treatment with

erythropoietins. Most cases of PRCA associated with EPREX occurred in patients receiving subcutaneous (SC) administration. The SC route should only be used when intravenous (IV) access is not readily available. 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 most of these PRCA patients antibodies to erythropoietins have been reported. In patients developing sudden lack of efficacy typical causes of non-response should be investigated. If no cause is identified, a bone marrow examination should be considered.

If pure red cell aplasia (PRCA) is diagnosed, EPREX must be immediately discontinued and testing for erythropoietin antibodies should be considered. If antibodies to erythropoietin are detected patients should not be switched to another ESA product as anti-erythropoietin antibodies cross-react with other ESAs. Other causes of pure red cell aplasia should be excluded, and appropriate therapy instituted.

Seizures

Seizures have occurred in patients receiving EPREX. Therefore, EPREX 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.

Iron Supplementation

Other causes of anaemia (iron, folate or Vitamin B₁₂ 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 and 100-200 mg/day orally for paediatrics) is recommended if serum ferritin levels are below 100 ng/mL.
- For cancer patients, iron supplementation (elemental iron 200-300 mg/day orally) is recommended if transferrin saturation is below 20%.
- For patients in an autologous predonation programme, iron supplementation (elemental iron 200 mg/day orally) should be administered several weeks prior to initiating the autologous predeposit in order to achieve high iron stores prior to starting EPREX therapy, and throughout the course of EPREX therapy.
- For patients scheduled for major elective orthopaedic surgery, iron supplementation (elemental iron 200mg/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.

General

EPREX should be used with caution in those patients with pre-existing hypertension, ischaemic vascular disease, or suspected allergy to any components of the product, porphyria or gout. The safety and efficacy of EPREX therapy have not been established in patients with underlying haematological diseases (e.g. haemolytic anaemia, sickle cell anaemia, thalassemia, 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.

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 is regularly monitored during the first 8 weeks of therapy.

Very rarely, exacerbation of porphyria has been observed in EPREX-treated patients with chronic renal failure. EPREX has not caused increased urinary excretion of porphyrin metabolites in normal volunteers, even in the presence of a rapid erythropoietic response. Nevertheless, EPREX should be used with caution in patients with known porphyria.

Increased serum uric acid may occur in patients whose haemoglobin is rising more than approximately 20 g/L per month. Consequently EPREX should be used with caution in patients with a history of gout.

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

Use in Pregnancy

The drug is classed as Category B3. EPREX should be administered during pregnancy only if clearly needed **and if the potential benefit justifies the potential risk to the foetus*. It is not known whether epoetin alfa (rch) crosses the placenta or whether it can cause fetal harm when administered to a pregnant woman. Animal studies have shown no evidence of teratogenic activity in rats or rabbits at epoetin alfa (rch) dosages up to 55 IU/kg/day administered intravenously. However, intravenous administration of epoetin alfa (rch) at dose levels of 20-500 IU/kg/day in rats causes decreased fertility, increased pre-and post-implantation loss, decreased fetal weight and retardation of ossification.

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

Use in Lactation

EPREX should be administered during lactation only if clearly needed. It is not known whether epoetin alfa (rch) is excreted in breast milk or whether it can cause harm to the infant when administered to a lactating woman. Intravenous administration of the drug to lactating rats at 500 IU/kg/day causes retardation of growth and development of the offspring.

Paediatric Use

Efficacy: Clinical trials of EPREX in children supported the following effects - correction of anaemia; reduction or elimination of transfusion-requirements; improvement of the bleeding tendency in uraemia; increased weight and appetite; and the reduction of cytotoxic antibodies. Possible but not conclusive effects were an improvement in exercise capacity and short-term cardiovascular effects. Long-term cardiovascular effects, effects on growth rate, improved prospects for renal transplantation, and improved quality of life were unproved.

Safety: Incomplete information is available, particularly on the rate of change of haemoglobin and blood pressure.

Dose: Available data supports a dose of 25 IU/kg three times a week rather than 50 IU/kg three times a week.

Genotoxicity

In a standard series of assays for genotoxic potential, epoetin alfa (rch) did not induce gene mutations or cause chromosomal damage.

Carcinogenicity

Long-term carcinogenicity studies have not been carried out. There are conflicting reports in the literature regarding whether erythropoietins may play a role as tumour proliferators (see Precautions – Use in Cancer Patients).

Interactions with Other Medicines

There are no known clinically significant drug 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.

Drugs that decrease erythropoiesis may decrease the response to EPREX.

Since cyclosporin is bound by red blood cells there is potential for a drug 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.

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

Effect on Ability to Drive and Operate Machinery

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

ADVERSE EFFECTS

The most frequent adverse drug reaction during treatment with epoetin 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 EPREX 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 PRECAUTIONS).

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

Hypertensive crises with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have also occurred during epoetin 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 EPREX was evaluated in 2136 anaemic subjects. Included were 228 epoetin 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]; 1,404 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 $\geq 1\%$ of EPREX-treated subjects in these trials are shown in Table 2.

Table 2. Summary of Adverse Drug Reactions Reported by ≥1% of Subjects in Clinical Registration Trials with EPREX.

System/Organ Class Adverse Drug Reaction	CRF											
	Predialysis		Dialysis		Oncology		HIV		ABD		Surgery	
	EPO N=131 n (%)	Placebo N=79 n (%)	EPO N=97 n (%)	Placebo N=46 n (%)	EPO N=1404 n (%)	Non- ESA N=930 n (%)	EPO N=144 n (%)	Placebo N=153 n (%)	EPO N=147 n (%)	Non- ESA N=112 n (%)	EPO N=213 n (%)	Placebo N=103 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

System/Organ Class	CRF											
	<u>Predialysis</u>		<u>Dialysis</u>		<u>Oncology</u>		<u>HIV</u>		<u>ABD</u>		<u>Surgery</u>	
	EPO	Placebo	EPO	Placebo	EPO	Non-ESA	EPO	Placebo	EPO	Non-ESA	EPO	Placebo
Adverse Drug Reaction	N=131	N=79	N=97	N=46	N=1404	N=930	N=144	N=153	N=147	N=112	N=213	N=103
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Respiratory, thoracic and mediastinal disorders												
Cough	5 (4)	1 (1)	9 (9)	8 (17)	98 (7)	66 (7)	37 (26)	22 (14)	2 (1)	2 (2)	10 (5)	NR
Resp tract congestion	NR	NR	9 (9)	2 (4)	NR	NR	1 (1)	NR	NR	NR	NR	NR
Skin and subcutaneous tissue disorders												
Rash ^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												
Embolism 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)
Deep vein thrombosis	NR	NR	NR	NR	24 (2)	6 (1)	NR	NR	2 (1)	2 (2)	10 (5)	3 (3)
Thrombosis	NR	NR	4 (4)	1 (2)	18 (1)	6 (1)	NR	NR	2 (1)	NR	3 (1)	NR
Hypertension ^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;

^aRash includes urticaria and angioedema

^bIncludes 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

^cHypertension includes hypertensive crisis and hypertensive encephalopathy

Post-marketing Experience

Adverse drug reactions identified during post-marketing experience with epoetin 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	≥1/1,000 and <1/100
Rare	≥1/10,000, <1/1,000
Very rare	<1/10,000, including isolated reports

Antibody-mediated pure red cell aplasia has been very rarely reported (<1/10,000 cases per patient-year) after months to years of treatment with EPREX.

Table 3. Adverse Drug Reactions Identified During Post-marketing Experience with EPREX by Frequency Category Estimated from Spontaneous Reporting Rates

System/Organ Class	
<i>Frequency</i>	<i>Adverse Drug Reaction</i>
Blood & Lymphatic System Disorders	
<i>Very rare</i>	Anti-Erythropoietin Antibody-Mediated Pure Red Cell Aplasia Thrombocythaemia

DOSAGE AND ADMINISTRATION

During therapy, haematological parameters should be monitored regularly. Doses must be individualised to ensure that haemoglobin is maintained at an appropriate level for each patient.

As a single anaphylactic reaction was observed in one patient during the course of clinical testing, it is recommended that the first dose be administered under medical supervision.

Adult patients scheduled for elective surgery

Before considering therapy with EPREX prior to elective surgery, it is important to investigate and provide appropriate treatment for potentially correctable anaemia.

In patients scheduled for elective surgery adequate antithrombotic prophylaxis is strongly recommended.

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 shorten the lead time before surgery to less than three weeks, 300 IU/kg EPREX should be given daily for 10 consecutive days prior to surgery, on the day of surgery, and for four days immediately thereafter. The administration of EPREX should be stopped as soon as the haemoglobin level reaches 150 g/L in the preoperative period, even if not all the planned EPREX doses have been 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 be started prior to EPREX therapy, to achieve adequate iron stores.

Anaemic adult surgery patients in an Autologous Pre-donation Programme (ABD)

The intravenous route should be used. The recommended dose is 300 – 600 IU/kg twice weekly for three weeks, together with at least 200 mg oral elemental iron daily.

Chronic Renal Failure Patients

In patients with chronic renal failure, where intravenous access is routinely available (haemodialysis patients) administration of EPREX by the intravenous route is preferable. Where intravenous access is not readily available (patient not yet on dialysis and peritoneal dialysis patients) EPREX may be administered subcutaneously (See PRECAUTIONS, Pure Red Cell Aplasia).

In patients maintained on haemodialysis, EPREX should always be administered after completion of dialysis.

Treatment with EPREX is divided into two stages:

Correction Phase

The initial dosage is 50 IU/kg body weight three times a week IV/SC. If haemoglobin does not increase by 10 g/L after 1 month of treatment, the dosage may be raised to 75 IU/kg three times per week – and if further increments are needed they should be at 25 IU/kg, three times per week, at monthly intervals, to achieve a haemoglobin not to exceed 120 g/L. This level should not be exceeded in patients with chronic renal failure. The maximum dosage should not exceed 3 x 200 IU/kg per week.

Maintenance Phase

The IV/SC dose has to be adjusted individually to maintain a haemoglobin not to exceed 120 g/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.

For patients who are converted from the subcutaneous to intravenous route, the same dose should be used, and the haemoglobin should be followed carefully (e.g. weekly) so that appropriate changes in EPREX dose can be made to keep the haemoglobin within the target range.

Dose adjustment

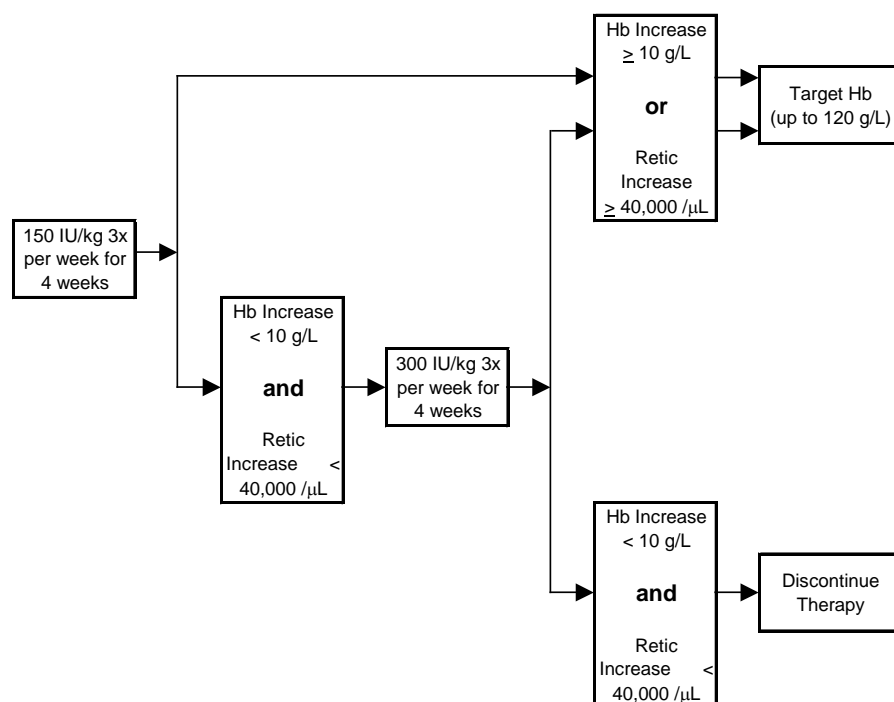
If the haemoglobin is increasing and approaching 120 g/L, the dose should be reduced by approximately 25%. If the haemoglobin continues to increase, the dose should be temporarily withheld until the haemoglobin begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose. If the haemoglobin increases by more than 10 g/L in any 2-week period, the dose should be decreased by approximately 25%. If dose reduction is needed the amount given per dose should be reduced or the number of weekly injections reduced or both.

Adult Patients with Cancer

Treatment should not be commenced unless haemoglobin falls below 100 – 110 g/L. The target haemoglobin concentration should be up to 120 g/L in men and women and it should not be exceeded.

The initial dose is 150 IU/kg given subcutaneously 3 times per week. If the haemoglobin has increased by at least 10 g/L (0.62 mmol/L) or the reticulocyte count has increased $\geq 40,000$ cells/microlitre above baseline after 4 weeks of treatment, the dose should remain at 150 IU/kg. If the haemoglobin increase is < 10 g/L (< 0.62 mmol/L) and the reticulocyte count has increased $< 40,000$ cells/microlitre above baseline, increase the dose to 300 IU/kg. If after an additional 4 weeks of therapy at 300 IU/kg, the haemoglobin has increased ≥ 10 g/L (≥ 0.62 mmol/L) or the reticulocyte count has increased $\geq 40,000$ cells/microlitre the dose should remain at 300 IU/kg. However, if the haemoglobin has increased < 10 g/L (< 0.62 mmol/L) and the reticulocyte count has increased $< 40,000$ cells/microlitre above baseline, response is unlikely and treatment should be discontinued.

The recommended dosing regimen is described in the following diagram:



Dose Adjustment

In oncology patients, rapid increases in haemoglobin concentrations or the use of erythropoietins in subjects with normal haemoglobin concentrations, may result in an increased risk of thrombotic adverse events (see PRECAUTIONS: Thrombotic Events)

Therefore a rate of rise in haemoglobin of greater than 10 g/L per 2 week period or 20 g/L per month or haemoglobin levels of > 120 g/L should be avoided.

If the haemoglobin is rising by more than 10 g/L per two-week period or 20 g/L per month or haemoglobin is approaching 120 g/L, reduce EPREX dose by about 25-50%. If the haemoglobin exceeds 120 g/L, discontinue therapy until it falls to below 120 g/L and then reinstitute EPREX at a dose 25% below the previous dose.

Administration Instructions

Parenteral drug products should be visually inspected for particulate matter and discolouration prior to administration. Product exhibiting particulate matter or discolouration must not be used. Do not shake, shaking may denature the glycoprotein, rendering it inactive.

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

Prepare EPREX for IV/SC injection from the pre-filled syringe.

Administer as IV/SC injection over 1-2 minutes. In patients on dialysis the injection should follow the dialysis procedure. Slow injection over 5 minutes may be beneficial to those who experience flu-like symptoms.

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

For subcutaneous route a maximum volume of 1 mL at one injection site should generally not be exceeded. In case of larger volumes, more than one site should be chosen for the injection. Subcutaneous injections are given in the limbs or the anterior abdominal wall.

The pre-filled syringes are fitted with the PROTECS™ needle guard device to help prevent needle stick injuries after use. The EPREX Consumer Medicine Information includes full instructions for the use and handling of pre-filled syringes.

OVERDOSAGE

The maximum amount of EPREX that can be safely administered in single or multiple doses has not been determined with respect to the direct effect of epoetin alfa (rch) as distinct from its effect on red cell mass.

The response to EPREX is dose related and individual. With excessive erythropoietic response to EPREX, dosing should be stopped and treatment begun as described above under PRECAUTIONS: Hypertension and Seizures. Phlebotomy may be performed if excessively high haemoglobin levels occur. Additional supportive care should be provided as necessary.

PRESENTATION AND STORAGE CONDITIONS

EPREX® is a sterile preservative-free phosphate buffered protein solution of Epoetin alfa (rch) in pre-filled syringes of 1,000 IU in 0.5 mL, 2,000 IU in 0.5 mL, 3,000 IU in 0.3 mL, 4,000 IU in 0.4 mL, 5000 IU in 0.5 mL, 6000 IU in 0.6 mL, 8000 IU in 0.8 mL, 10,000 IU in 1.0 mL, 20,000 IU in 0.5 mL, 30,000 IU in 0.75 mL and 40,000 IU (336 micrograms) in 1 mL. The formulation is stabilised with glycine (5 mg/mL) and polysorbate 80 (0.30 mg/mL). The pre-filled syringes are fitted with the PROTECS™ needle guard device.

All formulations also contain sodium chloride at 1.7 – 5.8 mg, sodium phosphate – monobasic dihydrate at 0.35 – 1.16 mg, sodium phosphate – dibasic dihydrate at 0.67 – 2.22 mg and sodium citrate at less than 5 mmol.

Each package contains 6 pre-filled syringes, except the 40,000 IU syringe that is sold singly.

Store at 2°C to 8°C. Do not freeze or shake. This temperature range should be closely maintained until administration to the patient. Store in original package in order to protect from light.

When the product is about to be used, it may be removed from the refrigerator and stored at room temperature (below 25°C) for a maximum single period of seven days.

The product should not be used, and discarded

- 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, or
- if there has been a refrigeration failure.

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

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine

DATE OF APPROVAL

Date of first inclusion on the ARTG: 17 September 1998

Date of most recent amendment: 2 May 2016

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™ PROTECS is a trademark of Janssen-Cilag Pty Ltd

**** Please note change(s) in Product Information***