PRODUCT NAME
EPREX®
Epoetin alfa

COMPOSITION

Epoetin alfa	2,000 IU or 16.8 micrograms per 0.5ml
Epoetin alfa	4,000 IU or 33.6 micrograms per 0.4ml
Epoetin alfa	10,000 IU or 84.0 micrograms per ml
Epoetin alfa	40,000 IU or 336 micrograms per ml

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

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: anti-anaemia, ATC code: B03XA01.

Mechanism of action
Erythropoietin (EPO) is a glycoprotein hormone produced primarily by the kidney in response to hypoxia and is the key regulator of red blood cell (RBC) production. EPO is involved in all phases of erythroid development, and has its principal effect at the level of erythroid precursors. After EPO binds to its cell surface receptor, it activates signal transduction pathways that interfere with apoptosis and stimulates erythroid cell proliferation. Recombinant human EPO (Epoetinu alfa), expressed in Chinese hamster ovary cells, has a 165 amino acid sequence identical to that of human urinary EPO; the 2 are indistinguishable on the basis of functional assays. The apparent molecular weight of erythropoietin is 32,000 to 40,000 dalton.

Pharmacodynamic responses to HSA-free Epoetin alfa, change in percent reticulocytes, hemoglobin, and total red blood cell counts as well as the area under the curve (AUCs) of these pharmacodynamic parameters, were similar between two dosing regimens (150 IU/kg SC three times per week to 40000 IU/mL SC once weekly).

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

Chronic renal failure
Epoetin alfa has been studied in clinical trials in adult anaemic CRF patients, including patients on dialysis and patients not yet on dialysis, to treat anaemia and maintain haematocrit within a concentration range of 30-36%.

In clinical trials at starting doses of 50-150 IU/kg three times per week, approximately 95% of all patients responded with a clinically significant increase in haematocrit. After approximately two months of therapy, virtually all patients were transfusion-independent. Once the haematocrit concentration range was achieved, the maintenance dose was individualised for each patient.

In the three largest clinical trials conducted in adult patients on dialysis, the median maintenance dose necessary to maintain the haematocrit between 30-36% was approximately 75 IU/kg given three times per week.

In a double-blind, placebo-controlled, multicentre, quality of life study in CRF patients on haemodialysis, clinically and statistically significant improvement was shown in the patients treated with Epoetin alfa compared to the placebo group when measuring fatigue, physical symptoms, relationships and depression (Kidney Disease Questionnaire) after six months of therapy. Patients from the group treated with Epoetin alfa were also enrolled in an open-label extension study which demonstrated improvements in their quality of life were maintained for an additional 12 months.]

Adult patients with renal insufficiency not yet undergoing dialysis
In clinical trials conducted in patients with CRF not on dialysis treated with Epoetin alfa, the average duration of therapy was nearly five months. These patients responded to Epoetin alfa therapy in a manner similar to that observed in patients on dialysis. Patients with CRF not on dialysis demonstrated a dose-dependent and sustained increase in haematocrit when Epoetin alfa was administered by either an intravenous or subcutaneous route. Similar rates of rise of haematocrit were noted when Epoetin alfa was administered by either route. Moreover, Epoetin alfa doses of 75-150 IU/kg per week have been shown to maintain haematocrits of 36-38% for up to six months.

In a study with extended interval maintenance dosing of Epoetin alfa (once weekly) some patients with longer dosing intervals did not maintain adequate haemoglobin levels and reached protocol-defined haemoglobin withdrawal criteria (0% in once weekly).

In clinical trials conducted in patients with CRF not on dialysis treated with Epoetin alfa, the average duration of therapy was nearly five months. These patients responded to Epoetin alfa therapy in a manner similar to that observed in patients on dialysis. Patients with CRF not on dialysis demonstrated a dose-dependent and sustained increase in haematocrit when Epoetin alfa was administered by either an intravenous or subcutaneous route. Similar rates of rise of haematocrit were noted when Epoetin alfa was administered by either route. Moreover, Epoetin alfa doses of 75-150 IU/kg per week have been shown to maintain haematocrits of 36-38% for up to six months.

A randomized prospective trial (CHOIR) evaluated 1432 anaemic chronic renal failure patients who were not undergoing dialysis. Patients were assigned to Epoetin alfa treatment targeting a maintenance haemoglobin level of 13.5 g/dL (higher than the recommended target haemoglobin level) or 11.3 g/dL. A major cardiovascular event (death, myocardial infarction, stroke or hospitalization for congestive heart failure) occurred among 125 (18%) of the 715 patients in the higher haemoglobin group compared to 97 (14%) among the 717 patients in the lower haemoglobin group (hazard ratio [HR] 1.3, 95% CI: 1.0, 1.7, p = 0.03).

Chemotherapy induced anaemia

Treatment of patients with Chemotherapy induced anaemia

Epoetin alfa has been studied in clinical trials in adult anaemic cancer patients with lymphoid and solid tumors, and patients on various chemotherapy regimens, including platinum and non-platinum-containing regimens. In these trials, Epoetin alfa administered three times a week (tiw) and once weekly has been shown to increase haemoglobin and decrease transfusion requirements after the first month of therapy in anaemic cancer patients. In some studies, the double-blind phase was followed by an open-label phase during which all patients received Epoetin alfa and a maintenance of effect was observed.

Available evidence suggests the hematopoietic response to Epoetin alfa therapy is similar between patients with non-myeloid hematologic and solid tumors and in patients with or without tumor bone marrow infiltration. Comparable intensity of chemotherapy in the Epoetin alfa and placebo groups in the chemotherapy trials was demonstrated by a similar area under the neutrophil time curve in patients treated with Epoetin alfa and placebo-treated patients, as well as by a similar proportion of patients in groups treated with Epoetin alfa and placebo-treated groups whose absolute neutrophil counts fell below 1000 and 500 cells/mcL.

In a prospective, randomised, double-blind, placebo-controlled trial conducted in 375 anaemic patients with various non-myeloid malignancies receiving non-platinum chemotherapy, there was a significant reduction of anaemia-related sequelae (e.g. fatigue, decreased energy, and activity reduction), as measured by the following instruments and scales: Functional Assessment of Cancer Therapy-Anaemia (FACT-An) general scale, FACT-An fatigue scale, and Cancer Linear Analogue Scale (CLAS).

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

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%). At the final analysis, 1653 deaths were reported. Median overall survival in the epoetin alfa plus SOC group was 17.8 months compared with 18.0 months in the SOC alone group (HR 1.07, 95% CI: 0.97, 1.18). The median time to progression (TTP) based on investigator-determined progressive disease (PD) was 7.5 months in the epoetin alfa plus SOC group and 7.5 months in the SOC group (HR 1.099, 95% CI: 0.998, 1.210). The median TTP based on IRC-determined PD was 8.0 months in the epoetin alfa plus SOC group and 8.3 months in the SOC group (HR 1.033, 95% CI: 0.924, 1.156).

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

Adult patients with low- or intermediate-1-risk MDS
A randomized, double-blind, placebo-controlled, multicenter study evaluated the efficacy and safety of epoetin alfa in adult anemic subjects with low- or intermediate-1-risk MDS.

Erythroid response was defined according to IWG 2006 criteria as a hemoglobin increase ≥ 1.5 g/dL from baseline or a reduction of RBC units transfused by an absolute number of at least 4 units every 8 weeks compared to the 8 weeks prior to baseline, and a response duration of at least 8 weeks.

Erythroid response during the first 24 weeks of the study was demonstrated by 27/85 (31.8%) of the subjects in the epoetin alfa group compared to 2/45 (4.4%) of the subjects in the placebo group (p<0.001).

Median time from baseline to first transfusion was statistically significantly longer in the epoetin alfa group compared to placebo (49 vs. 37 days; p=0.046). After 4 weeks of treatment the time to first transfusion was further increased in the epoetin alfa group (142 vs. 50 days, p=0.007). The percentage of subjects who were transfused in the epoetin alfa group decreased from 51.8% in the 8 weeks prior to baseline to 24.7% between weeks 16 and 24, compared to the placebo group which had an increase in transfusion rate from 48.9% to 54.1% over the same time periods.

Pharmacokinetic properties
Intravenous administration
Measurement of Epoetin 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 administration
Serum concentration following subcutaneous injection are lower than those following intravenous injection. Serum levels increase slowly and reach a peak 12 to18 hours. The peak serum concentration is 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. Concentration-time profiles of erythropoietin on Week 1 and Week 4 were similar during multiple dosing of 600 IU/kg/once weekly in healthy subjects.

The pharmacokinetic data indicate no apparent difference in half-life among adult patients above or below 65 years of age.

A study of 7 preterm very low birth weight neonates and 10 healthy adults given IV erythropoietin suggested that distribution volume was approximately 1.5 to 2 times higher in the preterm neonates than in the healthy adults, and clearance was approximately 3 times higher in the preterm neonates than in the healthy adults.

The half-life for the subcutaneous route of administration is approximately 24 hours. Mean half-life values in healthy subjects were 19.4 ± 8.1 and 15.0 ± 6.1 with multiple dosing of 150 IU/kg three times per week and 40,000 IU/ml once weekly, respectively.

In a study comparing 40,000 IU SC once weekly to 150 IU/kg SC three times per week dosing regimens of HSA-containing Epoetin alfa in healthy subjects, the following parameters were estimated using data corrected for predose endogenous erythropoietin concentration during Week 4:

	C_{max} (mIU/ml)	C_{min} (mIU/ml)	$t_{1/2}$ (h)
150 IU/kg TIW (n=24)	191 (100.1)	39 (17.9)	31.8
40,000 IU QW (n=22)	785 (427.3)	13 (9.5)	39.3

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

Based on AUC comparison, relative bioavailability of Epoetin alfa 40,000 IU once weekly versus 150 IU/kg three times per week was 176%.

In a study comparing 40,000 IU SC once weekly versus 150 IU/kg SC three times per week dosing of HSA-free Epoetin alfa in healthy subjects, the following parameters were estimated using data corrected for predose endogenous erythropoietin concentration during Week 4:

	C_{max} (mIU/ml)	C_{min} (mIU/ml)	$t_{1/2}$ (h)
150 IU/kg TIW (n=17)	143 (54.2)	18 (9.3)	19.4
40,000 IU QW (n=17)	861 (445.1)	3.8 (4.27)	15.0

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

Based on AUC comparison, relative bioavailability of Epoetinum alfa 40,000 IU/ml once weekly versus 150 IU/kg three times per week was 239%.

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

Pharmacokinetic parameters were estimated in healthy subjects and anemic cancer subjects receiving cyclic chemotherapy and either 150 IU/kg three times per week or 40,000 IU/ml once weekly of HSA-containing Epoetin alfa. The pharmacokinetic parameters of anemic cancer subjects were different from those observed in healthy subjects during Week 1 (when the anemic cancer subjects were receiving chemotherapy) but were similar during Week 3 (when the anemic cancer subjects were not receiving chemotherapy).

	C_{max} (mIU/ml)	C_{min} [b] (mIU/ml)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (ml/h/kg)
Healthy Subjects					
150 IU/kg TIW (n=6) [a]	163 (53.6)	28.6 (10.4)	9.00 (3.29)	25.0 (7.13) [n=4]	31.2 (11.5)
40,000 IU QW (n=6)	1036 (238)	9.25 (5.74)	21.0 (7.10)	28.8 (8.10)	12.6 (3.05)
Anemic Cancer Subjects: Week 1 when subjects were receiving chemotherapy					
150 IU/kg TIW (n=14)[a]	414 (312)	90.4 (41.4)	13.3 (12.4)	43.7 (3.94) [n=3]	20.2 (15.9)
40,000 IU QW (n=18)[a]	1077 (510)	116 (230)	38.5 (17.8)	35.3 (16.8) [n=11]	9.16 (4.69)
Anemic Cancer Subjects: Week 3 when subjects were not receiving chemotherapy					
150 IU/kg TIW (n=4) [a]	178 (57.5)	---	14.2 (6.67)	41.9 (14.8) [n=2]	23.6 (9.51)
40,000 IU QW (n=7)	897 (322)	---	22.3 (4.54)	38.8 (11.0)	13.9 (7.55)

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

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

Pharmacokinetics of HSA-free Epoetin alfa were studied in anemic cancer subjects receiving cyclic chemotherapy after the 150 IU/kg three times per week and 40,000 IU/ml once weekly dosing regimens. In general, there was a high degree of variability associated with the pharmacokinetic parameters in anemic cancer subjects. In general, the first pharmacokinetic profile of Epoetin alfa during Week 1 (when the anemic cancer subjects were receiving chemotherapy) demonstrated higher C_{max}, increased half-life, and lower clearance than the second pharmacokinetic profile during Week 3 or 4 (when the anemic cancer subjects were not receiving chemotherapy)

	C_{max}	C_{min} [b]	t_{max}	$t_{1/2}$	CL/F

	(mIU/ml)	(mIU/ml)	(h)	(h)	(ml/h/kg)
Week 1 when subjects were receiving chemotherapy					
150 IU/kg TIW (n=16)[a]	642 (402.7)	207 (301.4)	14.98 (8.8)	28.3 (19.2) [n=7]	12.1 (11.2)
40,000 IU QW (n=19) [a]	1289 (431.0)	148 (144.2)	48.74 (283)	76.2 (45.8) [n=9]	5.6 (1.8)
Week 3 or 4 when subjects were not receiving chemotherapy					
150 IU/kg TIW (n=9) [a]	357 (246.2)	---	20.67 (20.1)	30.0 (10.0) [n=6]	17.2 (7.8)
40,000 IU QW (n=11)	941 (372.7)	---	24.54 (10.8)	46.7 (22.3)	12.7 (7.5)

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

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

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

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

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

Non-clinical information

Chronic Toxicity

In some pre-clinical toxicological studies in dogs and rats, but not in monkeys, Epoetin 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 Epoetin alfa.

Carcinogenicity

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.

In animal studies, Epoetin 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.

Mutagenicity

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

Reproductive Toxicology

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

CLINICAL PARTICULARS

Indications

- **EPREX 2,000 IU; EPREX 4,000 IU; EPREX 10,000 IU:**
  EPREX 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.

EPREX 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.

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

EPREX 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).

EPREX 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.

Epoetinum alfa is indicated for the treatment of anemia (hemoglobin concentration of ≤10 g/dL) in adults with low- or intermediate-1-risk myelodysplastic syndromes (MDS) who have low serum erythropoietin (<200 mU/mL).

- **EPREX 40,000 IU:**
  EPREX is indicated for the treatment of anaemia and reduction of transfusion requirements in adult cancer patients receiving chemotherapy.

  Epoetinum alfa is indicated for the treatment of anemia (hemoglobin concentration of ≤10 g/dL) in adults with low- or intermediate-1-risk myelodysplastic syndromes (MDS) who have low serum erythropoietin (<200 mU/mL).

Dosage and Administration

General considerations for administration

- EPREX 2,000 IU; 4,000 IU; 10,000 IU may be administered by intravenous or subcutaneous injection.
- EPREX 40,000 IU : may be administered by subcutaneous injection only.

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.

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

Each EPREX syringe is for single use only; only one dose of EPREX should be administered from each syringe.

Intravenous injection

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

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

In haemodialysis patients, a bolus injection may be given during 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.

EPREX 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.

In situations where the physician determines that a patient or caregiver can safely and effectively administer EPREX subcutaneously, instruction as to the proper dosage and administration should be provided.

Dosage

- **EPREX 2,000 IU; EPREX 4,000 IU; EPREX 10,000 IU:**

Chronic renal failure patients

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

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 hemoglobin concentration should not exceed the upper limit of the target haemoglobin concentration (see *Special warnings and special precautions – Renal Failure Patients*).

Adult haemodialysis patients

In patients on hemodialysis, 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 hemoglobin 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 suggest that patients with a baseline hemoglobin (<6 g/dL or <3.7 mmol/L) may require higher maintenance doses than patients with a baseline haemoglobin (>8 g/dL or >5 mmol/L).

Paediatric Haemodialysis patients

The treatment is divided into two stages:

Correction Phase

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

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

Maintenance Phase

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

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

Weight (kg)	**Dose (IU/kg given 3x per 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, EPREX 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 hemoglobin concentration range (10–12 g/dL [6.21–7.45 mmol/L]) is achieved.

Maintenance Phase
The usual dose to maintain the target hemoglobin concentration range 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, EPREX 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 hemoglobin 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.

During the maintenance phase, EPREX can be administered either 3 times per week, and in the case of subcutaneous administration, once weekly.

Appropriate adjustment of dose and dose intervals should be made in order to maintain hemoglobin values at the desired level: Hb between 10 and 12 g/dL (6.2 – 7.5 mmol/L). Extending dose intervals may require an increase in dose.

The maximum dosage should not exceed 150 IU/kg 3 times per week, maximum of 10,000 IU once weekly.

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

Mildly anaemic patients (haematocrit of 33 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 EPREX 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 EPREX and should continue throughout the course of therapy.

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

In cases where there is a medical need to reduce the time before surgery to less than 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 EPREX 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.

- **EPREX 2,000 IU; EPREX 4,000 IU; EPREX 10,000 IU; EPREX 40,000 IU:**
  Cancer Patients
  Adult cancer patients:
  EPREX 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 10 to 12 g/dL (7.5 mmol/l) in men and women and it should not be exceeded.

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

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

  Alternatively, EPREX can be administered at an initial dose of 40,000 IU subcutaneously once weekly.

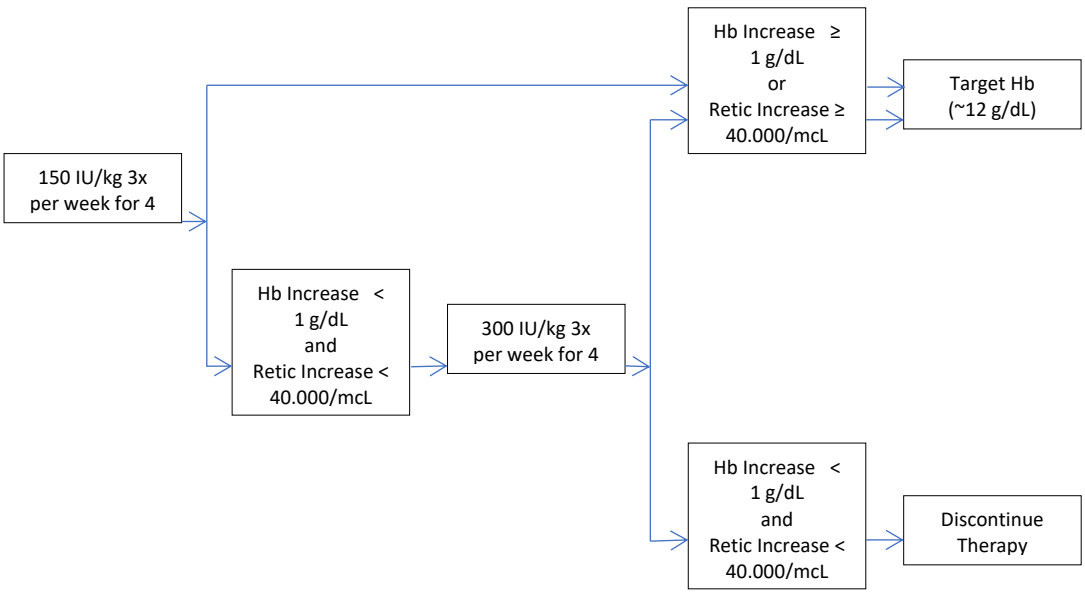
  If after 4 weeks of treatment at the initial dose, the haemoglobin has increased by at least 1 g/dL (0.6 mmol/L) [or the reticulocyte count has increased ≥ 40,000 cells/mcl above baseline] the dose should remain unchanged.

  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/mcl above baseline], in the absence of red blood cell transfusion, the dose should be increased to 300 IU/kg 3 times per week or 60,000 IU weekly.

  If after 4 weeks of additional therapy with 300 IU/kg 3 times per week or 60,000 IU weekly, the haemoglobin has increased ≥ 1 g/dL (≥ 0.6 mmol/L), or the reticulocyte count has increased ≥ 40,000 cells/mcl the dose should remain unchanged.

  If after 4 weeks of additional therapy with 300 IU/kg three times per week or 60,000 IU per week, the haemoglobin has increased < 1 g/dL (0.6 mmol/L) and the reticulocyte count has increased < 40,000 cells/mcl above baseline, response is unlikely and treatment should be discontinued.

  The recommended dosing regimen is described in the following diagram:



A rate of rise in haemoglobin of greater than 1 g/dL (0.6 mmol/l) per 2 week or 2 g/dL (1.25 mmol/L) per month or haemoglobin levels of > 12 g/ dL (>8.1 mmol/L) should be avoided. If the haemoglobin is rising by more than 1 g/dL

(0.6 mmol/l) per two week or 2 g/dL (1.25 mmol/L) per month or haemoglobin is approaching 12 g/dL (7.5 mmol/l), reduce the EPREX 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 EPREX therapy at a dose 25% below the previous dose.

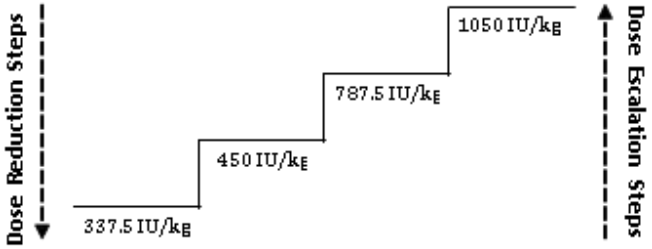
EPREX therapy should be administered to patients with anaemia (e.g. Hb ≤ 11 g/dl {6,8 mmol/l}).

Adult Patients with low- or intermediate-1-risk MDS
The subcutaneous route of administration should be used.
Epoetinum alfa should be administered to low- or intermediate-1- risk MDS patients with anemia (e.g. hemoglobin concentration ≤ 10 g/dL (6.2 mmol/L)).

The recommended starting dose is Epoetinum alfa 450 IU/kg (maximum total dose is 40000 IU) administered subcutaneously once every week.

It is recommended that response be assessed at week 8. If no erythroid response is achieved after 8 weeks according to IWG 2006 criteria (see section 5.1- *Pharmacodynamic properties - Clinical efficacy and safety*), and the hemoglobin concentration is below 11 g/dL (6.8 mmol/L), the dose should be increased from 450 IU/kg once every week to 1050 IU/kg once every week (maximum dose is 80000 IU per week).

Appropriate dose adjustments should be made to maintain hemoglobin concentrations within the target range of 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L). See diagram below for guidelines for stepwise dose adjustment. Epoetinum alfa should be withheld or the dose reduced when the hemoglobin concentration exceeds 12 g/dL (7.5 mmol/L). Upon dose reduction, if hemoglobin concentration drops ≥1 g/dL the dose should be increased.



A sustained hemoglobin concentration of greater than 12 g/dL (7.5 mmol/L) should be avoided.

Special populations
Treatment of pediatric surgery patients in an autologous predonation program
The safety and efficacy of EPREX in pediatric surgery patients in an autologous predonation program have not been established.

Treatment of pediatric patients scheduled for major elective orthopedic surgery
The safety and efficacy of EPREX in pediatric patients scheduled for major elective orthopedic surgery have not been established.

ADVERSE REACTIONS
Summary of the Safety Profile
The most frequent adverse drug reaction during treatment with EPREX is a dose-dependent increase in blood pressure or aggravation of existing hypertension. Monitoring of the blood pressure should be performed, particularly at the start of therapy.

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

Respiratory tract congestion, which includes events of upper respiratory tract congestion, nasal congestion and nasopharyngitis, have been reported in studies with extended interval dosing in adult patients with renal insufficiency not yet undergoing dialysis.

An increased incidence of thrombotic vascular events (TVEs), has been observed in patients receiving ESAs (see *Warnings and Precautions)*.

Clinical Trial Experience

Of a total 3714 subjects in 29 randomized, double-blinded, placebo or standard of care controlled studies, the overall safety profile of EPREX was evaluated in 2238 anemic subjects. Included were 228 EPREX-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 anemia 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, and 102 exposed subjects in 2 studies in MDS. Adverse drug reactions reported by ≥ 1% of subjects treated with EPREX in these trials are shown in the table below: ADB = autologous bood donation; NR = not reported;

Table 1. Summary of Adverse Drug Reactions Reported by ≥1% of Subjects in Clinical Studies With EPREX

	CRF													
	Predialysis		Dialysis		Oncology		HIV		ABD		Surgery		MDS	
	EPO	Placebo	EPO	Placebo	EPO	Non-ESA	EPO	Placebo	EPO	Non-ESA	EPO	Placebo	EPO	Placebo
System/Organ Class Adverse Drug Reaction	N=131 n (%)	N=79 n (%)	N=97 n (%)	N=46 n (%)	N=1404 n (%)	N=930 n (%)	N=144 n (%)	N=153 n (%)	N=147 n (%)	N=112 n (%)	N=213 n (%)	N=103 n (%)	N=102 n (%)	N=53 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)	1 (<1)	NR
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)	1 (<1)	1 (2)
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)	NR	NR
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)	NR	NR
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	NR	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)	NR	NR
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)	NR	NR
Peripheral edema	9 (7)	10 (13)	NR	NR	72 (5)	34 (4)	7 (5)	5 (3)	2 (1)	2 (2)	14 (7)	4 (4)	NR	NR
Metabolism and nutrition disorders														
Hyperkalemia	3 (2)	3 (4)	10 (10)	2 (4)	2 (<1)	2 (<1)	NR	NR	NR	NR	NR	1 (<1)	NR	NR
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)	NR	NR
Bone pain	1 (<1)	NR	6 (6)	1 (2)	47 (3)	26 (3)	3 (2)	NR	NR	1 (<1)	1(<1)	NR	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	NR	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)	NR	NR
Nervous system disorders														
Convulsion	1 (<1)	2 (3)	2 (2)	NR	12 (<1)	4 (<1)	2 (1)	2 (1)	NR	NR	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)	NR	NR
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	NR	NR
Resp tract congestion	NR	NR	9 (9)	2 (4)	NR	NR	1 (<1)	NR	NR	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)	NR	NR
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)	1 (<1)	NR
Deep vein thrombosis	NR	NR	NR	NR	24 (2)	6 (<1)	NR	NR	2 (1)	2 (2)	10 (5)	3 (3)	NR	NR
Thrombosis	NR	NR	4 (4)	1 (2)	18 (1)	6 (<1)	NR	NR	2 (1)	NR	3 (1)	NR	NR	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)	2 (2)	1 (2)

ADB=autologous blood donation; NR=not reported;

[a] Rash includes urticaria and angioedema

[b] Includes arterial and venous, fatal and non fatal events, such as deep venous thrombosis, pulmonary emboli, retinal thrombosis, arterial thrombosis (including myocardial infarction), cerebrovascular accidents (i.e. stroke including cerebral infarction and cerebral hemorrhage) transient ischemic attacks, and shunt thrombosis (including dialysis equipment) and thrombosis within arteriovenous shunt aneurisms

[c] Hypertension includes hypertensive crisis and hypertensive

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 EPREX 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 EPREX 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 EPREX.

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 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.

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

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

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

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

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

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

Pure Red Cell Aplasia
Antibody-mediated PRCA has been very rarely reported after months to years of subcutaneous epoetin treatment in chronic renal failure patients.

Cases also have been rarely reported in patients with hepatitis C treated with interferon and ribavirin, when ESAs are used concomitantly. ESAs are not approved in the management of anemia associated with hepatitis C.
In chronic renal failure patients developing sudden lack of efficacy, defined by a decrease in hemoglobin (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 B12 deficiency, aluminum intoxication, infection or inflammation, blood loss, hemolysis and bone marrow fibrosis of any origin) should be investigated. If the reticulocyte count corrected for anemia (i.e., the reticulocyte "index") is low (<20000/mm3 or <20000/mcL or <0.5%) platelet and white blood cell counts are normal, and if no other cause of loss of effect has been found, anti-erythropoietin antibodies should be determined and a bone marrow examination should be considered for diagnosis of PRCA.

If anti-erythropoietin, antibody-mediated PRCA is suspected, therapy with EPREX should be discontinued immediately. No other 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.

General
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.

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

An increased incidence of thrombotic vascular events (TVEs) has been observed in patients receiving ESAs (see Adverse Reactions). These include venous and arterial thromboses and embolism (including some with fatal outcomes), such as deep venous thrombosis, pulmonary emboli, retinal thrombosis, and myocardial infarction. Additionally, cerebrovascular accidents (including cerebral infarction, cerebral haemorrhage and transient ischaemic attacks) have been reported.

The reported risk of TVEs should be carefully weighed against the benefits to be derived from treatment with EPREX 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.

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

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

Certain formulations of EPREX 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

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 transferring 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 200 mg/day orally) should be administered throughout the course of EPREX therapy. If possible, iron supplementation should be initiated prior to starting EPREX therapy to achieve adequate iron stores.

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

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

The needle cover on the EPREX pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

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.

Geriatric Use

Among 1051 patients enrolled in the 5 clinical studies of EPREX for reduction of allogeneic blood transfusions in patients undergoing elective surgery 745 received EPREX and 306 received placebo. Of the 745 patients who received EPREX, 432 (58%) were aged 65 and over, while 175 (23%) were 75 and over. No overall differences in safety or effectiveness were observed between geriatric and younger patients. The dose requirements for EPREX in geriatric and younger patients

within the 4 studies using the three times per week schedule were similar. Insufficient numbers of patients were enrolled in the study using the weekly dosing regimen to determine whether the dosing requirements differ for this schedule.

Renal Failure Patients
Treatment of symptomatic anaemia in adult and paediatric chronic renal failure patients:
Chronic renal failure patients being treated with EPREX should have haemoglobin levels measured on a regular basis until a stable level is achieved, and periodically thereafter.

In chronic renal failure patients the rate of increase in haemoglobin should be approximately 1 g/dL (0.62 mmol/L) per month and should not exceed 2 g/dL (1.2 mmol/L) per month to minimise risks of an increase in hypertension. Dose should be reduced when haemoglobin approaches 12 g/dL.

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

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

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

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

Hyperkalaemia has been observed in isolated cases, through causality has not been established. Serum electrolytes should be monitored in chronic renal failure patients. If an elevated or rising serum potassium level is detected, then in addition to the appropriate treatment of the hyperkalaemia, consideration should be given to ceasing 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.

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

ESAs are growth factors that primarily stimulate red blood cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells. As with all growth factors, there is a concern that ESAs could stimulate the growth of tumours.

In controlled clinical studies, use of EPREX and other ESAs have shown:
- decreased locoregional control in patients with advanced head and neck cancer receiving radiation therapy when administered to achieve a hemoglobin concentration level of greater than 14 g/dL (8.7 mmol/L).
- shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to a hemoglobin concentration level of 12 to 14 g/dL (7.5-8.7 mmol/L)
- Another ESA (darbepoietin alfa) increased risk of death when administered to achieve a hemoglobin concentration level of 12 g/dL (7.5 mmol/L) in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for use in this patient population.

In view of the above, the decision to administer recombinant erythropoietin treatment should be based on a benefit-risk assessment with the participation of the individual patient, which should take into account the specific clinical context. Factors to consider in this assessment include: the type of tumour and its stage; the degree of anaemia; life-expectancy; the environment in which the patient is being treated; and patient preference (see *Pharmacological Properties, Pharmacodynamic properties*).

In order to ensure optimum response to EPREX, adequate iron stores should be assured, and folic acid and vitamin B_{12} deficiencies should be excluded prior to initiating therapy. In most cases, the ferritin values in the serum fall simultaneously

with the rise in packed cell volume. Therefore, iron 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 EPREX 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 EPREX, 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 EPREX.

Adult Perisurgery Patients (Without Autologous Blood Donation)
Good blood management practices should always be used in the perisurgical setting.

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

The use of EPREX 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 EPREX administration until hyperkalaemia has been corrected.
An increase in heparin dose during haemodyalis is frequently required during the course of therapy with EPREX 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 EPREX 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 EPREX.
All of these additive factors of anaemia should also be carefully considered when deciding to double the dose of EPREX 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 EPREX is a growth factor that primarily stimulates red blood cell production. However, the possibility that EPREX can act as a growth factor for any tumour type, particularly myeloid malignancies, cannot be excluded (see *Non-clinical information*).

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 EPREX or any other erythropoietin (see *Warnings and Precautions*, *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 EPREX.

The use of EPREX 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.

Patient who for any reason cannot receive adequate antithrombotic prophylaxis.

Surgery patients who for any reason cannot receive adequate antithrombotic prophylaxis.

The use of EPREX 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

INTERACTIONS
No evidence exists that indicates that treatment with EPREX alters the metabolism of other drugs. 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.

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

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.

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

Pregnancy, breast-feeding and fertility
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.

Epoetinum alfa should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (See *Non-clinical information).*

Studies in animals have shown reproduction toxicology (see *Non-clinical information*).

Breast-feeding
Erythropoietin is present in human milk. However, it is not known whether EPREX is distributed into human milk. EPREX should be used with caution in nursing women.

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

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

Overdose
The therapeutic margin of EPREX is very wide. Overdosage of EPREX 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. Additional supportive care should be provided as necessary.

PHARMACEUTICAL INFORMATION
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. EPREX syringes or vials 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.

Shelf life
18 months.

Nature and Contents of Container
EPREX is supplied in type I glass pre-filled syringes with FluroTec®-coated rubber stoppers.
The needle cover contains dry natural rubber (a derivative of latex) (see *Warning and Precautions*).
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 colored 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 unused product or waste material should be disposed of in accordance with local requirements.

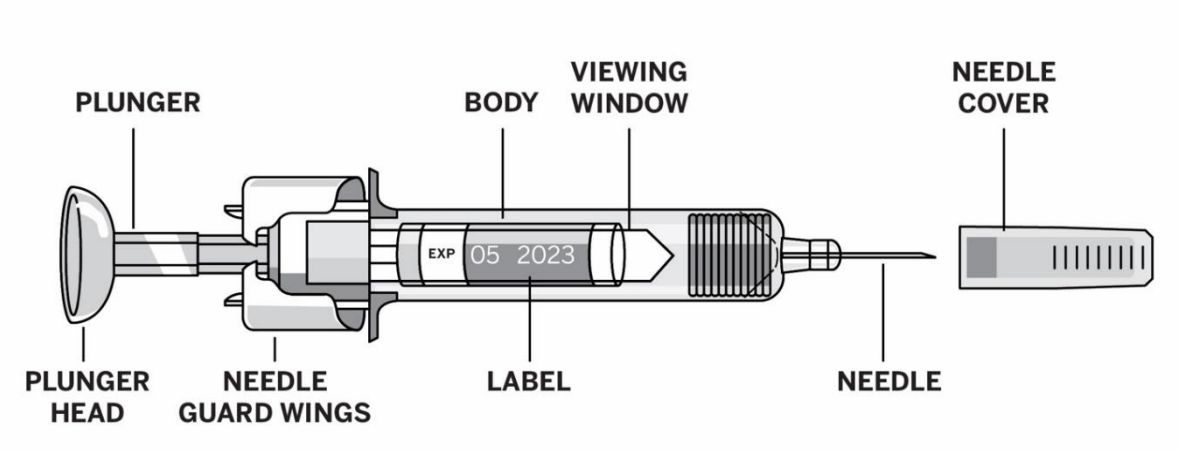
PATIENT INSTRUCTIONS FOR USE AND HANDLING AND DISPOSAL
Injecting EPREX under the skin yourself
At the start of your therapy, EPREX may be injected by medical or nursing staff. However, your doctor may decide that it is right for you to learn how to inject EPREX under the skin (subcutaneous) yourself. 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. Prolonged vigorous shaking may damage the product. If the product has been shaken vigorously, don't use it.

How to inject subcutaneously 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. Do not remove the syringe's needle cover while allowing it to reach room temperature.
- **Check the syringe**, to make sure it is the right dose, has not passed its expiry date, is not damaged, and the liquid is clear and not frozen.
- **Choose an injection site**. Good sites are the top of the thigh and around the abdomen but away from the navel. Vary the site from day to day.
- **Wash your hands. Use an antiseptic swab on the injection site**, to disinfect it.
- **Hold the pre-filled syringe by the body of the syringe with the covered needle pointing upward.**
- **Do not hold by the plunger head, plunger, needle guard wings, or needle cover.**
- **Do not pull back on the plunger at any time.**
- **Do not remove the needle cover from the pre-filled syringe until you are ready to inject your EPREX.**
- **Take the needle cover off the syringe** by holding the body and pulling the needle cover off carefully without twisting it. Don't push the plunger, touch the needle or shake the syringe.
- Do not touch the needle guard wings to prevent prematurely covering the needle with the needle guard.
- **Pinch a fold of skin** between your thumb and index finger. Don't squeeze it.
- **Push the needle in fully.**
- **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. **You may hear a click when the needle guard has been activated.**
- When the plunger is pushed as far as it will go, take out the needle and let go of the skin.
- Slowly take your thumb off the plunger. Allow the syringe to move up until the entire needle is covered by the needle guard.
- **When the needle is pulled out of your skin, there may be a little bleeding at the injection site. This is normal. You can press an antiseptic swab** over the injection site for a few seconds after the injection.

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

- Only take one dose of EPREX from each syringe. If any liquid remains in the syringe after an injection, the syringe should be properly disposed of, not reused. 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?
Give 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 sight and 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.: DKI2060001743A1

EPREX 4000 IU/0.4 ml
Box @ 6 pre-filled syringe @ 0.4 ml
Reg. No.: DKI2060001743B1

EPREX 10000 IU/ ml
Box @ 6 pre-filled syringe @ 1 ml
Reg. No.: DKI2060001743B1

EPREX 40000 IU/ ml
Box @ 1 prefilled syringe @ 1 ml
Reg. No.: DKI2060001743C1

HARUS DENGAN RESEP DOKTER

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi.

Manufactured by Cilag AG, Hochstrasse 201, 8200 Schaffhausen, Switzerland
Registered by PT Integrated Healthcare Indonesia, Jakarta – Indonesia
For adverse event and product quality complaint please contact drugsafety@jacid.jnj.com or Phone (021) 2935 3935

Based on CCDS ver.12 10Sep2021

INFORMASI PRODUK UNTUK PASIEN

EPREX® (Epoetin Alfa)
Injeksi

Baca informasi produk ini secara lengkap dan seksama sebelum Anda mulai menggunakan obat ini.
- Simpan informasi produk ini. Anda mungkin perlu untuk membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan berikan kepada orang lain. Karena dapat membahayakan mereka, walaupun tanda-tanda penyakit mereka sama seperti Anda.
- Jika Anda menemukan efek samping serius atau jika Anda menemukan efek samping yang tidak tercantum dalam informasi produk ini, laporkan kepada dokter atau apoketer Anda.

Apa yang ada dalam informasi produk ini

1. APAKAH EPREX® ITU DAN DIGUNAKAN UNTUK APA

EPREX® mengandung zat aktif epoetin alfa – suatu protein yang merangsang sumsum tulang untuk menghasilkan lebih banyak sel darah merah yang membawa hemoglobin (zat yang mengangkut oksigen). Epoetin alfa adalah Salinan dari protein eritropoietin manusia dan bekerja dengan cara yang sama.

- **EPREX® digunakan untuk mengobati anemia simptomatik yang disebabkan oleh penyakit ginjal**
- pada pasien anak-anak yang mendapatkan hemodialisis dan dewasa yang mendapatkan hemodialisis atau dialisis peritoneal
- pada orang dewasa dengan anemia berat yang belum menjalani dialisis.

Jika Anda memiliki penyakit ginjal, Anda mungkin kekurangan sel darah merah jika ginjal Anda tidak memproduksi eritropoietin yang cukup (yang diperlukan untuk produksi sel darah merah). EPREX® diresepkan untuk merangsang sumsum tulang Anda menghasilkan sel darah merah yang lebih banyak.

- **EPREX® digunakan untuk mengobati anemia jika Anda menerima kemoterapi** dan dokter Anda memutuskan bahwa Anda mungkin memerlukan transfuse darah. EPREX® dapat mengurangi kebutuhan transfusi darah.
- **EPREX® digunakan pada orang dengan anemia sedang yang mendonorkan darahnya sebelum operasi,** sehingga darahnya dapat dikembalikan kepada mereka selama atau setelah operasi. Karena EPREX® merangsang produksi sel darah merah, dokter dapat mengambil banyak darah dari orang-orang ini.
- **EPREX® digunakan pada orang dewasa dengan anemia sedang yang akan menjalani operasi ortopedi besar** *(misalnya operasi penggantian pinggul atau lutut)*, untuk mengurangi potensi kebutuhan transfusi darah.
- **EPREX® digunakan mengobati anemia jika Anda pasien dewasa yang menerima obat Zidovudin** (AZT) yang digunakan untuk mengobati **infeksi HIV.**
- **EPREX® digunakan untuk mengobati anemia pada pasien dewasa dengan sindrom mielodisplasia.** EPREX® dapat mengurangi kebutuhan transfusi darah.

2. APA SAJA YANG HARUS ANDA KETAHUI SEBELUM MENGGUNAKAN EPREX®

Jangan gunakan EPREX®:
- **Jika Anda memiliki tekanan darah tinggi** yang tidak terkontrol dengan obat-obatan.
- **Kejang**

- **Jika Anda alergi (hipersensitif)** terhadap Epoetin alfa atau bahan lain dari EPREX® (tercantum dalam Bagian 6 Informasi lainnya)
- **Jika Anda menjalani operasi ortopedi** (misalnya operasi pinggul atau lutut), dan Anda:
  - memiliki penyakit jantung yang parah
  - memiliki gangguan vena dan arteri yang berat
  - mengalami serangan jantung atau stoke dalam waktu dekat
  - tidak dapat meminum obat pengencer darah. EPREX® mungkin tidak cocok untuk Anda. Mohon diskusikan dengan dokter Anda. Saat menggunakan EPREX®, beberapa orang membutuhkan obat-obatan untuk mengurangi risiko pembekuan darah. **Jika Anda tidak dapat meminum obat-obatan yang dapat mencegah pembekuan darah, Anda tidak boleh menggunakan EPREX®.**
- **Jika Anda didiagnosis menderita Aplasia sel darah merah murni** (sumsum tulang belakang tidak dapat menghasilkan sel darah merah yang cukup) setelah sebelumnya menggunakan produk yang merangsang produksi sel darah merah (termasuk EPREX®). Lihat Bagian 4, Efek samping yang mungkin terjadi.
- Untuk merangsang produksi sel darah merah Anda (sehingga dokter dapat mengambil banyak darah dari Anda) **jika Anda tidak bisa mendapatkan transfusi dengan darah Anda sendiri** selama atau setelah operasi.

Hati-hati dengan EPREX®:

EPREX® dan produk lain yang merangsang produksi sel darah merah dapat meningkatkan risiko pembentukan gumpalan darah pada semua pasien. Risiko ini mungkin lebih besar jika Anda memiliki faktor risiko lain dalam pembekuan darah *(misalnya, jika Anda mengalami pembekuan darah di masa lalu atau kelebihan berat badan, memiliki diabetes, memiliki penyakit jantung atau Anda kehilangan kaki untuk waktu yang lama dikarenakan operasi atau penyakit)*. Beritahukan dokter Anda tentang hal-hal ini. Dokter Anda akan membantu Anda memutuskan apakah EPREX® cocok untuk Anda.

Hal ini penting untuk diberitahukan kepada dokter Anda jika salah satu dari hal-hal berikut ini terjadi pada Anda. Anda mungkin masih dapat menggunakan EPREX®, tapi diskusikan ini dengan dokter Anda terlebih dahulu.

- **Jika Anda tahu Anda menderita atau pernah menderita:**
  - **tekanan darah tinggi**
  - **kejang atau serangan epilepsi**
  - **penyakit hati**
  - **anemia dari penyebab lain**
  - **porfiria (kelainan darah langka)**
  - **alergi terhadap lateks**

- **Jika Anda seorang pasien kanker,** perhatikan bahwa produk-produk yang merangsang produksi sel darah merah (seperti EPREX®) dapat bertindak sebagai faktor pertumbuhan dan oleh karena itu secara teori dapat mempengaruhi perkembangan sel kanker Anda. **Tergantung pada kondisi Anda, transfusi darah mungkin lebih disukai. Harap diskusikan terlebih dahulu dengan dokter Anda.**
- **Jika Anda seorang pasien kanker,** perhatikan bahwa penggunaan EPREX® dikaitkan dengan kelangsungan hidup yang lebih singkat dan tingkat kematian pada kepala dan leher yang lebih tinggi, dan pada pasien kanker payudara metastasis yang menerima kemoterapi.
- **Jika Anda mengalami reaksi kulit yang parah,** ruam, yang mungkin parah, dapat menutupi seluruh Anda dan juga meliputi lepuh atau area kulit yang keluar, hentikan penggunaan EPREX® dan hubungi dokter Anda atau segera dapatkan bantuan medis.

Hati-hati dengan produk lain yang merangsang produksi sel darah merah:

EPREX® adalah salah satu kelompok produk yang merangsang produksi sel darah merah seperti yang dilakukan protein manusia, eritropoietin. Tenaga kesehatan profesional Anda akan selalu mencatat produk yang Anda gunakan.

Jika Anda diberikan produk lain dalam kelompok ini selain dari EPREX® selama pengobatan Anda, bicarakan dengan dokter atau apoteker Anda sebelum menggunakannya.

Menggunakan obat-obat lain:

EPREX® biasanya tidak bereaksi dengan obat-obat lain tapi harap beritahu dokter Anda jika Anda menggunakan (atau baru-baru ini menggunakan) obat-obat lain – termasuk obat-obat yang diperoleh tanpa resep dokter.

Jika Anda menggunakan obat siklosporin (misalnya digunakan setelah transplantasi ginjal), dokter Anda akan meminta pemeriksaan darah untuk memeriksa tingkat siklosporin dalam darah saat Anda menggunakan EPREX®.

Suplemen zat besi dan stimulan darah lainnya dapat meningkatkan efektivitas EPREX®. Dokter Anda akan memutuskan apakah tepat bagi Anda untuk menggunakannya.

Jika Anda pergi ke rumah sakit, klinik, atau dokter keluarga Anda, beri tahu mereka bahwa Anda sedang menjalani pengobatan dengan EPREX®. Ini mungkin dapat mempengaruhi pengobatan lain atau hasil tes.

Kehamilan, menyusui, dan kesuburan
Hal ini penting untuk beri tahu dokter Anda jika hal-hal berikut ini terjadi pada Anda. Anda mungkin masih dapat menggunakan EPREX®, tapi diskusikan ini dengan dokter Anda terlebih dahulu.
- Jika Anda hamil, berencana untuk hamil, atau berpikir Anda mungkin hamil.
- Jika Anda menyusui, atau berencana menyusui

3. BAGAIMANA CARA MENGGUNAKAN EPREX®

Selalu gunakan obat ini secara tepat seperti yang dikatakan dokter Anda. Tanyakan dokter Anda jika Anda tidak yakin.

Dokter Anda telah melakukan pengujian darah dan memutuskan Anda membutuhkan EPREX®.

EPREX® 2000 IU; 4000 IU; dan 10000 IU dapat diberikan melalui suntikan:
- **Baik** ke dalam vena atau tabung yang masuk ke vena (secara intravena)
- **Atau** di bawah kulit (subkutan)

EPREX® 40000 IU hanya dapat diberikan melalui suntikan di bawah kulit (subkutan).

Dokter Anda akan memutuskan bagaimana EPREX® akan disuntikkan. Biasanya suntikan akan diberikan oleh dokter Anda, perawat atau tenaga kesehatan profesional lainnya. Beberapa orang, bergantung pada alasan pengunaan EPREX®, selanjutnya dapat belajar cara menyuntikkan diri di bawah kulit: lihat **Petunjuk tentang cara menyuntikkan EPREX® secara subkutan oleh sendiri.**

EPREX® tidak boleh digunakan:
- setelah tanggal kadaluwarsa yang tertera pada label dan karton luar
- jika Anda tahu, atau berpikir obat mungkin tidak sengaja menjadi beku, atau
- jika ada kerusakan pada kulkas

Dosis EPREX® yang Anda terima tergantung pada berat badan dalam kilogram. Penyebab anemia Anda juga menjadi faktor untuk dokter Anda dalam menentukan dosis yang tepat.

Dokter Anda akan memantau tekanan darah Anda secara rutin selama penggunaan EPREX®.

Pasien dengan penyakit ginjal
- Dokter Anda akan mempertahankan kadar hemoglobin Anda antara 10 dan 12 g/dL pada orang dewasa dan 9.5 hingga 11 g/dL pada anak-anak, karena kadar hemoglobin yang tinggi dapat meningkatkan risiko pembekuan darah dan kematian.
- **Dosis awal** EPREX® yang umum untuk dewasa dan anak-anak adalah 50 Internasional Unit (IU) per kilogram (/kg) berat badan yang diberikan tiga kali seminggu.
- Untuk pasien yang menjalani dialisis peritoneal, EPREX® dapat diberikan:

- dua kali seminggu untuk pasien dewasa
- tiga kali seminggu untuk pasien pediatrik

- Untuk pasien hemodialisis dewasa dan pediatrik, EPREX® dapat diberikan tiga kali seminggu.
- Untuk pasien dewasa dan anak-anak, EPREX® diberikan sebagai suntikan ke pembuluh darah atau tabung yang masuk ke pembuluh darah. Ketika jalur (melalui pembuluh darah atau tabung) tidak tersedia, dokter Anda akan memutuskan bahwa EPREX® harus disuntikkan melalui bawah kulit (melalui subkutan). Hal ini termasuk untuk pasien yang menjalani dialisis dan belum melakukan dialisis.
- Dokter Anda akan melakukan pengujian darah secara rutin untuk melihat bagaimana reaksi anemia Anda dan dapat menyesuaikan dosis, biasanya tidak lebih sering daripada setiap empat minggu.
- Setelah anemia Anda diobati, dokter Anda akan melanjutkan memeriksa darah Anda secara rutin. Dosis dan frekuensi pemberian EPREX® selanjutnya dapat disesuaikan lebih lanjut untuk mempertahankan respons Anda terhadap pengobatan.
- Jika Anda berada pada interval dosis EPREX® yang lebih lama (lebih dari satu kali seminggu), Anda mungkin tidak dapat mempertahankan kadar hemoglobin yang memadai dan Anda mungkin memerlukan peningkatan dosis atau frekuensi penggunaan EPREX®.
- Anda mungkin akan diberikan suplemen zat besi sebelum atau selama pengobatan dengan EPREX® agar lebih efektif.
- Jika Anda menjalani perawatan dialisis saat Anda memulai pengobatan dengan EPREX®, pengaturan dialisis Anda perlu disesuaikan. Dokter Anda akan memutuskan ini.

Pasien dewasa yang menjalani kemoterapi

- Dokter Anda dapat memulai pengobatan dengan EPREX® jika kadar hemoglobin Anda kurang dari atau 10 g/dL.
- Dokter Anda akan mempertahankan kadar hemoglobin Anda pada 10 dan 12 g/dL karena semakin tinggi kadar hemoglobin dapat meningkatkan risiko pembekuan darah dan kematian.
- Dosis awal **antara** 150 IU/kg berat badan tiga kali seminggu atau 40000 IU secara subkutan sekali dalam seminggu.
- EPREX® diberikan melalui suntikan di bawah kulit.
- Dokter Anda akan melakukan pengujian darah, dapat menyesuaikan dosis, tergantung dari bagaimana respon anemia Anda terhadap pemberian EPREX®.
- Anda mungkin akan diberikan suplemen zat besi sebelum atau selama pengobatan dengan EPREX® agar lebih efektif.
- Anda biasanya akan melanjutkan pengobatan dengan EPREX® selama satu bulan setelah selesai kemoterapi.

Pasien dewasa yang mendonorkan darah

- Dosis yang biasa digunakan adalah 600 IU/kg berat badan dua kali seminggu selama tiga minggu.
- EPREX® diberikan melalui suntikan ke dalam vena, selama 3 minggu sebelum operasi Anda, setelah Anda mendonorkan darah.
- Anda mungkin akan diberikan suplemen zat besi sebelum atau selama pengobatan dengan EPREX® agar lebih efektif.

Pasien dewasa yang dijadwalkan untuk operasi ortopedi besar

- **Dosis yang disarankan** yaitu 600 IU/kg berat badan satu kali seminggu.
- EPREX® diberikan melalui suntikan di bawah kulit selama tiga minggu sebelum operasi atau pada hari operasi.
- Jika ada kebutuhan medis untuk mengurangi waktu sebelum operasi, Anda akan diberikan dosis harian sebanyak 300 IU/kg hingga sepuluh hari sebelum operasi, pada hari operasi, dan selama empat hari segera setelah operasi.
- Jika pengujian darah Anda menunjukkan kadar hemoglobin yang tinggi sebelum operasi, pengobatan akan dihentikan.
- Anda mungkin akan diberikan suplemen zat besi sebelum atau selama pengobatan dengan EPREX® untuk membuatnya lebih efektif.

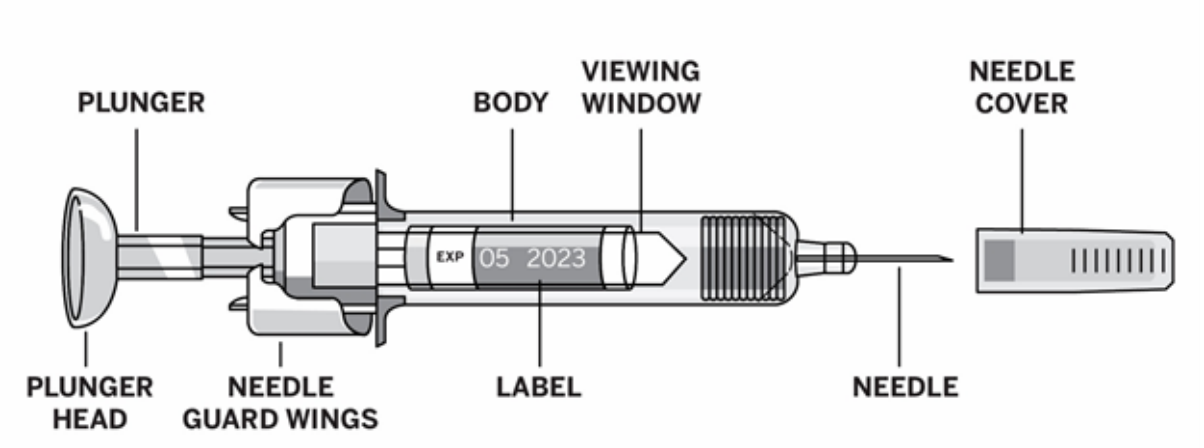
Pasien dewasa dengan sindrom mielodisplasia

- Dokter Anda dapat memulai pengobatan dengan EPREX® jika kadar hemoglobin Anda kurang dari atau sama dengan 10 g/dL. Tujuan dari pengobatan adalah untuk mempertahankan kadar hemoglobin

berada di antara 10 dan 12 g/dL karena kadar hemoglobin yang tinggi dapat meningkatkan risiko pembekuan darah dan kematian.
- EPREX® dapat diberikan melalui suntikan di bawah kulit.
- Dosis awal yaitu 450 IU per kilogram berat badan seminggu sekali.
- Dokter Anda akan melakukan pengujian darah dan dapat menyesuaikan dosis, tergantung dari bagaimana respon anemia Anda terhadap pemberian EPREX®.

Petunjuk tentang cara menyuntik sendiri EPREX® secara subkutan menggunakan *pre-filled syringe*:
Ketika pengobatan dimulai, EPREX® biasanya disuntikkan oleh dokter atau perawat. Kemudian, dokter Anda mungkin menyarankan Anda atau pengasuh anda untuk mempelajari cara mnyuntikkan EPREX® di bawah kulit (secara subkutan) sendiri.

- **Jangan mencoba menyuntikkan diri sendiri kecuali Anda telah dilatih untuk melakukannya oleh dokter atau perawat Anda.**
- **Selalu gunakan EPREX® sesuai petunjuk yang diberikan oleh dokter atau perawat.**
- **Hanya gunakan EPREX® yang telah disimpan dengan benar- lihat Bagian 5, Bagaimana cara menyimpan EPREX®.**
- Produk ini hanya untuk sekali pakai.
- Produk tidak boleh digunakan, dan harus dibuang jika:
  o segel rusak,
  o cairan berwarna atau
  o terdapat partikel di dalamnya,
  o mungkin telah dibekukan, atau
  o terjadi kegagalan selama pendinginan.
- Setiap produk atau bahan limbah yang tid)ak terpakai harus dibuang sesuai dengan persyaratan setempat.
- **Jika EPREX® disuntikkan di bawah kulit (secara subkutan), jumlah yang disuntikkan biasanya tidak lebih dari satu milliliter (1 mL) dalam satu kali suntikan.**
- **EPREX® diberikan tunggal dan tidak dicampur dengan cairan lain untuk suntikan.**
- **Jangan kocok suntikan EPREX®. Getaran yang kuat dalam waktu lama dapat merusak produk. Jilka produk terguncang dengan keras, jangan digunakan.**
- **Pre-filled syringe dilengkapi dengan perangkat pelindung jarum PROTECS™ untuk membantu mencegah luka akibat jarum suntik setelah penggunaan. Hal ini tertera pada kemasan.**



- **Keluarkan jarum suntik dari kulkas.** Cairan harus mencapai suhu kamar. Ini biasanya membutuhkan waktu antara 15 sampai 30 menit. Jangan lepaskan penutup jarum suntik selama membiarkannya mencapai suhu kamar.
- **Periksa jarum suntik,** untuk memastikan dosis yang tepat, belum melewati tanggal kadaluwarsa, tidak rusak, dan cairan bening dan tidak beku.
- **Pilih area suntikan.** Area yang baik adalah bagian atas paha dan sekitar perut tetapi jauh dari pusar. Variasikan area dari hari ke hari.
- **Cuci tangan Anda. Usapkan antiseptik pada area penyuntikkan,** untuk mendisinfeksi.

- **Pegang *pre-filled syringe* pada bagian tubuh jarum suntik dengan jarum tertutup mengarah ke atas.**
- **Jangan pegang kepala pendorong, pendorong, sayap pelindung jarum, atau penutup jarum.**
- **Jangan menarik pendorong kapan saja.**
- **Jangan lepaskan penutup jarum dari *pre-filled syringe* sampai Anda siap untuk menyuntikkan EPREX®.**
- **Jangan menyentuh klip pengaktifan jarum** dengan memegang badan dan menarik penutup jarum dengan hati-hati tanpa memutarnya. Jangan mendorong pendorong, menyentuh jarum atau mengocok syringe.
- **Jangan menyentuh sayap pelindung jarum untuk mencegah menutupi jarum dengan pelindung jarum sebelum waktunya.**
- **Jepit lipatan kulit** antara ibu jari dan jari telunjuk. Jangan memeras.
- **Dorong jarum masuk sepenuhnya.**
- **Dorong dengan ibu jari Anda sejauh mungkin untuk menyuntikkan seluruh cairan.** Dorong perlahan dan merata, jaga agar lipatan kulit terjepit. **Pelidung jarum tidak akan aktif kecuali seluruh dosis telah diberikan. Anda mungkin mendengar bunyi klik saat pelindung jarum telah diaktifkan.**
- **Saat pendorong didorong sejauh mungkin**, keluarkan jarum dan lepaskan kulit.
- **Perlahan-lahan lepaskan ibu jari dari pendorong.** Biarkan jarum suntik bergerak ke atas sampai seluruh jarum ditutupi pelindung jarum PROTECS™.
- Ke**tika jarum dicabut dari kulit Anda, mungkin ada sedikit pendarahan di area penyuntikkan. Hal ini normal. Anda dapat menekan antiseptic usap** pada area suntikan selama beberapa detik setelah injeksi.
- **Buang bekas jarum suntik Anda** dalam wadah yang aman – lihat Bagian 5, Cara menyimpan EPREX®.
- Ambil satu dosis EPREX® dari setiap jarum suntik. Jika ada cairan yang tertinggal di dalam jarum suntik setelah disuntik, jrum suntik harus dibuang dengan benar, tidak digunakan kembali.

Jika Anda menggunakan EPREX® lebih dari seharusnya:

Segera beritahu dokter atau perawat Anda jika Anda merasa terlalu banyak menyuntikkan EPREX®. Efek samping dari kelebihan dosis EPREX® kecil kemungkinan terjadi.

Jika Anda lupa untuk menggunakan EPREX®:

Lakukan suntikan berikutnya segera setelah Anda ingat. Jika Anda dalam satu hari dengan suntikan selanjutnya, lupakan suntikan yang terlewat dan lanjutkan dengan jadwal normal Anda. Jangan menggandakan suntikan.

Jika Anda seorang pasien dengan hepatitis C dan menerima interferon dan ribavirin:

Anda harus membicarakan hal ini dengan dokter Anda karena kombinasi epoetin alfa dengan interferon dan ribavirin dapat menyebabkan hilangnya efek dan pengembangan kondisi yang disebut aplasia sel darah merah murni *(PRCA)*, bentuk anemia parah, dalam kasus yang jarang terjadi. **EPREX® tidak disetujui untuk pengobatan anemia yang terkait dengan hepatitis C.**

Jika Anda memiliki pertanyaan lebih lenjut tentang penggunaan produk ini, tanyakan kepada dokter, perawat, atau apoteker Anda.

4. EFEK SAMPING YANG MUNGKIN TERJADI

Seperti semua obat-obatan, EPREX® dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

Segera beritahu dokter atau perawat Anda jika Anda menemukan salah satu efek dalam daftar ini.

Efek samping yang paling sering terjadi yang diamati dalam uji klinis epoetin alfa adalah:
- **Tekanan darah tinggi**
- **Diare**
- **Mual**
- **Muntah**

- **Demam**
- **Sakit kepala**
- **Gejala mirip flu:** lebih sering terjadi pada awal pengobatan

Efek samping lain:

- **Jalur pernapasan yang tersumbat,** seperti hidung tersumbat dan sakit tenggorokan, telah dilaporkan pada pasien dengan penyakit ginjal yang belum menjalani dialisis.
- **Reaksi alergi** termasuk ruam, gatal-gatal, dan reaksi alergi parah yang dapat meliputi: bengkak pada wajah, bibir, mulut, lidah atau tenggorokan; kesulitan menelan atau bernapas.
- **Tekanan darah tinggi meningkat** disertai **sakit kepala**, terutama secara tiba-tiba , sakit kepala yang menusuk seperti migren, **perubahan fungsi otak atau kejang** mungkin merupakan tanda peningkatan tekanan darah secara tiba-tiba. Hal ini membutuhkan perhatian segera dari dokter. Peningkatan tekanan darah mungkin memerlukan perawatan dengan obat-obatan (atau penyesuaian terhadap obat apapun yang sudah Anda gunakan untuk tekanan darah tinggi).
- **Gumpalan darah** (Trombosis vena dalam atau *DVT*), biasanya di kaki.
- **Penghambatan pembuluh darah oleh gumpalan darah.**
- **Gumpalan darah** termasuk yang**: bergerak ke paru-paru, menyebabkan nyeri dada dan sesak napas; menghambat pasokan darah ke mata, yang menyebabkan penglihatan kabur atau kebutaan; memblokir arteri; menyebabkan serangan jantung, stroke, atau pemblokiran sementara aliran darah ke bagian otak (stroke ringan).**
- **Tingginya kadar kalium dalam darah** yang dapat menyebabkan irama jantung yang tidak normal.
- **Menggigil**
- **Iritasi atau nyeri ditempat suntikan**
- **Tangan, pergelangan kaki, dan kaki bengkak**
- **Nyeri sendi**
- **Nyeri pada tulang**
- **Nyeri tangan dan kaki**
- **Nyeri otot**
- **Kejang**
- **Ruam kulit**
- **Gatal**
- **Gejala aplasia sel darah merah murni *(PRCA)* – jenis anemia dimana sumsum tulang tidak memproduksi sel darah merah. PRCA menyebabkan jumlah sel darah merah tiba-tiba menjadi sangat rendah.**

PRCA dilaporkan sudah sangat jarang terutama pada pasien dengan penyakit ginjal setelah berbulan-bulan hingga bertahun-tahun pengobatan dengan EPREX® dan produk lain yang merangsang produksi sel darah merah.

- Peningkatan kadar sel darah kecil (trombosit), yang biasanya terlibat dalam pembekuan darah, terutama ketika memulai pengobatan

Jika Anda menjalani hemodialisis:

- **Gumpalan darah** (thrombosis) dapat terbentuk pada saluran dialisis Anda. Ini lebih mungkin terjadi jika Anda memiliki tekanan darah rendah atau jika fistula Anda memiliki komplikasi.
- **Gumpalan darah** juga dapat terbentuk dalam sistem hemodialisis Anda. Dokter Anda mungkin memutuskan untuk meningkatkan dosis heparin selama dialisis.

Segera beritahu dokter atau perawat Anda jika mengetahui adanya salah satu efek tersebut, atau jika Anda melihat adanya efek lain saat Anda menerima pengobatan dengan EPREX®.

5. BAGAIMANA CARA MENYIMPAN EPREX®

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini jika telah melewati tanggal kadaluwarsa yang tertera pada dus dan label setelah tulisan EXP. Tanggal kadaluwarsa merujuk pada hari terakhir pada bulan tersebut.

Simpan pada suhu 2°C-8°C (36°F sampai 46°F) di kulkas. Anda dapat mengeluarkan EPREX® dari kulkas dan simpan pada suhu ruangan (hingga suhu 25°C) selama tidak lebih dari 7 hari. Setelah suntikan dikeluarkan dari kulkas dan mencapai suhu ruangan (hingga suhu 25°C) harus langsung digunakan dalam 7 hari atau dibuang.

Janagan dikocok dan beku.

Simpan pada kemasan asli untuk melindungi dari cahaya.

Jangan gunakan obat ini jika Anda melihat bahwa segel sudah rusak atau jika cairan berwarna atau Anda melihat partikel melayang di dalamnya. Jika dalam pengamatan kedua hal tersebut ditemukan, maka produk tidak boleh digunakan.

Jangan membuang obat apapun melalui limbah pembuangan atau limbah rumah tangga. Tanyakan kepada apoteker Anda cara membuang obat yang tidak digunakan lagi. Langkah-langkah ini dapat membantu melindungi lingkungan.

6. INFORMASI LAINNYA

Apa isi EPREX®:

Zat aktifnya adalah: Epoetin Alfa
Bahan lainnya adalah: disodium fosfat dihidrat, glisin, air untuk injeksi, polisorbat 80, natrium klorida, natrium dihydrogen fosfat dihidrat

Seperti apa EPREX® dan isi kemasannya:

EPREX® tersedia dalam larutan untuk injeksi yang diisi dalam jarum suntik. *Pre-filled syringe* dilengkapi dengan perangkat pelindung jarum PROTECS™. EPREX® adalah larutan jernih dan tidak berwarna.

EPREX® tersedia dalam jarum suntik kaca tipe I dengan sumbat karet berlapir FluroTec®.

EPREX 2000 IU/0.5 ml
DUS @ 6 pre-filled syringe @ 0.5 ml
Reg. No.: DKI2060001743A1

EPREX 4000 IU/0.4 ml
DUS @ 6 pre-filled syringe @ 0.4 ml
Reg. No.: DKI2060001743B1

EPREX 10000 IU/ ml
DUS @ 6 pre-filled syringe @ 1 ml
Reg. No.: DKI2060001743B1

EPREX 40000 IU/ ml
DUS @ 1 pre-filled syringe @ 1 ml
Reg. No.: DKI2060001743C1

HARUS DENGAN RESEP DOKTER

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi.

Diproduksi oleh:
Cilag AG, Hochstrasse 201, 8200 Schaffhausen, Switzerland

Didaftarkan oleh:
PT Integrated Healthcare Indonesia, Jakarta – Indonesia

Untuk pelaporan efek yang tidak diinginkan dan keluhan produk silahkan menghubungi drugsafety@jacid.jnj.com atau telepon (021) 2935-3935

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