janssen

TRADEMARK
EPREX
Epoetin alfa

COMPOSITION

Epoetinum alfa	2000 IU or 16.8 micrograms per 0.5ml
Epoetinum alfa	4000 IU or 33.6 micrograms per 0.4ml
Epoetinum alfa	10,000 IU or 84.0 micrograms per ml

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

PHARMACOLOGICAL PROPERTIES
Epoetinum alfa is a purified glycoprotein hormone that stimulates the formation of erythrocytes from precursors of the stem cell compartment. Epoetinum alfa is produced from mammalian cells into which the gene coding for human erythropoietin has been inserted.

Epoetinum alfa obtained by gene technology is identical in its amino acid sequence to erythropoietin that has been isolated from the urine of anaemic patients. The protein fraction of the molecule contributes about 58% of the molecular weight and consists of 165 amino acids. The four carbohydrate chains are attached to the protein via three N-glycosidic bonds and one O-glycosidic bond to the protein. The apparent molecular weight of erythropoietin is approximately 32,000-40,000 daltons.

Pharmacodynamic proteries
ATC code: B03XA01.

Erythropoietin is a mitosis-stimulating factor and differentiating hormone which stimulates erythropoiesis.

The biological efficacy of Epoetinum alfa has been demonstrated in vivo in various animal models (normal and anaemic rats, polycythaemic mice). After administration of Epoetinum alfa, the number of erythrocytes, the haemoglobin values, the reticulocyte counts and the ^{59}Fe-incorporation rate increase.

It could be shown with the aid of cell cultures of human bone marrow cells, that Epoetinum alfa stimulates erythropoiesis specifically and does not affect leucopoiesis. Cytotoxic actions of Epoetinum alfa on bone marrow cells could not be detected.

Erythropoietin is a growth factor that primarily stimulates red cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells. There is insufficient information to conclusively establish whether the use of ESAs has an adverse effect on time to tumour progression or progression-free survival when used as recommended.

Studies have explored the effect of ESAs on survival and/or tumour progression of exogenous erythropoietin with higher haemoglobin targets.

A randomized, open-label, multicenter study was conducted in 2098 anemic 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%).

An increased 3H-thymidine incorporation in the erythroid nucleated spleen cells has been found in vitro (mouse spleen cell culture) after incubation with epoetinum alfa.

Pharmacokinetic properties
Intravenous route
Measurement of Epoetinum alfa following multiple dose intravenous (IV) administration revealed a half-life of approximately 4 hours in normal volunteers and a somewhat more prolonged half-life in renal failure patients

approximately 5 hours. A half-life of approximately 6 hours has been reported in children.

Subcutaneous route
Following subcutaneous injection, serum levels of Epoetinum alfa are much lower than the levels achieved following I.V. injection, the levels increase slowly and reach a peak 12 to18 hours postdose. The peak is always well below the peak achieved using the intravenous route (approximately 1/20th of the value).

There is no accumulation: serum levels remain the same, whether data are collected 24 hours after the first injection or 24 hours after the last injection.

The half-life is difficult to evaluate for the subcutaneous route and is estimated about 24 hours.

The bioavailability of subcutaneous injectable Epoetinum alfa is much lower than that of the intravenous drug: approximately 20%.

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

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

Epoetinum alfa did not show any changes in bacterial and mammalian cell culture mutagenicity tests and an *in vivo* micronucleus test in mice.

Long-term carcinogenicity studies have not been carried out. There are conflicting reports in the literature regarding whether erythropoietin may play a role as tumour proliferators. These reports are based on *in* vitro findings from human tumour samples, but are of uncertain significance in the clinical situation.

CLINICAL PARTICULARS
Therapeutic indications

Epoetinum alfa can be used for the treatment of anaemia associated with chronic renal failure in adult patients on haemodialysis and peritoneal dialysis and in paediatrics patients on hemodialysis.

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

Epoetinum alfa can be used for the treatment of anaemia and reduction of transfusion requirements in adult patients receiving chemotherapy.

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

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

Treatment of anemia in symptomatic HIV-infected patients being treated with AZT and who are transfusion-dependent.

POSOLOGY AND METHOD OF ADMINISTRATION
Method of administration
Epoetinum alfa may be administered by intravenous or subcutaneous injection.

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

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

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

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

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

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

Subcutaneous injection
The maximum volume per injection site should be 1 ml. In case of larger volumes, more than one injection site should be used.

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

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

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

In patients with chronic renal failure and clinically evident ischaemic heart disease or congestive heart failure, maintenance haemoglobin concentration should not exceed the upper limit of the target haemoglobin concentration (see Special warnings and special precautions – Renal Failure Patients).

Iron status should be evaluated prior to and during treatment and iron supplementation should be administered if necessary. Other causes of anaemia [such as Vitamin B_{12} or folate deficiency] should be excluded before starting therapy with Epoetinum alfa. Non-response to Epoetinum alfa therapy should prompt a search for causative factors. These include: iron, folate, or Vitamin B_{12} deficiency; aluminum intoxication; intercurrent infections; inflammatory or traumatic episodes; occult blood loss; haemolysis; and bone marrow fibrosis of any origin.

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 adjustment 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 individualized 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 > 5 mmol/l).

Paediatric Haemodialysis patients:
The treatment is divided into two stages:

Correction Phase

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

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

Maintenance Phase
Adjust dosage in order to maintain haemoglobin values at the desired level: Hb between 9.5 – 11 g/dL (5.9 – 6.8 mmol/l).

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

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

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

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

The treatment is divided into two stages:
Correction Phase
50 IU/kg 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 [6.21–7.45 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 three times per week.

Adult Predialysis Patients [Adult Patients With End Stage Renal Insuffiency]
In patients with renal insufficiency not yet undergoing dialysis, where intravenous access is not readily available, Epoetinum alfa may be administered subcutaneously.

The treatment is divided into two stages:
Correction Phase
50 IU/kg three times per week.

If necessary by a dosage increase with 25 IU/kg increments (three times per week until the desired goal is achieved (this should be done in steps of at least four weeks).

Maintenance Phase
Dosage adjustment in order to maintain haemoglobin values at the desired level: Hb between 10 and 12 g/dl (6.2 – 7.5 mmol/l) is between 17 and 33 IU/kg three times per week.

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

<u>Cancer Patients</u>
Adult cancer patients:
Epoetinum alfa therapy should be administered to patients with anemia (e.g. Hb ≤ 10.5 g/dl [6.5 mmol/l].

The subcutaneous route of administration should be used.

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

Epoetinum alfa therapy should continue until one month after the end of chemotherapy. However, the need to

continue Epoetinum alfa therapy should be re-evaluated periodically.

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

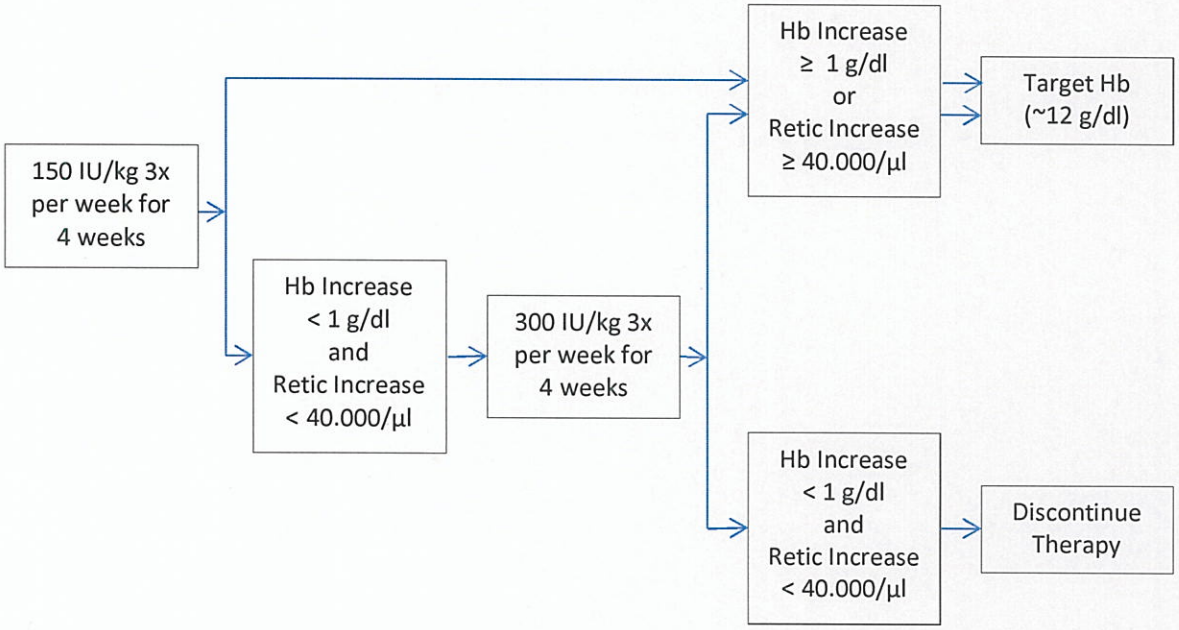
If after 4 weeks of treatment at the initial dose, the haemoglobin has increased by at least 1 g/dL (0.6 mmol/L) [or the reticulocyte count has increased ≥ 40,000 cells/µl above baseline] the dose should remain unchanged.

If after 4 weeks of treatment at the initial dose, the haemoglobin has not increased is by ≥ 1 g/dL (< 0.6 mmol/l) [and the reticulocyte count has not increased by ≥ 40,000 cells/µl above baseline], the dose should be increased to 300 IU/kg 3 times per week.

If after 4 weeks of additional therapy with 300 IU/kg 3 times per week, the haemoglobin has increased ≥ 1 g/dL (≥ 0.6 mmol/l), [or the reticulocyte count has increased ≥ 40,000 cells/µl] the dose should remain unchanged.

If after 4 weeks of additional therapy with 300 IU/kg three times per week, the haemoglobin has increased < 1 g/ dL (0.6 mmol/l) [and the reticulocyte count has increased < 40,000 cells/µl above baseline], response is unlikely and treatment should be discontinued.

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



A rate of rise in haemoglobin of greater than 1 g/dL (.6 mmol/l) per 2 week or 2 g/dL (1.25 mmol/L) per month or haemoglobin levels of > 12 g/ dL (>8.1 mmol/L) should be avoided. If the haemoglobin is rising by more than 1 g/dL (.6 mmol/l) per two week or 2 g/dL (1.25 mmol/L) per month or haemoglobin is approaching 12 g/dL (7.5 mmol/l), reduce the Epoetinum alfa dose by about 25-50% depending upon the rate of rise of haemoglobin. If the haemoglobin exceeds 12 g/dL (7.5 mmol/l), withhold therapy until it falls below 12 g/dL (7.5 mmol/l) and then reinitiate Epoetinum alfa therapy at a dose 25% below the previous dose.

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

Iron status should be evaluated for all patients prior to treatment with Epoetinum alfa. Iron deficiency, if present, should be corrected before allowing a patient to enroll in an autologous blood donation programme. In anaemic patients, the cause of anaemia should be explored before starting therapy with Epoetinum alfa.

All patients being treated with Epoetinum alfa should receive adequate iron supplementation (*eg,* 200 mg oral elemental iron daily) throughout the course of Epoetinum alfa treatment. In order to achieve high iron stores prior to starting Epoetinum alfa therapy, iron supplementation should be started as soon as possible, even several weeks prior to initiating the autologous predeposit.

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

prior to surgery.

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

All patients should receive adequate iron replacement. Iron replacement (*e.g.*, at least 200 mg of oral elemental iron daily) should be initiated no later than the beginning of treatment with Epoetinum alfa and should continue throughout the course of therapy.

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

In cases where there is a medical need to reduce the time before surgery to less than three weeks, the recommended dosage regimen is 300 IU/kg given daily for 10 consecutive days before surgery, on the day of surgery and up to 4 days after surgery. When performing haematologic assessments during the preoperative period, if the haemoglobin level reaches 15 g/dL (9.38 mmol/l), or higher, administration of Epoetinum alfa should be stopped and further dosages should not be given. Care should be taken to ensure that at the outset of the treatment patients are not iron deficient.

UNDESIRABLE EFFECTS
For safety with respect to transmissible agents, see Special Warnings and Precautions for Use.

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

Other common adverse drug reactions observed in clinical trials of Epoetinum alfa are diarrhoea, nausea, headache, influenza-like illness, pyrexia, rash, vomiting, deep vein thrombosis, pulmonary embolism, seizures. Influenza-like illness including headaches, joint pains, myalgia, and pyrexia, dizziness and tiredness, may occur especially at the start of treatment.

Frequencies may vary depending on the indication see table below.

The overall safety profile of Epoetin alfa 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 Epoetin alfa-treated subjects in these trials, additional clinical trials and from post-marketing experience are listed below by SOC and frequency.

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10000, < 1/1000); very rare (< 1/10000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Blood and lymphatic system disorders	Uncommon	Thrombocythaemia (cancer patients)
	Frequency not known	Erythropoietin antibody-mediated pure red cell aplasia [1]
		Thrombocythaemia (chronic renal failure patients)
Immune system disorders	Frequency not known	Anaphylactic reaction
		Hypersensitivity
Nervous system disorders	Very common	Headache (cancer patients)
	Common	Seizures (chronic renal failure patients)
		Headache (chronic renal failure patients)
	Uncommon	Cerebral haemorrhage [2]
		Seizures (cancer patients)
	Frequency not known	Cerebrovascular accident [2]
		Hypertensive encephalopathy
		Transient ischaemic attacks
Eye disorders	Frequency not known	Retinal thrombosis
Vascular disorders	Common	Deep vein thrombosis [2] (cancer patients)
		Hypertension
	Frequency not known	Deep vein thrombosis [2] (chronic renal

		failure patients)
		Arterial thrombosis
		Hypertensive crisis
Respiratory, thoracic, and mediastinal disorders	Common	Pulmonary embolism [2] (cancer patients)
	Frequency not known	Pulmonary embolism [2] (chronic renal failure patients)
Gastrointestinal disorders	Very common	Nausea
	Common	Diarrhoea (cancer patients)
		Vomiting
	Uncommon	Diarrhoea (chronic renal failure patients)
Skin, and subcutaneous tissue disorders	Common	Rash
	Frequency not known	Angioneurotic oedema
		Urticaria
Musculoskeletal, connective tissue, and bone disorders	Very common	Arthralgia (chronic renal failure patients)
	Common	Arthralgia (cancer patients)
	Uncommon	Myalgia (cancer patients)
	Frequency not known	Myalgia (chronic renal failure patients)
Congenital and familial / genetic disorders	Frequency not known	Porphyria
General disorders and administration site conditions	Very common	Pyrexia (cancer patients)
		Influenza like illness (chronic renal failure patients)
	Common	Influenza like illness (cancer patients)
	Frequency not known	Drug ineffective
		Peripheral oedema
		Pyrexia (chronic renal failure patients)
		Injection site reaction
Investigations	Frequency not known	Anti-erythropoietin antibody positive [1]
Injury, poisoning, and procedural complications	Common	Shunt thromboses including dialysis equipment (chronic renal failure patients)

[1] The frequency cannot be estimated from clinical trial
[2] Including cases with a fatal outcome

Surgery patients
In patients scheduled for major elective orthopaedic surgery, with a baseline haemoglobin of 10 to 13 g/dl, the incidence of thrombotic/vascular events (most of which were deep vein thrombosis) in the overall patient population of the clinical trials appeared to be similar across the different Epoetin alfa dosing groups and placebo group, although the clinical experience is limited. Moreover, in patients with a baseline haemoglobin of > 13 g/dl, the possibility that Epoetin alfa treatment may be associated with an increased risk of postoperative thrombotic/vascular events cannot be excluded.

Serious adverse drug reactions include venous and arterial thromboses and embolism (including some with fatal outcomes), such as myocardial ischaemia, myocardial infarction, aneurysms, clotting of an erythropoietic agents, deep venous thrombosis, pulmonary emboli, arterial thrombosis, retinal thrombosis, and shunt thrombosis (including dialysis equipment). Thrombocytosis has been observed. Additionally, cerebrovascular accidents (including cerebral infarction and cerebral haemorrhage) and transient ischaemic attacks have been reported in clinical trials of Epoetinum alfa.

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

Hypertensive crisis with encephalopathy-like symptoms (e.g. headaches and confused state), generalised tonocloncal seizures and seizures, requiring the immediate attention of a physician and intensive medical care, have occurred also during Epoetinum alfa treatment in patients with previously normal or low blood pressure. Particular attention should be paid to sudden stabbing migraine-like headaches as a possible warning signal.

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 Warnings and Special Precautions for Use).

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.

Cancer Patients
An increased incidence of thromboembolic events has been reported in cancer patients receiving ESAs, including Epoetinum alfa (see Special Warnings and Special Precautions for Use and Pharmacodynamic Properties). Hypertension may occur in Epoetin alfa treated patients. Consequently, haemoglobin and blood pressure should be closely monitored.

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

Very common	≥1/10
Common	≥1/100 and <1/10
Uncommon	≥1/1,000 and <1/100
Rare	≥1/10,000 and <1/1,000
Very rare	<1/10,000, including isolated reports

Pure red cell aplasia (erythroblastopenia) has been reported in chronic renal failure patients after months to years of treatment with EPREX or other erythropoietic agents. In most of these patients, antibodies to erythropoietins have been observed. (See Special Warnings and Special Precautions-, Pure Red Cell Aplasia).

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

Blood & Lymphatic System Disorders	
Very rare	Erythropoietin Antibody-Mediated Pure Red Cell Aplasia
Investigations *Very rare*	Anti-erythropoietin Antibody Positive

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

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

In all patients receiving Epoetinum alfa, blood pressure should be closely monitored and controlled as necessary. Epoetinum alfa should be used with caution in the presence of untreated, inadequately treated or poorly controllable hypertension. 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 Epoetinum alfa therapy. If blood pressure cannot be controlled, Epoetinum alfa treatment should be discontinued.

Epoetinum alfa should be used with caution in patients with history of seizure.

Epoetinum alfa 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 Epoetinum alfa therapy have not been established in patients with underlying haematologic diseases (e.g. haemolytic anaemia, sickle cell anaemia, thalassemia, porphyria).

The safety of Epoetinum alfa has not been established in patients with hepatic dysfunction. Due to decreased metabolism, patients with hepatic dysfunction may have increased erythropoiesis with Epoetinum alfa.

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

[Certain formulations of Epoetinum alfa contain albumin, a derivative of human blood. When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unkown or emerging viruses and other pathogens. It is strongly recommended that every time that Eprex is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patients and the batch of the product].

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

Pure Red Cell Aplasia

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

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

In chronic renal failure patients developing sudden lack of efficacy, defined by a decrease in haemoglobin (1 to 2 g/dL per month) with increased need for transfusions, a reticulocyte count should be obtained and typical causes of non-response (e.g., iron folate or Vitamin B_{12} deficiency, aluminum intoxication, infection or inflammation, blood loss, haemolysis) should be investigated. If the reticulocyte count corrected for anaemia (i.e., the reticulocyte "index") is low (< 20,000/mm^3 or < 20,000/ul or < 0.5%) platelet and white blood cell counts are normal, and if no other cause of loss of effect has been found, anti-erythropoietin antibodies should be determined and a bone marrow examination should be considered for diagnosis of PRCA.

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

Renal Failure Patients

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 Posology and Method of Administration. Haemoglobin levels greater than 12 g/dl may be associated with a higher risk of cardiovascular events, including death.

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

In order to ensure optimum response to Epoetinum alfa, 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, 200-300 mg/day orally 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 Epoetinum alfa 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 Epoetinum alfa frequently require an increase in heparin dose during dialysis. If heparinisation is not optimal, occlusion of the dialysis system is possible.

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

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

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

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

In cancer patients receiving chemotherapy, should the rate of increase in haemoglobin exceed 1 g/dL per two week or 2 g/dL per month or the haemoglobin concentration is approaching 12 g/dL or the haemoglobin concentration exceeds 12 g/dL, the dose adjustment detailed in Section Posology and Method of Administration – Cancer Patients should be followed to minimize potential risk factors of thrombotic events. (See section Posology and Method of Administration – Cancer Patient – Adult Cancer Patients).

As an increased incidence of thrombotic vascular events (TVEs) has been observed in cancer patients receiving ESAs (see section Side Effects), this risk should be carefully weighed against the benefit to be derived from treatment with Epoetinum alfa 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 Epoetinum alfa 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 Epoetinum alfa than in those receiving placebo (see Pharmacodynamic Properties).

In clinical studies ESAs 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 12g/dL. In the BEST study Epoetinum alfa 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 12g/dL. See Pharmacodynamic Propertiies.

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

In order to ensure optimum response to Epoetinum alfa, 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 supplemention, *eg,* 200-300 mg/day orally is recommended for all cancer patients whose transferring saturation is below 20 %.

In cancer patients receiving chemotherapy, the 2-3 week delay between ESA administration and the appearance of erythropoietin-induced red cells should be considered when assessing whether or not Epoetinum alfa therapy is appropriate (in particular for patients at risk of transfusion).

HIV-Infected Patients

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

Adult Surgery Patients in an Autologous Pre-Donation Programme
All special warnings and special precautions associated with autologous blood donation programmes, especially routing volume replacement, should be respected in patients being supplemented with Epoetinum alfa.

Adult Perisurgery Patients (Without Autologous Blood Donation)
In patients scheduled for major elective orthopaedic surgery the cause of anaemia should be established and treated, if possible, before the start of Epoetinum alfa treatment.

In patients scheduled for major elective orthopaedic surgery thrombotic events can be a risk and this possibility should be carefully weighed against the benefit to be derived from the treatment in this patient group.

Patients scheduled for major elective orthopaedic surgery should receive adequate antithrombotic prophylaxis, as thrombotic and vascular events may occur in surgical patients, especially in those with underlying cardiovascular disease. In addition, special precaution should be taken in patients with predisposition for development of DVTs. Moreover, in patients with a baseline haemoglobin of > 13 g/dL (8.1 mmol/l]), the possibility that Epoetinum alfa treatment may be associated with an increased risk of postoperative thrombotic/vascular events cannot be excluded. Therefore, it should not be used in patients with baseline haemoglobin > 13 g/dL (8.1 mmol/l]).

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

Chronic renal failure patients treated with EPREX by the subcutaneous route should be monitored regularly for loss of efficacy, defined as absent or decreased response to EPREX treatment in patients who previously responded to such therapy. This is characterized by a sustained decrease in haemoglobin despite an increase in EPREX dosage.
Hyperkalaemia has been observed in isolated cases. In chronic renal failure patients, correction for anaemia may lead to increased appetite, and potassium and protein intake. Dialysis prescriptions may have to be adjusted periodically to maintain urea, creatinine and potassium in the desired range. Serum electrolytes should be monitored in chronic renal failure patients, if an elevated (or rising) serum potassium level is detected then consideration should be given to ceasing Epoetinum alfa administration until hyperkalaemia has been corrected.
An increase in heparin dose during haemodyalis is frequently required during the course of therapy with Epoetinum alfa as a result of the increased packed cell volume. Occlusion of the dyalisis system is possible if heparinisiation is not optimum.
Based on information available to date, correction of anaemia with Epoetinum alfa in adult patients with renal insufficiency not yet undergoing dialysis does not accelerate the rate of progression of renal insufficiency.
All other causes of anaemia (iron deficiency, haemolysis, blood loss, vitamin B12 or folate deficiencies) should be considered and treated prior to initiating therapy with Epoetinum alfa.
All of these additive factors of anaemia should also be carefully considered when deciding to double the dose of Epoetinum alfa in cancer patients.
In patients with chronic renal failure and clinically evident ischaemic heart disease or congestive heart failure, maintenance haemoglobin concentration should not exceed the upper limit of the target haemoglobin concentration as recommended under section Posology and the Method of Administration
Growth factor potential Epoetinum alfa is a growth factor that primarily stimulates red blood cell production. However, the possibility that Epoetinum alfa can act as a growth factor for any tumour type, particularly myeloid malignancies, cannot be excluded (see Preclinical Safety Data).

In patients developing sudden lack of efficacy defined by a decrease in haemoglobin (1 to 2 g/dl per month) with increased need for transfusions, a reticulocyte count should be obtained and typical causes of non-responses (e.g. iron, folate or, vitamin B12 deficiency, aluminium intoxication, infection or inflammation, blood loss and haemolysis) should be investigated.

If reticulocyte count corrected for anaemia (i.e. the reticulocyte "index") is low (< 20000/mm^3 or < 20000/microliter or 0.5%) platelet and white blood cell counts are normal, and if no other cause of loss of effect has been found, anti-erytrhopoietin antibodies should be determined and bone marrow examination should be considered for diagnosis of PRCA.
If anti-erythropoietin, antibody-mediated PRCA is suspected, therapy with Epoetin alfa Hexal should be discontinued immediately. No other erythropoietin therapy should be commenced because of the risk of cross-reaction. Appropriate therapy such as blood transfusions may be given to patients when indicated.

A paradoxical decrease in haemoglobin and development of severe anaemia associated with low reticulocyte counts should prompt to discontinue treatment with epoetin and perform anti-erythropoietin antibody testing. Cases have

been reported in patients with hepatitis C treated with interferon and ribavirin, when Epoetin are used concomitantly. Epoetins are not approved in the management of anemia associated with hepatitis C.

CONTRAINDICATIONS
Patients who develop Pure Red Cell Aplasia (PRCA) following treatment with any erythropoietin should not receive Epoetinum alfa or any other erythropoietin (see section Special Warnings and Special Precautions for Use – Pure Red Cell Aplasia).

Uncontrolled hypertension.

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

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

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

Patients who for any reason cannot receive adequate antithrombotic prophylaxis.

The use of Epoetinum alfa in the indication "to facilitate autologous blood collection" is contraindicated in patients with:
- Myocardial infarction or stroke in the month preceding treatment
- Unstable angina pectoris
- Increase risk of deep venous thrombosis such as history of venous thromboembolic disease

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
No evidence exists that indicates that treatment with Epoetinum alfa alters the metabolism of other drugs. However, since cyclosporin is bound by red blood cells there is potential for a drug interaction. If Epoetinum alfa is given concomitantly with cyclosporin, blood levels of cyclosporin should be monitored and the dose of cyclosporin adjusted as the haematocrit rises.

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

Pregnancy and lactation
Use During Pregnancy
In animal studies, Epoetinum alfa has been shown to decrease foetal body weight, delay ossification and increase foetal mortality when given in weekly doses of approximately 20 times the recommended human weekly dose. These changes are interpreted as being secondary to decreased maternal body weight gain.

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

In chronic renal failure patients, Epoetinum alfa should be used during pregnancy only if the potential benefit justifies the potential risk to the foetu.

See Properties - *Preclinical Safety Data – Reproduction Toxicology).*

Studies in animals have shown reproduction toxicology (see Preclinical Safety Data).

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

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

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

Effects on ability to drive and use machines
Due to the increased risk of hypertension during the initial phase of Epoetinum alfa treatment, patients with chronic renal failure should use caution when performing potentially hazardous activities, such as driving or operating machinery, until the optimal maintenance dose of Epoetinum alfa has been established.

Overdose
Overdose of Epoetinum alfa may produce effects that are extensions of the pharmacological effects of the hormone (critical increase of haemoglobin or haematocrit levels). Phlebotomy may be performed if excessively high haemoglobin or haemotocrit levels occur.

PHARMACEUTICAL PARTICULARS
List of excipients
Polysorbate 80
Sodium chloride
Disodium phosphate dihydrate
Sodium dihydrogen phosphate dihydrate
Glycine
Water for injections

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

Special precautions for storage
EPREX syringes are to be stored between 2°C to 8°C [36°F to 46°F] in the refrigerator, away from the freezer compartment. Do not freeze or shake. Keep the syringes in the original carton to protect from light.

Shelf life
18 months.

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

Instructions for use and handling and disposal
Do not administer by intravenous infusion or in conjunction with other drug solutions.

[The product is for single use only.]

The product should not be used, and should be discarded if:
- the seal is broken
- the liquid is coloured or
- particles are in it,
- it may have been frozen, or
- there has been a refrigeration failure.
- You know or suspect that the product has been left at room temperature for more than 60 minutes before injection.

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

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

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

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

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

How to inject yourself using a prefilled syringe
The pre-filled syringes are fitted with the PROTECS™ needle guard device to help prevent needle stick injuries after use. This is indicated on the packaging.

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

- **Check the syringe**, to make sure it is the right dose, has not passed its expiry date, is not damaged, and the liquid is clear and not frozen.

- **Choose an injection site.** Good sites are the top of the thigh and around the tummy (abdomen) but away from the navel. Vary the site from day to day.

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

- **Take the cover off the syringe** by holding the barrel and pulling the cover off carefully without twisting it. Don't push the plunger, touch the needle or shake the syringe.

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

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

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

- **Push the plunger with your thumb as far as it will go to inject all of the liquid.** Push it slowly and evenly, keeping the skinfold pinched. The needle guard will not activate unless the entire dose is given.

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

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

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

- **Dispose of your used syringe** in a safe container.

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

What to do if you use too much EPREX?
Tell the doctor or nurse immediately if you think too much EPREX has been injected.

What to do if you forget to use EPREX?
Make the next injection as soon as remember. If you are within a day of your next injection, forget the missed one and carry on with your normal schedule. Do not double up the injection.

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

Vial and pre-filled syringes should be protected from light.

Other important points
EPREX should not be used:
- after the expiry date on the label;
- if the seal is broken;
- if the liquid is coloured or you can see particles floating in it;
- if you know, or think that it may have been accidentally frozen;
- if there has been a refrigerator failure.
- You know or suspect that the product has been left at room temperature for more than 60 minutes before injection.

Always keep medicine out of the reach of children.

How to dispose of EPREX
Medicine should not be disposed of via waste water or in household waste. Ask your pharmacist how to dispose of

medicines no longer required. These measures will help to protect the environment.

HOW SUPPLIED
EPREX 2000 IU/0.5 ml
Box @ 6 pre-filled syringe @ 0.5 ml
Reg. No.: DKI1060000843A1

EPREX 4000 IU/0.4 ml
Box @ 6 pre-filled syringe @ 0.4 ml
Reg. No.: DKI1060000843B1

EPREX 10000 IU/ ml
Box @ 6 pre-filled syringe @ 1 ml
Reg. No.: DKI1060000843B1

HARUS DENGAN RESEP DOKTER

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi.

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